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Risks and Benefits of Selective Serotonin Reuptake Inhibitors in the Treatment of Depression

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Summary

Depression is a common, life-disrupting, potentially lethal illness that can affect both sexes and all ages. Its peak onset is in the early adult years. It is more common than hypertension in primary care practice. Recent studies show that fewer than 1 in 20 depressed patients are correctly diagnosed and adequately treated. Depression periodically destroys the productivity of those with the condition, and

depressed patients have a worse quality of life than patients with debilitating, chronic conditions such as arthritis, hypertension, diabetes mellitus and back pain.

Suicide occurs in as many as 15% of patients with depression, especially those with recurrent episodes and hospitalisations, and may even occur in those with in subsyndromal depression. Suicide is one of the leading causes of death, and individuals who complete suicide have usually experienced mood disorders, mainly depression. Current data support a decreased frequency of suicidal ideation with all antidepressants, including selective serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitors (SSRIs).

Modern pharmacotherapy is the cornerstone for effective treatment of depression. As they are well tolerated, even in the presence of comorbid medical illness, and easier to manage, SSRIs enhance compliance. A fully adequate antidepressant dosage is suitable for patients of all ages and can be used by non-psychiatrist physicians for the treatment of the acute episode, as well as the frequent recurrences that often require long term maintenance antidepressant medication.

SSRIs have fewer drug interactions than older antidepressants, and even the SSRI inhibition of hepatic cytochrome P450 enzymes has proven only very infrequently to be of clinical importance.

SSRIs also effectively treat anxious depression, dysthymia and atypical depression. Fluoxetine may provide more rapid onset of therapeutic effect because it can be started at closer to its usual full therapeutic dosage than other SSRIs or older antidepressants. SSRIs, in particular fluoxetine, are more suitable for use as long-term maintenance therapy in these chronic relapsing diseases. These factors and the high efficacy rate, increased safety in overdose, reduced incidence of adverse effects (mostly decreasing with time) and superiority in ease of maintaining patients in adequate treatment plans provides fluoxetine with an overall superior therapeutic profile.

Nearly 4 decades ago, investigators noticed that iproniazid caused elevation of mood in some patients being treated for tuberculosis. That discovery led to a major breakthrough in the way major depressive disorder was regarded and treated: it gave great impetus to the concept of depression as a biochemical disturbance of the CNS and provided the basis for the first effective pharmacotherapy of depression.

Recent research has shown depression to be a chronic condition with a lifetime risk of approximately 20% for women and 10% for men.[1-5] However, despite the availability of effective pharmacological treatment for nearly 40 years, it is estimated that only about 2.5% of people who meet the criteria for major depression ultimately receive appropriate treatment.[1-7] Patients who respond to treatment gradually return to euthymia during several weeks to a few months of adequate antidepressant pharmacotherapy.[8]

However, the overall clinical efficacy of past available antidepressants used in clinical practice has been significantly hampered by the frequency of untoward treatment-emergent events, intolerable adverse effects, and difficulty in adjusting the dosage. Together, these 3 factors have contributed significantly to decreased compliance, subtherapeutic dosages, or premature discontinuation of treatment. This in turn is associated with incomplete remission and/or more frequent relapse, all of which leave patients open to the morbidity of major depressive disorder, including suicide. The need for improvement over available agents led researchers to seek drugs with more advantageous tolerability profiles.

In the past 20 years,[9] drug development has

shifted from the discovery of compounds by chance to rationally targeting specific mechanisms of action believed to be important in the pathophysiology of psychiatric syndromes.[10] Selective serotonin (5-hydroxytryptamine, 5-HT) reuptake inhibitors (SSRIs) were the first class of psychiatric medications to be developed based on molecular targeting. A major consequence of the introduction of such agents has been greater compliance among patients, as a result of fewer adverse effects and less complicated dosage schedules.

Easier management is also expected to enhance physician attention to diagnosis, and increase the likelihood of using adequate dosages and adequate durations of antidepressant pharmacotherapy. Depression is a common chronic disorder that frequently presents in nonpsychiatric practice (e.g. primary care), where it is often underdiagnosed and undertreated.[11] In addition, the high morbidity and mortality associated with this disorder[12,13] may well be decreased. According to Nemeroff,[14] antidepressants are more efficacious than most classes of drugs, with the exception of antimicrobial agents and a few other drug classes.

Nearly 3 out of every 4 outpatients being treated for depression with antidepressants will respond successfully during this treatment,[3,5,6,15] and individual patients who do not respond to one antidepressant sometimes respond to another.[3] However, as many as 1 of 3 outpatient responders may in fact be placebo or spontaneous responders,[3,14] so *specific* drug responders could number as low as 50% of those treated. However, this is of little importance to the clinician faced with the decision of whether or not to treat since there is no reliable manner to identify the potential placebo or spontaneous responder *before* treatment.

Apart from efficacy, which is about the same for all antidepressants, drug choice is, by and large, based on tolerability and ease of administration because these factors relate so strongly to compliance. Since the advent of SSRIs, safety has become another factor in drug choice, since the SSRIs are better tolerated in overdose than any of the tricyclic antidepressants (TCAs), heterocyclic antidepressants (HCAs) or older monoamine oxidase inhibitors (MAOIs).[3,14,16,17] Drug acquisition costs, once thought to be of major importance, are now being shown to be less important in the context of the overall cost effectiveness of antidepressant treatment.[18-20]

In this review, we discuss the tolerability profiles and efficacy of the currently used SSRIs: fluoxetine, paroxetine, sertraline, fluvoxamine and citalopram. Most attention is given to the first 3 agents, which are the most widely used.

1. Epidemiology of Depression

In weighing up the advantages and disadvantages of a specific drug, it is crucial for the clinician to bear in mind some data on the epidemiology of depression. The disorder is associated with high mortality, morbidity and economic cost.[21] Depression is more common than hypertension in primary care practice.[22] It occurs from childhood to senescence, but most patients are initially affected during early adulthood and their most productive later adult years, between 20 and 50 years of age. 15% of patients with (especially recurrent) major depression ultimately commit suicide.[23] Moreover, 45 to 70% of all people who commit suicide have an affective disorder.[6,23,24] In addition, 19 to 42% of those who commit suicide have previously attempted suicide, and 10% of those who attempt suicide will eventually succeed within 10 years.[25] Although probably underestimated, suicide ranks as the eighth leading cause of death in the US, higher than AIDS.[26,27] Depression can affect the outcome of other clinical entities. For example, it increases mortality among patients following myocardial infarction.[12]

The costs of depression, not only to individuals and their families, but also the indirect costs to the healthcare system, employers and society, are enormous.[28] These costs may be substantially diminished by successful diagnosis and antidepressant treatment, especially if accomplished early in the course of the disease[21,29-32] and if compliance is maintained at adequate dosage for adequate time.[18]

2. Pharmacotherapy in Depression

Pharmacotherapy has been shown by Elkin et al.[15] to be the most effective treatment for moderate to severe depression. Prior to the advent of focused systems of psychotherapy, no evidence existed for efficacy of dynamic psychotherapeutic approaches in the treatment of depression. Pharmacotherapy and focused structured psychotherapy (e.g. cognitive behavioural or interpersonal therapy) are perhaps equally effective in the management of mild depression, but recovery is more rapid with pharmacotherapy.[15] Where indicated, psychotherapy may assist in the resolution of other psychological problems as patients recover from their depression with the assistance of pharmacotherapy. In some cases, concomitant psychotherapy may also assist in inducing remission from depression[33] and contribute to a decreased relapse rate.

3. Place of Selective Serotonin Reuptake Inhibitors

The major drawbacks in the use of older agents for treating depression are the poor tolerability and safety profiles as well as the multiple daily doses that are often required, all of which decrease compliance and lead to suboptimal dosage and premature discontinuation of treatment.[19,20,31]

SSRIs possess 4 major advances over the older antidepressants:

1. A more benign tolerability profile with fewer adverse events; most of those which do occur are mild and transient in nature.[34,35] It is estimated that only 20 to 25% of patients taking TCAs receive adequate therapeutic dosages,[36-38] because of the desire to avoid the associated adverse effects.

