Fluoxetine: A Suitable Long-Term Treatment

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A review of fluoxetine's safety profile, especially during long-term treatment, is presented. Key safety advantages for fluoxetine include lower adverse events and dropout rates compared with tricyclic antidepressants and other selective serotonin reuptake inhibitors (SSRIs), safety in overdose, and safe use in special population groups such as women in pregnancy. Prospectively ascertained pregnancy outcomes following exposure to SSRIs, mainly fluoxetine, consistently show no teratogenic effects as assessed in the postnatal period and in comparison with controls. An additional advantage of fluoxetine is the absence or mildness of discontinuation symptoms following treatment interruption, probably a consequence of fluoxetine's long half-life in comparison with other SSRIs. The available data on these topics confirm the suitability of long-term fluoxetine treatment.

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Fluoxetine, the first selective serotonin reuptake inhibitor (SSRI), has been in clinical use for over a decade.[1] First developed as an antidepressant, it has also been shown effective in the treatment of patients with anxiety disorders (obsessive-compulsive disorder, panic), premenstrual dysphoric disorder, and bulimia. However, its main clinical use remains the treatment of depressive disorders.

Depression, in spite of its wide clinical heterogeneity, is often a chronic and recurrent disorder. Extended antidepressant maintenance treatment has reduced the risk of relapse or illness recurrence.[2] In fact, maintenance treatment should be one of the therapeutic goals in the adequate management of depression.[3–5] Consequently, fluoxetine's safety profile during long-term treatment becomes an extremely important issue. Therefore, recent clinical data on adverse events, events following overdose, discontinuation symptoms, and use during pregnancy will be summarized.

ADVERSE EVENTS

The side effect profile of fluoxetine is mild—especially when compared with the older antidepressants such as monoaminoxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs)—since it does not interact with tyramine-containing foods and sympathomimetic agents or induce anticholinergic effects.

The most common adverse events caused by SSRIs include nausea, nervousness, sleep disturbances (insomnia), headache, and sexual dysfunction. These side effects are quite similar among SSRIs, varying only in their frequencies,[1] but they are qualitatively different from those often observed with TCAs: dry mouth, blurred vision, constipation, sedation, postural hypotension, cardiac effects, and dizziness.[6] Certainly, such different side effect profiles reflect their mechanisms of action, which imply not only more selectivity for the serotonergic system, but also a lack of or very mild direct action of the SSRIs on receptors to other neurotransmitters (e.g., acetylcholine, norepinephrine, histamine).

A meta-analysis of 42 randomized controlled studies compared treatment discontinuation rates due to side effects and lack of efficacy among SSRIs and TCAs.[7] The pooled results showed that significantly fewer patients receiving SSRIs discontinued treatment because of side effects (14.9%) compared with those on treatment with TCAs (19%) ($p < .01$). The placebo- ($N = 7$) and TCA-controlled studies, analyzed separately, also showed a significant difference in discontinuation rates caused by side effects: SSRIs (19%) versus TCAs (27% [$p < .01$]). There was a clinically significant advantage for the SSRIs compared with TCAs in terms of the treatment's acceptability. Moreover, data from 3 placebo-controlled studies[8–10] included in this meta-analysis allowed comparison of dropouts due to adverse events for different doses of fluoxetine, paroxetine, and sertraline. Interestingly, the 20-mg fluoxetine dose, considered therapeutic to the majority of patients, did not differ from placebo in the percentage

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of patients (8%) dropping out of treatment for adverse events. In addition, fluoxetine's dropout rates were consistently smaller than those observed with paroxetine and sertraline, except at the 60-mg dose, the highest dose utilized.

A large, parallel clinical study conducted at the Center for Medication Monitoring at the University of Texas at Galveston reported a postmarketing surveillance of adverse events by outpatients self-monitoring their treatment with fluoxetine (N = 1577) or sertraline (N = 1209).[11] The results showed that almost 1 (31.4%) of every 3 patients taking sertraline called at least once to report 1 or more adverse events compared with only about 1 (19.7%) of every 5 patients taking fluoxetine, and this difference was significant ($p < .001$). Also, the number of patients discontinuing treatment because of perceived side effects was different: sertraline (5.1%) versus fluoxetine (2.1% [$p < .01$]). These data suggest that some of the adverse events associated with fluoxetine were even more common in sertraline-treated patients.