2. Easier administration. Fluoxetine often requires no titration, and can be administered once daily.[39] Other SSRIs require minimal titration compared with older antidepressant drugs and can also be routinely given once daily.[34]

3. SSRIs have been shown to be involved in far fewer drug interactions, especially those of a serious nature (e.g. involving sedatives, sympathomimetics, alcohol, antiarrhythmics), compared with older antidepressants.[14,40] This has proven true in clinical practice even though, as a class, the SSRIs inhibit at least one of the cytochrome P450 (CYP) isoenzymes, which results in the *potential* to enhance (sometimes beyond the appropriate therapeutic range) the effects of other concomitant drugs that are metabolised by these enzymes.

4. The SSRIs are better tolerated in overdose than the irreversible MAOIs, TCAs, HCAs and amfebutamone (bupropion).[35] The safety of SSRIs in overdose contrasts with that of the still widely used TCAs, which cause more deaths from overdose than any other prescription drug category (table I).[16] This safety in overdose occurs despite the fact that antidepressant drugs are prescribed for patients who have an illness in which suicide is a recognised risk. The increased safety of SSRIs compared to older drugs is true even though, in a mixed overdose situation, all SSRIs can potentially increase the plasma and tissue concentrations of a number of co-ingested drugs by inhibiting the hepatic CYP enzyme metabolism of those drugs.[41]

The utility of an antidepressant with a more benign tolerability profile becomes even greater, since emerging data point to the fact that for most patients, depression is a recurrent disorder with episodes increasing in frequency throughout life,[42-47] and many patients require long term maintenance treatment with antidepressants. Recent data show that at least 50% of patients who have had a single episode of depression will experience recurrence.[48,49] Therefore, one goal of management is

Table I. Fatal toxicity index of antidepressant drugs (reproduced from Tollefson,[35] with permission)

Drug	No. of fatal poisonings per million prescriptions
Amitriptyline	166
Maprotiline	115
Imipramine	105
Doxepin	99
Trimipramine	93
Clomipramine	34
Fluoxetine	10[a]

a Extrapolated from one reported fatal overdose in 100 000 patients.

to identify those in need of long term pharmacotherapy and enhance their compliance during continuation therapy after the initial period of acute recovery. In many cases, very long or lifetime prophylactic therapy will then be appropriate.

In this regard, SSRIs have been shown to be efficacious in reducing relapse and recurrence rates by more than 50% when compared with placebo.[50-52] Furthermore, SSRIs have proven extremely useful in the management of depression in patients with concomitant medical conditions such as cardiac disease and stroke, because of their improved tolerability.[3,53,54] Over 35 million patients have been treated with SSRIs since they were first used in Europe in the mid-1980s.[40]

4. Comparisons With Older Antidepressants

Nemeroff[14] has stated that the ideal antidepressant for elderly patients should have no clinically significant cardiotoxic or orthostatic effects, cause little sedation and no impairment of memory, and not impair physical ability. In our opinion, based on an extensive review of the literature, SSRIs can be considered to be the first-line agent for all depressed patients including elderly patients, and we shall review some of the data to support this assertion. Due to the higher selectivity of drug effect with SSRIs, as exemplified by the absence of unwanted CNS and peripheral receptor blockade, which occurs with older antidepressants, SSRIs tend to be better tolerated in patients with comorbid medical conditions.[55,56] In addition, as has been pointed out,[10] drugs that are rationally developed to affect only the mechanism mediating a desired response tend to have a wider therapeutic index than drugs discovered by chance. The latter drugs frequently have either multiple mechanisms of action (e.g. TCAs) or such a basic mechanism of action that they have an impact on a wide variety of systems (e.g. MAOIs). Patients receiving drugs like TCAs, with multiple mechanisms of action occurring over a relatively narrow concentration range, are likely to experience multiple effects, both desired and undesired.

SSRIs have high specificity for serotonin uptake blockade and do not cause unwanted blockade of peripheral and central adrenergic, cholinergic and histaminergic receptors, which is characteristic of the TCAs and MAOIs. TCAs are associated with a wide range of adverse effects resulting from unwanted receptor blockade. Muscarinic blockade produces effects such as dry mouth, blurred vision, memory impairment, constipation, urinary retention and sinus tachycardia. These drugs also block α_1-adrenergic receptors, which may cause orthostatic hypotension and tachycardia, as well as histaminergic blockade, which may cause sedation and bodyweight gain. These adverse effects are shared by HCAs to various degrees.

In addition to their unwanted receptor blockade, TCAs have a direct dose-related quinidine-like effect on the myocardium that can induce potentially life-threatening cardiac conduction disturbances, especially in patients with pre-existing, even subclinical, cardiac disease.[57-59] This effect is thought to be mediated through the inhibition of sodium fast channels and occurs at concentrations only one order of magnitude higher than the concentration needed to inhibit the neuronal uptake pump for norepinephrine (noradrenaline) and serotonin, the putative mechanism of action mediating their antidepressant effect. In susceptible individuals, these effects can occur at usual full therapeutic doses of TCAs.

The efficacy of SSRIs in major depression has now been established in numerous controlled double-blind studies and through vast clinical experience.[60] Tollefson,[17] commenting on the use of SSRIs for the treatment of depression, mentioned that the efficacy of these agents is similar to (or perhaps slightly better than) that of TCAs, a view supported by others;[61-63] however, these findings have not been universally reported.[64,65]

Boyer and Feighner[66] reviewed comparative efficacy studies of SSRIs and older antidepressants (mainly secondary and tertiary amine TCAs) and found that of 25 comparisons with fluoxetine, no differences were found in 23, and fluoxetine was

significantly superior in 2 of them. For fluvoxamine, no significant differences were found, with the exception of 1 study, which found fluvoxamine to be superior to the 'gold standard' TCAs. Among 9 studies of paroxetine, 7 found no significant differences, 1 found imipramine to be superior to paroxetine, and 1 found the opposite. Of 8 studies on citalopram, 6 found no significant differences between this drug and the TCA comparator, 1 showed citalopram to be superior, and 1 found that clomipramine was superior to citalopram. There were 3 studies on sertraline, of which 1 showed amitriptyline to be superior to sertraline and 2 showed no significant differences between the 2 agents. Overall, these findings[66] support the conclusion that there is no clearly definable superiority in efficacy for any one class of antidepressants over another.

In some studies, in which there was overall superior efficacy of SSRIs as compared to TCAs, this was clearly related to the more benign adverse event profile of these drugs.[66,67] Better tolerability, combined with ease of administration, compared with TCAs, MAOIs and some HCAs, increases compliance in patients being treated for depression, particularly patients being treated over long periods of time,[68] and the elderly and patients with comorbid medical conditions.[69]

The high specificity of SSRIs translates into a unique and relatively benign adverse-effect profile with superior patient acceptance and compliance, which in clinical trials, results in greatly diminished withdrawal rates in SSRI-treated groups, compared with TCA- and MAOI-treated patients. For example, Boyer and Feighner[66] and others[67,70] compared short term withdrawal rates during tertiary or secondary amine TCA and SSRI treatment, and showed SSRI compliance to be significantly superior (10 to 20% dropout in SSRI group, as opposed to 30 to 35% in TCA group and 5 to 10% in the placebo group).

Besides sharing many similar adverse effects with TCAs, the older MAOIs are associated with potentially life-threatening interactions with dietary tyramine, or proximal (within 2 weeks for paroxetine, sertraline, clomipramine and citalopram, and 4 weeks for fluoxetine) or concurrent administration of serotonergic agents. This can be a problem in the long term management of patients who might be compliant with the drug regimen, but not adequately compliant with dietary restrictions or who inadvertently ingest tyramine-containing foods. MAOIs are also associated with greater risk in overdose compared with SSRIs.

In summary, the SSRIs, being more pharmacologically selective than the older agents such as TCAs, HCAs and MAOIs, have better tolerability and are safer in overdose than these older agents. They have been shown to be at least as clinically efficacious as these agents and to have improved compliance and lower dropout rates in a number of clinical studies. It is worth mentioning that the clinical premise that patients who do not respond to one antidepressant class can become responders when switched to an agent of another drug group remains true for SSRIs, which are reported to be effective among a significant percentage of TCA-resistant patients with depression.[71,72]

5. Pharmacology

In order to attain the most benefit from available agents, clinicians need to be familiar with the specific characteristics of individual agents which can vary within each class. The structure of the individual SSRIs varies. The activity patterns of these drugs can have class similarities with some between-drug differences in activity which can be helpful as guidelines provided one is careful in considering that *in vitro* receptor-specific metabolic and *in vivo* pharmacokinetic data do not precisely predict clinical response or adverse effects.

5.1 Receptor Activity

An overview of receptor activity of SSRIs is useful in understanding the behaviour and advantages of these compounds and as an additional guide in their clinical use. Some of the most important findings from receptor studies with SSRIs are that: (i) clinically, all SSRIs have negligible activity at muscarinic and histaminergic receptors;[9,14,40,53]

Table II. Receptor binding affinities of selective serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitors.[74-78] None of these agents has significant affinity for dopamine D_2 receptors

Drug	Reuptake blockade of selective serotonin			Receptor blockade			
	serotonin	norepinephrine (noradrenaline)	dopamine	histamine H_1	muscarine	serotonin 5-HT_2	α adrenergic
Paroxetine	++	–	–	–	+	–	–
Fluoxetine	++	–	–	–	±	–	–
Sertraline	++	–	±	–	±	–	–
Fluvoxamine	++	–	–	–	±	–	–
Citalopram	++	–	–	–	±	–	–
Desipramine	–	++	–	+	+	–	++
Imipramine	+	+	–	+	++	+	+

Symbols: ++ = pronounced; + = mild; ± = probably not clinically significant; – = nil.

(ii) although relative differences in weak adrenoceptor affinity exist across the class, they do not appear to be of clinical significance;[53] (iii) no significant dopaminergic receptor activity has been demonstrated;[53] (iv) the clinical relevance of *in vitro* γ-aminobutyric acid (GABA)ergic activity is unclear;[53,73] and (v) corticotrophin-releasing factor antagonism, which would reduce the elevated discharge rates in the locus coeruleus of depressed patients, has been hypothesised as a mechanism of action for antidepressant activity – such a role has not been established for SSRIs.

In vitro studies of paroxetine have reported some activity at muscarinic cholinergic receptors, suggesting an increased chance of anticholinergic activity, compared with other SSRIs.[66] However, even paroxetine does not clearly display clinically significant anticholinergic activity, and the blurred vision and constipation seen occasionally with this agent are most probably related to the serotonergic innervation of the pupil and gut, rather than 'true' anticholinergic effects.[53] For sertraline, characteristics include more potent inhibition activity at adrenergic receptor sites than other SSRIs (which nevertheless is also very low and unlikely to be clinically meaningful) and higher (but apparently not clinically significant) *in vitro* affinity for the σ receptor binding site (this receptor has been implicated in psychotic symptomatology). Finally, there are differences in patterns of hepatic enzyme inhibition between the various SSRIs (section 6).

Despite some individual variability, SSRIs have a favourable tolerability profile. This generally derives from their lack of unwanted receptor blockade (α_1-adrenergic, muscarinic, cholinergic, histaminergic) [table II].[3,79] The main established action of the SSRIs, thought to be related to their therapeutic effect, is to increase synaptic serotonin transmission through inhibition of synaptic serotonin reuptake and consequent metabolism.

Different hypotheses have been raised regarding postsynaptic 5-HT_{1A} and 5-HT_2 receptor binding in explaining serotonergic-related antidepressant activity and an interaction between these two sites has been advocated. Additionally, the role of somatodendritic 5-HT_{1A} and hetero receptors as feedback inhibitors of synaptic serotonin release, as serotonin 'leaks' from the adjacent serotonin synthesising cell body, is still incompletely understood. These somatodendritic receptors may be functionally downregulated in the face of continued increased serotonin concentration secondary to ongoing SSRI action, and this could permit continued serotonin synthesis, release and trans-synaptic transmission during long term SSRI treatment.[80] One theory for the potential augmenting effect of the 5-HT_{1A} blocker pindolol is via its purported inhibition (blockade) of somatodendritic 5-HT_{1A} receptors.[81]

5.2 Pharmacokinetics

The metabolism and associated pharmacokinetics of SSRIs varies between drugs. *In vivo*, fluoxetine has an extended half-life of 3 days and a highly active metabolite (norfluoxetine), which has a half-life of about 1 week,[3] while other pure SSRIs or TCAs and HCAs generally have half-lives of 1 day or less. This provides a clear advantage for fluoxetine over these drugs, regarding missed doses over intervals of a few days, since plasma fluoxetine and norfluoxetine concentrations remain in the therapeutic range.

Continued experience with fluoxetine has revealed other advantages stemming from its extended half-life. For example, patients are very unlikely to experience withdrawal symptoms or relapse in situations of inadvertent occasional noncompliance or abrupt discontinuation of drug. Withdrawal syndromes, sometimes severe, have been documented with abrupt discontinuation of TCAs[82] and, more recently, with the other SSRIs,[83] all of which have comparatively short half-lives, similar to most TCAs. Patients suddenly discontinuing these shorter half-life drugs[82] (with the possible exception of sertraline[81,83]) may experience symptoms ranging from sleep disturbance, gastrointestinal upset, headache and fatigue to depression or mania. On the other hand, the extended half-life of fluoxetine requires a longer waiting period (4 to 5 weeks *vs* 2 to 3 weeks for other SSRIs) following discontinuation if standard MAOIs are being considered as alternative drugs because of the risk of an interaction between the drugs. However, this particular medication shift is becoming very infrequent. Progressive accumulation resulting from the extended half-life of fluoxetine and its metabolite does not occur. At constant dosages, steady state is reached after 5 or 6 weeks, even if hepatic metabolism by usual CYP isoenzymes is inhibited, presumably because of alternative metabolic pathways.[84]

Experience with more than 25 million patients treated with fluoxetine, and many millions more with other SSRIs, has shown that clinically important adverse effects secondary to drug interactions with SSRIs are rare (with the exception of the interactions with MAOIs, particularly the older (nonselective irreversible) ones. Nevertheless, physicians must remain aware of these possibilities, which are discussed in section 6.

Agent-specific pharmacokinetic considerations are shown in table III.

Table III. Agent-specific pharmacokinetic considerations for the selective serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitors[40,50,73,85]

Drug	Active metabolites	Half-life of parent (metabolite)[a]	Comments
Fluoxetine	Norfluoxetine	++++ (++++++)	Metabolite has a half-life of about 1 week; it possesses both serotonin and (to a lesser extent) norepinephrine (noradrenaline) reuptake-blocking selectivity;[80] racemic compound (pharmacokinetic differences in enantiomers and their metabolites not clinically significant)
Sertraline	Demethylsertraline	+ (++++)	Extended half-life of metabolite is of little clinical significance, since the ability of the metabolite to inhibit serotonin reuptake is much weaker than that of the parent compound[73]
Paroxetine	None	+	Paroxetine has a slightly shorter half-life than the other short half-life SSRIs, which may contribute to its pronounced tendency to withdrawal or breakthrough depression when doses are missed[81,86]
Fluvoxamine	None	+	Pharmacology suggests tendency to induce withdrawal symptoms, as with other short half-life compounds, but no controlled data are available
Citalopram	Demethylcitalopram	+ (+++)	Racemic compound (differences in pharmacokinetics and metabolism of the enantiomers and their metabolites not clinically important)

a The more '+'s, the longer the half-life.

An important consideration regarding the metabolism of all these drugs is that pharmacokinetic studies in the elderly[73] reveal that, although pharmacokinetic behaviour is not remarkably changed, potentially the drugs are more slowly metabolised (especially paroxetine and citalopram), and therefore, lower initial dosages may be appropriate in elderly patients. In general, elderly patients should be started on lower dosages of SSRIs. Age-related pharmacokinetic changes with paroxetine are significant enough to cause the manufacturer to advise a lower starting dose in elderly patients (10 mg/day, with gradual upward titration to a maximum of 40mg instead of the usual maximum dose of 50mg).[87]

All of the SSRIs are well absorbed after oral administration, and this is not diminished by concomitant food intake, thus providing excellent bioavailability.[73] The absorption of sertraline is enhanced when taken with meals, compared with between meals,[73] and it is possibly best administered in this manner.