Another large study, conducted by Prescription-Event Monitoring (PEM) with data derived from general practitioner prescriptions and supplied by the Prescription Pricing Authority in England, compared the safety and side effect profile of 4 SSRIs: fluoxetine, sertraline, paroxetine, and fluvoxamine.[12] The results, comprising a final cohort for each of the 4 SSRIs exceeding 10,000 patients, showed that fluvoxamine was associated with a higher incidence of adverse events than the other 3 SSRIs. The overall frequency of adverse events reported (across all side effects), expressed as incidence densities per 1000 patient-months during the first month of treatment, was 45.9% for fluvoxamine, 21.4% for paroxetine, 15.7% for sertraline, and 14.9% for fluoxetine. Nausea and/or vomiting was the most frequently reported event and clinical reason for stopping therapy. The adverse event incidences were not different in the older patient (≥ 70 years) subgroup. It is noteworthy that the overall incidence densities of adverse events with SSRIs per 1000 patient-months dropped significantly during the entire treatment period. For the maximum period analyzed (6 months), the incidence densities were 17.6% for fluvoxamine, 7.6% for paroxetine, 7.0% for fluoxetine, and 6.2% for sertraline.

Arias et al.[13] compared, in a naturalistic setting, the efficacy and tolerability of SSRIs and venlafaxine during a 6-month period in 194 outpatients with mood disorders who were attending a primary psychiatric care center in Spain. The tolerability, assessed by recording spontaneously reported adverse effects, indicated that 45.4% of patients experienced 1 or more adverse effects. However, reporting rates for each treatment differed significantly, with fluoxetine having the lowest (26%) and fluvoxamine the highest (68.8%) incidences.

Considering that weight gain is an adverse event frequently observed during long-term treatment with TCAs, a recent prospective study assessed the effects of extended SSRI-treatment on weight.[14] Patients with depression (N = 284) were randomly assigned to double-blind treatment with fluoxetine, sertraline, or paroxetine. The responders to the acute phase of treatment continued on medication for a total of 26 to 32 weeks. Patients who completed the trial (N = 139) were included in the analysis, comparing their mean percent change in weight to baseline values and comparing the number of patients in each group who gained ≥ 7% in weight. The results showed that patients treated with paroxetine had a significant weight gain from baseline to endpoint; those receiving fluoxetine had a small decrease in weight; and the group on sertraline treatment had a modest, nonsignificant weight decrease. Among the 3 treatments, the number of patients with weight gain (≥ 7%) was significantly greater for those receiving paroxetine (25.5%), compared with those receiving fluoxetine (6.8%) and sertraline (4.2%).

It is important to emphasize that the most common adverse events with fluoxetine are transient and resolve spontaneously over time.[15] This prospective study[15] examined the safety of fluoxetine, 20 mg/day, in a large sample of patients undergoing treatment for depression during 6 months (N = 299 [at entry of the continuation treatment phase] and N = 174 [completers]). The proportion of patients reporting insomnia, somnolence, diarrhea, and nausea was recorded every 2 weeks, and consistently decreased over time, by either resolving in the majority of patients or becoming significantly less frequent with continued treatment.

SAFETY IN OVERDOSE

While there have been debates on whether antidepressants increase aggression and suicidal behavior in patients, it has been shown that suicide is a risk factor in depressed patients and such risk continues during the initial phase of antidepressant therapy.[1] A prospective study from clinical practice, reflective of the real world, examined events following overdose.[16] The data were obtained from a series of 622 patients consecutively admitted for overdose to an emergency room of 9 hospitals. Of the total number of patients, 124 had overdosed on TCAs, and only 16 had overdosed on fluoxetine. First, it is important to consider fluoxetine's safety profile in possibly preventing the need for patients who overdose to go to an emergency room. None of the patients who had taken large amounts of fluoxetine were agitated, had QRS alteration or terminal R wave, or needed intubation for coma. However, all of these events were observed in patients who had overdosed on TCAs.[16] Additionally, of those overdosing on fluoxetine, only 13% (vs. 49% on TCAs) had tachycardia and 19% (vs. 74% on TCAs) were admitted to an intensive care unit.