The metabolic elimination of SSRIs is delayed by hepatic or severe renal disease, in the presence of which dosages should be lowered or administered less frequently.[73]

There is no therapeutic window for SSRIs. No relationship has been found between plasma concentrations of the parent drug, metabolites or 'ratios' of drug/metabolite to therapeutic efficacy or toxic concentrations.[88]

5.3 Tolerability

SSRIs are associated with their own specific adverse effect profile, which tends to be milder than those of older antidepressant agents, and contributes to the documented higher compliance rates across studies.[35,89,90]

5.3.1 Gastrointestinal

The most common adverse effect associated with SSRIs is nausea, which, we believe is generally better described as 'mild dyspepsia'; vomiting has been reported, but only rarely, with all drugs in this class. Nausea occurs in up to 20% of patients receiving fluoxetine; this adverse effect is typically mild and transient, and usually dosage related.[91] In a 1985 review of comparative studies, the 3% discontinuation rate of fluoxetine due to nausea was similar to that observed for imipramine.[91]

Loss of appetite can occur transiently and may be associated with some bodyweight loss. Although it is good clinical practice to monitor bodyweight in severely underweight patients, the evidence shows that bodyweight loss associated with SSRI therapy (which may particularly occur with fluoxetine) is more pronounced in overweight patients and in those with carbohydrate craving.[92,93] The bodyweight loss associated with SSRIs, if present, is generally mild (2kg) and self limited.[92,94] This tendency to slight bodyweight reduction can be beneficial to many depressed patients (some of whom may have increased bodyweight secondary to treatment with older antidepressants), especially those who are already overweight or fall into the category of hyperphagic depression. However, the clinician must be aware of the (rarely observed) potential for abuse in patients presenting with symptoms of anorexia nervosa or bulimia nervosa, who may erroneously believe that SSRIs will produce progressive bodyweight loss. The latter has not been observed in our experience or reported in the literature. In fact, fluoxetine-induced bodyweight loss in long term animal and human obesity studies has been nonprogressive, with bodyweight gradually returning to pretreatment levels.[92] A tendency to develop diarrhoea can occur with SSRIs and is also generally transient and dosage related.[40]

5.3.2 Neurological

Although having an overall more favourable profile of behavioural toxicity than conventional antidepressants, SSRIs have also been associated with increased anxiety, nervousness and insomnia in a minority of patients.[40,53] These tend to occur early in treatment and may appear *de novo* or temporarily enhance pre-existing anxiety symptoms. However, the presence of anxiety in depression may in fact be a predictor of high likelihood of response to fluoxetine or other SSRIs.[95] Dosage reduction or the introduction of a benzodiazepine

during the first few weeks of therapy can help such patients. Experience with SSRIs has shown that anxiety decreases, as measured by anxiety factors in the Hamilton Depression Rating Scale (HDRS) scores, in depressed patients.[91,96] Paroxetine may be associated with unwanted daytime somnolence in perhaps 20% of patients, while fluoxetine may be most likely to induce, initially at least, emergent symptoms of anxiety, nervousness and restlessness, which are transient; sertraline is associated with a higher incidence of sexual dysfunction and gastrointestinal problems.[53,97] Rarely, tremor can occur in association with SSRI use, and may respond to dosage reduction or the addition of a β-blocker or a benzodiazepine if it persists.[98,99]

5.3.3 Sexual Dysfunction

TCAs and MAOIs reduce erectile function and are contraindicated in patients with erectile impotence. These drugs and, to an even greater degree, the SSRIs have also been associated with inability to ejaculate, delayed ejaculation and anorgasmia.[100,101] There is no reliable, safe or easy solution to overcoming these adverse effects, although dosage reduction or switching to another SSRI may help.[102] Some patients have found relief over the weekend by stopping the shorter half-life compounds on Friday and resuming them on Sunday.[103]

In view of the dissociation often observed between relatively rapid (2 to 3 days) subsidence of emerging adverse events related to fluoxetine and its known extended half-life, it is possible that interruption of therapy for a few days could diminish or abolish complaints of sexual dysfunction in patients receiving this drug. A technique that we have used, which requires confirmation in a prospective controlled study, is to prescribe the entire week's dosage of fluoxetine spread over a few days (e.g. starting Sunday night or Monday through to Wednesday or Thursday morning).

Finally, it is sometimes possible to produce a significant degree of amelioration of this adverse effect by treating with gradually increasing doses of cyproheptadine (a serotonin and histamine antagonist) up to as high as 32 mg/day, as needed, or amantadine in usual clinical dosages, until symptoms abate.[104,105] In patients with bronchial asthma or glaucoma, cyproheptadine should be used with caution because of its atropine-like effects. As with all antihistamines, daytime drowsiness may occur, and may be dosage-related.

5.3.4 Other

The currently used SSRIs have not been implicated in causing allergic reactions, such as were observed with zimeldine, an early SSRI, which is no longer available. In fact, there have been reports of patients who had an allergic reaction with zimeldine, but who have been treated with currently available SSRIs with no such complications.[66] Nevertheless, in the event of any pruritic rash occurring, discontinuation of the current SSRI is advisable.

An extremely rare, but serious, central serotonin syndrome has been reported during SSRI therapy.[106] The risk of this idiosyncratic event increases markedly with concomitant or proximal administration of a serotonin-enhancing agent, such as a MAOI or precursor agent such as tryptophan, to an SSRI regimen. Consequently, SSRIs should never be used proximal to or concomitant with one of these agents. The syndrome can present as abdominal pain, diarrhoea, sweating, fever, arthralgia, tachycardia, elevated blood pressure, delirium, myoclonus, increased motor activity, irritability, hostility and mood change. It can lead to hyperpyrexia, shock or death in severe cases.[107] Tollefson[17] recommends waiting at least 5 half-lives of the parent SSRI or of its active metabolite (if longer) before starting MAOI therapy. Consistent with this advice, Ciraulo and Shader[108] recommend waiting for 5 weeks after stopping fluoxetine and 2 weeks after stopping one of the other SSRIs.

6. Drug Interactions

6.1 Benzodiazepines

Data point to the fact that SSRIs are relatively free of cumulative CNS depression in combination with benzodiazepines.[98,99] This represents an advance over TCAs, HCAs and MAOIs, which have

cumulative depressant effects with CNS sedatives, anticholinergic agents or histaminergic compounds. However, it has been reported that fluvoxamine and, to a lesser extent, the other SSRIs, which inhibit one or more hepatic CYP isoenzymes, increase plasma diazepam and alprazolam concentrations. However, when these anxiolytics are used appropriately, this does not present a clinically significant problem because benzodiazepines should be started at low dosages and increased only as needed to obtain anxiolytic effects while observing for unwanted effects (e.g. excessive sedation, increased agitation, disorientation).

It must be kept in mind that since benzodiazepines do not treat depression, their indiscriminate use in patients with depression should be strongly discouraged. Nevertheless, the fact that SSRIs do not significantly increase sedation when used with such agents make SSRIs a valuable tool for physicians treating depression in patients who have a clear clinical indication for short-term concomitant benzodiazepine administration. Benzodiazepines may be indicated temporarily in a minority of depressed patients presenting with pronounced anxiety or in those who develop anxiety when SSRI therapy is initiated.

6.2 Drugs Metabolised by Cytochrome P450 Enzymes

Other drugs that may interact with SSRIs are those that are metabolised by or affect the function of the same hepatic enzymes that metabolise the SSRIs, especially certain CYP enzymes. Within the CYP enzyme group, some 3 dozen different isoenzymes have been identified, with the 2D6, 3A3, 3A4 and 2C isoenzymes being the most relevant to our consideration of drug-drug interactions with SSRI antidepressants. For extensive reviews of CYP enzyme activity and drug-drug interactions see Nemeroff et al.[41]

Since all SSRIs inhibit some of the CYP isoenzymes to a degree, plasma and tissue drug concentrations of other concomitantly administered compounds normally metabolised by these isoenzymes might be increased during SSRI administration. This inhibition has been observed in the approximately 90% of Caucasian, Mexican American, African American and Asian individuals who are extensive metabolisers (EM) with regard to the activity of CYP2D6.[109] Individuals with this EM CYP2D6 genotype can be transformed into 'apparent' (phenotypic) poor metaboliser (PM) types in the presence of the CYP2D6 isoenzyme inhibitor SSRI compounds. This could produce increases in plasma and tissue concentrations of concomitantly administered drugs normally metabolised by the CYP isoenzyme (table IV). Those individuals genetically endowed with low activity (amount) of CYP2D6 isoenzyme will already be phenotypic PM types and will be unable to process much of any compound that requires metabolic action by that isoenzyme. Administration of SSRIs to these

Table IV. Newer antidepressants and potentially important drug interactions (adapted from Nemeroff et al.,[41] with permission)

Antidepressant	Enzyme system inhibited	Drugs that may be affected
Fluoxetine	2D6	Secondary amine TCAs, haloperidol, class 1C antiarrythmics
	2C	Phenytoin, diazepam
Sertraline	2D6	Secondary amine TCAs, antipsychotics, class 1C antiarrythmics
	2C	Tolbutamide, diazepam
Paroxetine	2D6	Secondary amine TCAs, antipsychotics, class 1C antiarrythmics, trazodone
Fluvoxamine	1A2	Theophylline, clozapine, haloperidol, amitriptyline, clomipramine, imipramine
	2C	Diazepam, warfarin
	3A4	Carbamazepine, alprazolam, terfenadine, astemizole
Citalopram	2D6 (? other isoenzymes)	Desipramine, imipramine (? all TCAs); further studies needed with other combinations[a]

a Serotonin syndrome, seizures and death reported in at least 3 patients treated with citalopram combined with reversible monoamine oxidase inhibitors, moclobemide plus benzodiazepines, or alcohol (ethanol).

Abbreviation: TCA = tricyclic antidepressant.

patients will produce little change in the metabolism of xenobiotics processed by the 2D6 isoenzyme. No genetic polymorphism has yet been identified for CYP3A3 or CYP3A4 isoenzymes and all individuals so far studied are EM regarding this isoenzyme, but activity can be inhibited by some SSRIs.[41,109]

Concomitant administration of SSRIs and drugs with a narrow therapeutic index normally metabolised by CYP isoenzymes, such as TCAs, has the potential to increase plasma and tissue concentrations of the latter compounds, with subsequent emergence of adverse events, or (in this case) the emergence of therapeutically planned and desirable events (remission of depression) when these drugs are combined as an adjuvant treatment in patients not responsive to either drug alone.

Dosage adjustments are often necessary for drugs with a narrow therapeutic index when combined with SSRIs. Inhibition of CYP2D6, CYP3A3, CYP3A4 or CYP2C by various SSRIs can raise plasma and tissue concentrations of TCAs,[110] warfarin (coumadin), anticonvulsants [valproic acid (sodium valproate), carbamazepine], certain antipsychotics (including clozapine), quinidine and some other antiarrhythmic drugs, β-blockers and some opioids.[41,109] Therefore, dosage adjustment of these compounds may be required in patients receiving SSRIs. For example, a recent report documented increased warfarin concentrations and prothrombin time in a patient receiving warfarin and fluoxetine.[111]

SSRI-induced enzyme inhibition is dosage related and has been reported with all SSRIs, although the particular isoenzymes involved vary with the particular SSRI and concomitant drug administered.[112] Crewe et al.[112] ranked a number of antidepressants according to their *in vitro* ability to inhibit CYP2D6 in the following order: paroxetine > fluoxetine (norfluoxetine) > sertraline > citalopram > fluvoxamine > clomipramine and amitriptyline. However, the relative *in vitro* inhibition is not remarkably different between the 3 most widely used and most potent inhibitors of the isoenzyme, paroxetine, fluoxetine and sertraline, and the latter 2 are closest together (table V).[112] Citalopram inhibits CYP2D6 far more weakly than any of the 3 most widely used SSRIs (fluoxetine, sertraline and paroxetine), but it does inhibit other isoenzymes.[112]

In vivo studies of fluoxetine and paroxetine (at full therapeutic dosages) found them to be equal in inhibiting CYP2D6, as revealed by decrease in desipramine metabolism with resultant increased plasma concentrations.[109] In the same report, low doses of sertraline (50mg) produced less interference with desipramine metabolism (less increase in steady-state desipramine concentrations, compared with other SSRIs).[109] However, the dose of sertraline studied was often a clinically subtherapeutic dose,[113] and higher doses would be expected to proportionately increase drug concentrations.[114] This would cause greater inhibition of CYP2D6 and further elevate plasma and tissue concentrations of desipramine.[114]

When using compounds with a narrow therapeutic index in conjunction with SSRIs, monitoring of plasma concentrations of these compounds and/or their active metabolites, or measuring their physiological effects, is advisable (e.g. ECG during concomitant TCA administration or prothrombin levels during warfarin administration), and clinical monitoring of individual patients is mandatory.

Table V. Inhibition constants (K_i) for cytochrome P450 2D6–mediated inhibition of 2-dehydrosparteine metabolism in human liver microsomes (reproduced from Crewe et al.,[112] with permission)

Drug (and major metabolites)	K_i (μmol/L)
Paroxetine	0.15
(M-1 glucuronide)	>200
(M-1 sulphate)	120
Fluoxetine	0.60
(norfluoxetine)	0.43
Sertraline	0.70
Citalopram	5.1
Fluvoxamine	8.2
Clomipramine	2.2
Desipramine	2.3
Amitriptyline	4.0
Quinidine	0.03

Nevertheless, despite clear *in vitro* and more recent *in vivo* evidence of the inhibiting effects of all SSRIs on various isoenzymes of the CYP enzyme system, and reported increases in TCA plasma concentrations during concomitant SSRI administration, it is reassuring that the adverse events related to this form of enzyme inhibition have proven to be rarely of clinical importance. This conclusion is similar to that expressed by Nemeroff et al.[41] Our search of the literature revealed only rare reports of significant drug-drug interactions with SSRIs, even after 10 years of extensive post-marketing use.

Physicians must keep the possibility of potential drug-drug interactions clearly in mind. A further caveat of caution is appropriate here because it is not currently possible to accurately predict in which patients, and to what degree, plasma concentrations of TCAs or other drugs may be enhanced in the presence of concomitant SSRI administration. It is useful for clinicians to refer to a table of potential drug-drug interactions that can possibly complicate concomitant drug administration with SSRIs so that appropriate monitoring can be pursued (table IV).

6.3 Highly Protein-Bound Drugs

SSRIs tend to be highly protein bound (especially sertraline, paroxetine and fluoxetine),[3,53,73,85] and may displace other drugs bound to plasma proteins (e.g. warfarin and digitalis), thereby increasing the concentration of the free (non–protein-bound) and generally 'active' fraction of these compounds. This propensity of SSRIs to displace compounds bound to plasma proteins may work in conjunction with SSRI inhibition of CYP metabolism to further elevate levels and enhance the activity of co-administered compounds. Although clinical experience to date has not revealed frequent or severe problems with these combinations, awareness of this potential is appropriate.

7. Intentional Overdose

Patients with depression are at high risk of suicide attempts. The older antidepressant drugs are among the most commonly used agents in suicide, in part because patients with depression have access to these prescription drugs. One of the major advantages of SSRIs is their safety in overdose, in contrast with TCAs, HCAs and MAOIs.[53] Overall, TCAs cause more deaths from overdose than any other prescription drug. Our own extensive experience with suicidal patients corresponds with that of Tollefson's[17] recommendation that SSRIs are first-line therapy for patients at risk of drug overdose.

In a review of the number of deaths per million prescriptions, Leonard reported,[53] consistent with the findings of others in the United States and Europe,[35,79] that the number of suicides per million prescriptions of SSRIs is orders of magnitude lower than that reported for TCAs and MAOIs (table I). The few deaths observed in clinical trials with many thousands of depressed patients were usually limited to situations in which patients overdosed with a combination of SSRIs and other drugs.[96,115-118] Worldwide post-marketing experience with these compounds confirms the finding that there is little documentation of deaths in suicide attempts using SSRIs alone,[119] although there have been several case reports of suicide with citalopram alone.[120]

Symptoms of SSRI overdose include tachycardia, sedation, tremor, nausea and emesis. Aggressive supportive measures are recommended as sufficient therapy. There is little risk of serious cardiovascular or neurological complications, and patients have recovered without lasting harm from overdoses of up to 3000mg of fluoxetine, over 37 times the usual recommended daily dose.[115]

Experience with sertraline up to January 1997 (over 10 million patients have been exposed to the drug) revealed 16 accidental overdoses and 190 intentional overdoses (personal communication, Pfizer Inc.); few of these were fatal when sertraline alone was ingested.

During worldwide clinical trials with paroxetine in more than 4000 patients, 28 cases of overdose were reported, of which 9 were overdoses with paroxetine alone; there were no deaths (per-

sonal communication, SmithKline Beecham). Postmarketing experience with paroxetine up to December 1995, with over 7.5 million patients treated, revealed 135 validated overdoses and 19 fatalities. However, all but 2 fatalities involved other drugs and/or alcohol (ethanol), or external factors (e.g. hypothermia secondary to exposure). Over a 2-year period, overdoses with paroxetine in 28 children were reported to the Pittsburgh Poison Control Center, Pittburgh, USA (dose 10 to 800mg); no case had a fatal outcome (personal communication, SmithKline Beecham).

We have been unsuccessful in obtaining similar data on citalopram and fluvoxamine. However, of the 354 cases of deliberate or accidental overdose of fluvoxamine reported up to 1992,[85] there were 19 fatalities, only 2 of which were associated with the ingestion of fluvoxamine alone; an estimated 4.5 million patients had been exposed by that time.

It must be borne in mind that 20 to 40% of patients with affective disorders show suicidal behaviour.[115] Some studies have found decreased tritiated imipramine binding sites (serotonin uptake pump) in the frontal cortex of individuals who have committed suicide,[121] compared with the frontal cortex of individuals killed suddenly in accidents. Findings of low CSF 5-hydroxyindole acetic acid (5-HIAA) levels,[122] a serotonin metabolite, also contribute to the current concepts of psychobiology of suicide impulsivity and aggression.[123]

Although suicidal ideation and behaviour can emerge at any point during the course of antidepressant treatment of depressive illness, untreated patients are at a greater risk of attempting suicide. Episodes of anger attacks and aggressive behaviour may occur in patients with untreated depression, and contribute to impulsive suicidal acts.[124] Since SSRIs are safer in overdose than older antidepressants, SSRIs can be recommended as first-line agents for patients at risk of overdose or those manifesting suicidal thinking or with a history of suicidal behaviour. Obviously, non-responsive patients (for any reason) remain at risk, similar to their pre-treatment state, and a re-evaluation of their diagnosis and therapy is indicated.

Although questions have been raised about the association between SSRIs and the emergence of suicidal ideation, several studies have concluded from all the data available that suicidal ideation may emerge during treatment with all types of antidepressants, but that a causal relationship to antidepressants has not been established.[24,116] Retrospective postmarketing studies[117] and evaluation of premarketing clinical study data in thousands of fluoxetine-treated patients[96] have revealed no evidence of a relationship between fluoxetine therapy and suicide. On the contrary, there is evidence for an apparent decrease in suicidal ideation as measured by the HDRS.[24,96,117,125] The same conclusion has been drawn in relation to paroxetine,[118,125] and extensive clinical experience to date supports this with all SSRIs and TCAs,[96] and implies the same for all antidepressants.

A review of 8 recently completed drug comparator and/or placebo-controlled, double-blind trials of depressed outpatients receiving 1 of 6 drugs (etoperidone, fluparoxan, nefazodone, adinazolam, dothiepin, fluoxetine) confirm the decrease in suicidal ideation observed in responders during treatment, and this correlated with overall treatment response.[119]

8. Uses in Medical Illnesses

There are a variety of medical conditions that can cause or worsen depression or make the management of this disorder a further challenge to the clinician. SSRIs play an important role in the treatment of depression in these settings.

8.1 Cardiovascular Disease

Depression is commonly seen (20 to 25%) in patients following an acute myocardial infarction, in cardiac patients with poor prognosis and hospitalised patients with coronary artery disease (CAD).[54] It is notable that depression is the strongest independent predictor (apart from the CAD itself) of negative outcome in patients with CAD.[126,127] Because of the absence of significant

effects on heart rate and rhythm or on blood pressure, SSRIs are the drugs of choice to treat depression in patients with heart conduction disease, orthostatic hypotension, ventricular arrhythmias, ischaemic heart disease or past acute myocardial infarction.[40]

TCAs have quinidine-like effects and slow intraventricular conduction and should be avoided in patients with heart block and those maintained on other drugs (e.g. procainamide, flecainide and other group Ia antiarrhythmics) that slow intraventricular impulse conduction. TCAs also produce orthostatic hypotension and rebound tachycardia, posing a risk to patients with coronary artery disease or with congestive heart failure, especially those with left ventricular impairment, and patients taking drugs such as diuretics or vasodilators which may exacerbate TCA-induced hypotension.[128] Therefore, although TCAs have been used safely in patients with cardiac conditions, it is appropriate that these drugs should be used with caution in such patients, if at all. In our own clinical experience, we have used SSRIs almost exclusively as first-line drugs in patients with the above cardiovascular problems over the past 10 years, without significant drug-induced untoward effects.

MAOIs share some of the same adverse effects as TCAs, in particular, induction of hypotension and enhancement of sympathomimetic agents.[3] For these reasons, and considering that a 'safer' option is available, all of the older agents should be reserved as second-line alternatives in patients with cardiac disease, and prescribed only for those whose symptoms of depression fail to respond to SSRIs.

8.2 Neurological Disease

SSRIs are among the drugs preferred for patients at higher risk of seizures, since they reduce the seizure threshold much less than older antidepressants.[40] The combination of older antidepressants and antipsychotics can further reduce the seizure threshold. Therefore, SSRIs are useful in patients with depression and epilepsy as well as in patients with factors predisposing to seizure activity such as head trauma, medications that reduce the seizure threshold, and substance abuse.[40]

Depressed patients with organic brain syndrome benefit from SSRIs and experience essentially no cholinergic effects.[129] The same can be said for the elderly or patients with stroke up to 30% of whom are reported to have depressive symptomatology.[130] The anticholinergic effects of the TCAs and HCAs can increase the chance of confusional states developing in these populations. Stroke patients also benefit from the lower incidence of cardiovascular adverse effects of SSRIs compared to older drugs that might precipitate hypotension or cardiac arrhythmias, and all the SSRIs have been used successfully and with better tolerability in such patients.[8,40]

Various reports reveal that up to 50% of patients with Parkinson's disease have depression.[131] The anticholinergic effects of some older antidepressants may, in some cases, contribute to improved motor performance in these patients. Long term administration of SSRIs can, secondary to enhanced serotonergic transmission, inhibit dopamine neuron activity and, theoretically, could worsen Parkinson's disease. However, a single prospective study of the use of fluoxetine in Parkinson's disease did not find clinical worsening of extrapyramidal symptoms.[131] Evidence that a deficient serotonin system might play a role in Parkinson's disease[132] and could be helped by SSRIs awaits further study and clarification.

8.3 Cancer

Up to 25% of patients with cancer report clinically significant depressive symptoms, and this is especially true in those with an uncertain or poor prognosis, chronic pain or physical impairment. In patients for whom the anticholinergic activity of TCAs can be detrimental (e.g. post abdominal surgery, patients with stomatitis), SSRIs are particularly preferred.[40] TCAs, when tolerated in fully effective antidepressant dosages, may be useful in patients with severe bodyweight loss because of the tendency of these drugs to increase appetite and induce bodyweight gain when taken long term.

However, the anticholinergic effects of these drugs could produce significant constipation and gastrointestinal problems as well as other adverse effects (hypotension, falls and fractures), particularly in patients who are partially bedridden or inactive.

It is possible to hypothesise, based on the known adverse effects of SSRIs, that these drugs might decrease appetite and exacerbate bodyweight loss in patients with cancer, depressed anorectic medically ill patients or patients with anorexia nervosa. However, we have been unable to find reports in the literature supporting this, and we are unaware of any prospective controlled studies in this regard. The tendency of SSRIs to produce mild to moderate bodyweight loss appears to be restricted to patients who are overweight at the beginning of treatment. Progressive continued bodyweight loss does not persist, even in these patients, unless other measures to reduce caloric intake below expenditure are involved.[133]

8.4 Gastrointestinal Disease

SSRIs can be useful in depressed patients with chronic constipation, a condition that could be worsened by TCAs because of their anticholinergic effects, especially in the elderly and postoperative or chronically ill patients. By the same token, we have seen patients with diarrhoea and irritable bowel syndrome benefit from this effect of TCAs.

9. Use in the Elderly

Depression in the elderly is frequently underdiagnosed and undertreated.[6,134] An analysis of symptoms of depression in hospitalised older persons identified a vulnerable group more likely to have a subsequent negative health outcome.[135] This is in part caused by the fact that symptoms of depression such as changes in appetite and sleep, complaints of anergia, and evidence of social withdrawal may erroneously be regarded as related to the aging process. Managing depression in the elderly is further complicated by the fact that this population is more likely to have concomitant medical disorders, to be taking other medications that may interact with antidepressants, and to excrete and metabolise drugs less efficiently than the younger population. The elderly are particularly vulnerable to the orthostatic hypotensive effect of older antidepressants which may cause postural hypotension, dizziness and fainting.[3] These factors, and also the blurred vision associated with anticholinergic blockade, may cause elderly patients to be more susceptible to falls.[76]

The ideal antidepressant for use in the elderly population should have no cardiotoxic or orthostatic effects, little sedative potential, and should not impair memory or produce physical disability.[14] Therefore, the SSRIs may be particularly effective for elderly patients because of the virtual absence of cardiovascular and anticholinergic adverse effects.

Doxepin, one of the most frequently prescribed older antidepressants in geriatric patients, has been compared with fluoxetine[136] and paroxetine.[137] After 6 weeks, the SSRIs were shown to be as efficacious as doxepin. The lower incidence of serious adverse events (dizziness, drowsiness, confusion) and anticholinergic-related adverse effects led to a lower discontinuation rate among the SSRI-treated groups. Sertraline has been compared with amitriptyline in elderly patients with depression and was found to be as effective as, and to have a more acceptable tolerability profile than, the TCA.[138]

A recent publication[139] underscored the need for frequent long term full-dosage maintenance antidepressant therapy in the elderly population. This is especially true in those whose first episode occurs over the age of 50 years and in those with delayed treatment or slow response to treatment in the index episode. SSRIs lend themselves to successful long term maintenance therapy because of their benign, generally transient adverse-effect profile, safety in overdose and ease of administration.

Individual pharmacokinetic characteristics of the SSRIs must be taken into account when they are used in the treatment of older patients. Fluoxetine pharmacokinetics are reported to be basically unchanged in this population,[129,140] but changes

have been noted in studies of sertraline and paroxetine.[73] These changes are significant enough with paroxetine to recommend lower starting dosages (10 mg/day instead of the usual 20 mg/day), with a gradual upward titration to a maximum of 40 mg/day (instead of the usual 50 mg/day).

Besides being effective antidepressants, the virtual absence of cardiovascular and anticholinergic effects with SSRIs is especially useful in the elderly population in which events such as orthostatic hypotension or confusion can be more common and conditions such as glaucoma and prostate disease more prevalent than in the younger population. All these events and conditions may be worsened by the older antidepressant drugs because of their known pharmacological actions.[8-10,18,41]

10. Depression and Childbearing

One problem faced by physicians is counselling a patient with a history of depression who wants to become pregnant. The general guideline that applies to these patients and those who become depressed during pregnancy is to try to avoid any agents that have not been widely proven to be harmless to the fetus. In the case of mild depression, alternative approaches to medication, e.g. interpersonal or cognitive behavioural therapy, may be helpful until pregnancy is over or at least until past the first trimester when organogenesis has progressed and medications can be used with less concern regarding adverse events if they are still necessary. If nonpharmacological approaches are used, close clinical monitoring is essential and consideration should be given to promptly adding pharmacotherapy or electroconvulsive therapy (ECT) if clinical deterioration occurs or the patient fails to respond.

In patients with more severe depression, the risk to the fetus must be weighed against symptoms of depression that could potentially jeopardise both the mother and the fetus. Some factors to be considered include severity of depression, risk of potentially harmful behaviour such as suicidality and other forms of impulsiveness and aggressive behaviour, and inability to maintain reasonable bodyweight gain during pregnancy. In these situations, the possibility of fetal harm secondary to antidepressants, now recognised as very unlikely, support the priority of the pregnant woman's need for treatment.[141-143] There is no evidence to suggest that any antidepressant (with the probable exception of lithium) is teratogenic. The long clinical experience with TCAs largely substantiates their safety, and recent studies with fluoxetine and the extensive post-marketing experience with this drug support its safety.[142]

Based on preclinical studies,[40] extensive personal experience, review of case reports to date and (most importantly) recent prospective studies in pregnancy,[141,142,144,145] it appears that fluoxetine is as 'safe' as the TCAs when used during pregnancy. One study[144] reported an increased risk of perinatal complications in mothers taking fluoxetine, although another[145] found no such relationship. Overall, these controlled data strongly suggest that fluoxetine is probably the antidepressant of choice when pharmacotherapy is indicated for the treatment of depression in pregnancy or in patients with a high likelihood of becoming pregnant during antidepressant treatment. A recent study involving about 750 women exposed to fluoxetine in the first trimester of pregnancy, and followed prospectively, found no increase in congenital malformations above that seen in the general (unmedicated) population (i.e. 3 to 4%).[146] One prospective study[142] found no abnormalities in developmental milestones up to age 7 years in children whose mothers received fluoxetine during pregnancy. Since the incidence of depression is high among young women of childbearing age and many pregnancies are unplanned, the data on fluoxetine are very reassuring for individuals who are already receiving this antidepressant drug when they conceive.

Although fewer data are available regarding the use of other SSRIs during pregnancy, their lack of teratogenicity in animal studies is supported by the absence of post-marketing data suggesting teratogenicity.

All SSRIs can be excreted in breast milk; however, the limited data available to date have not included reports of adverse events in breastfeeding infants of mothers receiving treatment with SSRIs.[147] The American Academy of Paediatrics does not advise against breastfeeding during SSRI therapy.[148]

11. Use in Depressive Subtypes and Comorbid Psychiatric Conditions

To date, no single antidepressant stands out as having superior efficacy (i.e. greater frequency of acute remission) for all kinds or any one subtype of major depression. The choice of a specific agent must be based on tolerability and specific patient-related characteristics, especially medication acceptance and compliance, consideration of comorbid medical and psychiatric conditions and, since the advent of the SSRIs, safety in overdose.

A particularly important consideration in choosing a specific antidepressant is the need for relatively long term treatment; a minimum of 4 to 6 months continuation therapy after full remission is required, with subsequent gradual antidepressant discontinuation.[149] It may be appropriate to continue antidepressant treatment for many years or even permanently as prophylaxis, since depression is a chronic relapsing illness.[150] Patients with early onset of depression (before age 20 years), with their first episode occurring after age 50 years, or those with multiple episodes (especially 2 or more episodes in the previous 5 years) are candidates for full-dosage prophylactic therapy.[150] When this is the case, SSRIs are the antidepressant of choice, particularly fluoxetine, as its long half-life assists in preventing withdrawal symptoms, relapse or recurrence (this can occur with short half-life antidepressants when a few doses or several days of missed medication occurs) [see section 5.2].

The Danish University Antidepressant Group has raised the question of whether citalopram or paroxetine are as effective as older antidepressants in the treatment of severe depression.[151,152] However, we have found fluoxetine to be as effective as full-dose imipramine in hospitalised severely depressed patients.[153]

11.1 Anxious Agitated Depression

One of the early observations regarding the use of SSRIs was the lack of sedating properties compared with older TCAs.[40] Some clinicians have postulated that this might be disadvantageous for patients with features such as anxiety or agitation, which are common in depression. Several retrospective analyses of therapeutic trials and new prospective studies have shown that fluoxetine is indeed efficacious in depression, regardless of baseline psychomotor activity or features such as anxiety or insomnia.[154-156]

In fact, it appears that SSRIs may be particularly effective in treating depression presenting with anxiety.[95] This fact is noteworthy and consistent with many studies of SSRIs that have used the HDRS, which incorporates a significant emphasis on estimating anxiety, somatic symptoms and sleep disturbances.[157] Consequently, the favourable therapeutic comparison of SSRIs with sedating TCAs or other antidepressants in treating anxious depression as measured using the HDRS is even more significant.

Similar findings to those reported after fluoxetine treatment have been reported with paroxetine.[158] Trials with fluvoxamine have shown this agent to be as effective as benzodiazepines in treating anxiety in a general practice study of patients with mixed anxiety and depression,[159] but superior in the treatment of depression in these patients.[160]

As a comorbid feature of depression, anxiety tends to subside as the entire syndrome improves and has been shown to be one of the earliest symptoms to begin to improve during antidepressant therapy.[161] In choosing an antidepressant agent, the clinician must weigh the benefits of a rapid reduction in anxiety levels, which could be beneficial in some patients (e.g. when acute compliance is a management problem because of anxiety), against the detrimental factor of having to deal with sedation and impairment of psychomotor performance,

which can lead to premature drug discontinuation – a particular problem in patients who need to continue to work during treatment and in the high percentage of patients who need long term prophylactic therapy. We believe that SSRIs are the best drugs available for long term maintenance prophylactic therapy because of their good tolerability, which contributes to long term compliance. The long half-life of fluoxetine is a further argument for the selection of this drug (see section 5.2).

The efficacy and tolerability of citalopram is similar to that of other SSRIs and the TCAs. More than a dozen controlled studies involving over 2500 depressed patients receiving citalopram, many with comorbid anxiety, have supported the clinical efficacy of the drug.[162] However, one report found clomipramine was perhaps more effective than imipramine or citalopram.[163] A controlled study of 217 depressed outpatients found citalopram to be better tolerated than fluvoxamine.[164] The SSRIs are also very useful in the treatment of patients with panic disorder,[165] as well as depressed patients with anxiety or panic attacks;[166] however, low dosages or increased dosage intervals are generally essential, at least initially to reduce the risk of precipitating panic attacks and/or increasing anxiety.[167]

In summary, it has been found that fluoxetine, paroxetine and sertraline decrease measured anxiety as promptly as the older sedating agents. Furthermore, data from the National Institute of Mental Health (NIMH) Collaborative Depression Study have clearly shown that improvement in sleep is *not* predictive of, or correlated with, global clinical improvement.[161] SSRIs are not only efficacious in reducing the anxiety, agitation and insomnia associated with depression, they generally have a more benign tolerability profile, and are associated with better acceptance resulting in higher compliance rates during maintenance therapy and long term prophylaxis. The SSRIs have proven to be first-line agents in patients with depression associated with anxiety features and in patients needing long term psychiatric pharmacological therapy.[149]

11.2 Delusional or Psychotic Major Depression

Some data[168] point to the possibility that delusional-psychotic depression is a separate entity, although this remains controversial. Response rates to antidepressants or antipsychotics alone are lower (perhaps by 30%) for delusional depression than for nonpsychotic depression,[151] and some delusional patients will eventually require ECT. About two-thirds of delusionally depressed patients achieve remission when antidepressant therapy is combined with antipsychotic agents,[168] but there is no evidence that one antidepressant works better than another.

A recent study of 30 patients with psychotic depression treated with combined therapy of fluoxetine and perphenazine showed a response rate of 73%, equivalent to the best response rates of patients with psychotic depression treated with older antidepressants plus an antipsychotic.[151]

11.3 Dysthymic Depression

Dysthymia tends to occur at an early age, and has an insidious onset and a chronic course. The biology of dysthymia is not well understood, and further research is needed on the aetiology and treatment of this illness.

The relevance of identifying and treating dysthymic patients cannot be overemphasised, since the condition is prevalent, disrupts quality of life, and is responsive to therapy with SSRIs as well as older antidepressants.[7] Dysthymia is underdiagnosed and undertreated.[7] Studies show that most of these patients go on to develop major depressive episodes superimposed on the dysthymia (so-called double depression).[169] These patients, even after recovering from the major depressive episode, are at a greater risk of relapse into major depression if they continue to experience dysthymic symptoms. This risk increases with the duration of the dysthymic episode.[170] Dysthymic patients are also at risk of suicide.[7]

The better tolerability profile of the SSRIs is especially helpful in increasing compliance among

those patients who consider the less favourable tolerability profiles or dietary restrictions associated with older antidepressants unacceptable when weighed against the potential benefits of drug therapy. This is especially true with regard to long term 'continuation' treatment after recovery from acute depression, and even more so with those patients in need of longer term prophylactic therapy. The chronicity of dysthymia argues strongly for the use of SSRIs as first-line acute and prophylactic therapy, because of the safety of these drugs in overdose and generally better patient acceptance, reflected in increased long term compliance.[169]

11.4 Atypical Depression

Patients with atypical depression meet criteria for major depressive disorder, but are further characterised by having excessive mood reactivity (complete but transient remission from depressed mood in response to positive environmental factors) and one or more associated features of overeating, oversleeping (or extreme fatigue) or chronic hypersensitivity to rejection; some authors add complaints of 'leaden heaviness' of extremities.[171]

There is a considerable amount of data indicating that these patients respond better to MAOIs than to TCAs.[171-173] However, considering that many patients with atypical depression respond to SSRIs, some investigators have recommended that SSRIs be tried first because of their favourable tolerability profile.[174] There is some evidence to suggest that SSRIs are as effective as MAOIs in the treatment of patients with atypical depression, although the number of patients studied was relatively small.[7,175]

Therefore, it is reasonable to use SSRIs as first-line drugs in the treatment of patients with atypical depression.

12. Maintenance Therapy

Long term, double-blind, placebo-controlled studies of maintenance or 'prophylactic' treatment have demonstrated the ability of TCAs to maintain euthymia in most patients (>80%) with major depressive disorder for periods of up to 3 years;[149,176,177] in a small extension study, euthymia was maintained for up to 5 years[178] if full-dosage TCA therapy (e.g. imipramine 200 mg/day) could be tolerated and maintained.

More recently, fluoxetine,[52,169,179,180] sertraline[177] and paroxetine[181] (*vs* placebo) have been shown to be as effective as imipramine[176] (also *vs* placebo) in 1-year maintenance studies after recovery and completion of a 3- or 4-month euthymic continuation phase. Long term efficacy studies have shown the superiority of citalopram over placebo in preventing relapse when full therapeutic doses are continued, usually 20 to 40 mg/day.[162] The extended half-life of fluoxetine may provide increased protection against relapse as well as the already documented reduced likelihood of withdrawal symptoms, compared with shorter half-life SSRIs, when a few days of medication are missed.[182]

13. Conclusion

We have reviewed data comparing the individual SSRIs in the treatment of depression and we believe that, as a class, they are superior to TCAs and MAOIs. The SSRIs have numerous advantages over these older agents, such as comparable efficacy, a more benign adverse-effect profile that enhances patient compliance, a broader spectrum of activity – they are effective in various clinical subtypes of depression – markedly improved safety in overdose and an easier dosage schedule.

Treatment with the older antidepressants is often associated with adverse events such as sedation, bodyweight gain, dry mouth, constipation, urinary retention, cardiac effects (tachycardia, orthostatic hypotension, depression of cardiac conduction) and vision disturbances (blurred vision). These effects are particularly problematic in the elderly, those with comorbid medical illness and in the significant percentage of patients with depression who need long term prophylactic therapy. It is estimated that only 20 to 25% of patients taking TCAs receive adequate therapeutic dosages,[36-38] in an attempt to avoid the adverse effects of these

drugs. Noncompliance and premature discontinuation of treatment result from these adverse effects and leave patients subject to the mortality, morbidity and economic burden that is associated with depression.

Although SSRIs present with their own unique spectrum of adverse effects, such as sexual dysfunction, dyspepsia, nausea, diarrhoea, insomnia, headaches, and mild nervousness or agitation, studies have shown TCAs to have the highest discontinuation rates resulting from adverse events; discontinuation because of adverse events with SSRIs was, in many instances, not significantly different from the rate with placebo.[10]

Clinicians may be wary of prescribing full dosages of TCAs because of their potential lethality in overdose and thus may see patients who do not respond, simply because they are taking subtherapeutic doses. SSRIs are more likely to be prescribed at full therapeutic dosages, thus providing an optimal chance of remission and minimising the risk of inadequate treatment, with a resultant effectively untreated depressive state with its continued morbidity and potential for suicide.

The easier dosage schedule of SSRIs allows for full therapeutic dosages from the beginning of treatment in almost all instances, with little requirement for titration compared with older antidepressants. These factors further increase acceptance and compliance, increasing the chance of successful treatment.

The costs of depression (e.g. hospitalisation, disruption of work and family) both for the individual and for society are high. The risk of not treating depression clearly outweighs the minimal risks of treating the disease. Pharmacotherapy is the primary treatment of this disorder, and this can shorten the duration of episodes. SSRIs have contributed remarkably to improving the risk-benefit ratio of the treatment of depression; improved compliance and easier management play a big role in this. Although TCAs are less expensive per tablet than other antidepressants, the need to closely and more extensively monitor patients during treatment significantly increases the cost of overall treatment.[13]

Withdrawal symptoms and possible relapse of depression can occur on cessation of therapy with SSRIs that have shorter half-lives. This does not occur with fluoxetine, probably because of its slow elimination secondary to its long half-life.

Effectively treating depression with a well-tolerated drug can not only alleviate the suffering of millions of patients, but decrease the cost of healthcare and the risk of disability for individuals who have affective disorders, a significant proportion of the work force in our society. Easier management, higher acceptance and effectiveness of SSRIs have turned these drugs into the most widely prescribed first-line agents for treatment of depression in the US, and their continued increase in use suggests that they will generally supplant other drug classes worldwide.

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