DISCONTINUATION SYMPTOMS

An overview of discontinuation symptoms after interruption of treatment with antidepressants, which emphasizes the data on SSRIs, has been published.[17] SSRI discontinuation symptoms acquire a special importance during long-term treatment with these agents because the premarketing clinical studies of a new compound usually do not identify discontinuation symptoms upon treatment withdrawal. This is due to the following reasons: (1) short duration of clinical trials; (2) lack of a follow-up of patients after medication withdrawal; and (3) absence of a standardized search of discontinuation signs and symptoms. The recognition of discontinuation symptoms usually happens later during the widespread clinical use of a new medication. In general, the initial descriptions, which come from case reports, are followed by pharmacovigilance databases, and ultimately by studies specifically designed to explore the issue of discontinuation symptoms. Then it becomes possible to properly identify the symptom profile, as well as symptom prevalence and risk factors. This long process is presently taking place with the SSRIs.

Briefly, the first reports on SSRI discontinuation symptoms were made following withdrawal of fluoxetine and fluvoxamine.[18–20] Approximately at this same time (1992–1993) in the United Kingdom, the Committee on Safety of Medicines and Medicines Control Agency noted that they were receiving a large number of reports on suspected withdrawal reactions with paroxetine, but not with other SSRIs.[21] The physicians' spontaneous reporting of symptoms occurring after withdrawal of 4 SSRIs (fluoxetine, fluvoxamine, paroxetine, and sertraline) was therefore compared.[22] The data from 430 reports showed that the most frequently occurring discontinuation symptoms were clustered into the following 6 main categories: (1) general: dizziness, light-headedness, sweating, headache, and insomnia; (2) sensory changes: paresthesia, numbness, and visual disturbances; (3) motor effects: imbalance and tremor; (4) neuropsychiatric/psychological: anxiety, agitation, hallucinations, confusion, and mood changes; (5) gastrointestinal: mainly nausea; and (6) other: palpitation. In spite of such diversity of reported symptoms, dizziness, paresthesia, tremor, anxiety, nausea, and palpitation occurred more often than any other symptoms. Furthermore, it was estimated that paroxetine had 10 times more reports than fluvoxamine and sertraline, and approximately 100 more than fluoxetine. These comparative reporting rates represented an estimate of the number of reports per 1000 prescriptions. Therefore, the estimated total prevalence of discontinuation symptoms per 1000 prescriptions was very low: 0.3 reports for paroxetine, 0.03 reports for fluvoxamine and sertraline, and 0.002 reports for fluoxetine.

Coupland et al.[23] undertook a retrospective chart review of 171 outpatients who had been supervised during tapering and discontinuation of clomipramine (the most "serotonergic" tricyclic), fluoxetine, fluvoxamine, paroxetine, and sertraline. The most common symptoms were dizziness, lethargy, paresthesia, nausea, vivid dreams, irritability, and lowered mood. In addition, anxiety, insomnia, and headache were also recorded. The frequency of patients with discontinuation symptoms was significantly higher for clomipramine (30.8%), paroxetine (20%), or fluvoxamine (14%) than for sertraline (2.2%) or fluoxetine (0%). The onset of symptoms occurred usually within 2 to 3 days after the last dose of medication, but sometimes also during tapering from paroxetine or sertraline. Patients who restarted paroxetine had disappearance of the symptoms within 24 hours. In patients who remained unmedicated because of mild symptoms, symptoms persisted for up to 21 days (mean = 11.8 days) after onset.

SSRI discontinuation symptoms seem to have mild-to-moderate intensity, and as mentioned, may occur even after tapering the medication or with missed doses in noncompliant patients.[24] Furthermore, their treatment is relatively simple. Those patients with mild symptoms benefit from the information that the symptoms are transitory, and that information usually suffices. In patients with moderate-to-severe symptoms, it is advisable to restart the medication and thereafter proceed with a very slow tapering, or to substitute the original medication for an SSRI with a long half-life.[25]

The hypothetical mechanisms of SSRI discontinuation symptoms include (1) decrease in serotonin available at the synapse as a consequence of down-regulated serotonin receptors (5-HT_2 and/or 5-HT_{1A}); (2) secondary effects dependent on other neurotransmitter systems such as noradrenergic, dopaminergic, cholinergic, and GABAergic (associated with a variety of clinical symptoms); (3) cholinergic rebound effect (mainly for clomipramine and paroxetine); and (4) biological or cognitive sensitivity differences in individual patients.

The "hyposerotonergic" hypothesis, relative to the other theories, is supported by a greater body of research evidence as reviewed by Schatzberg and colleagues.[26] In this context, it is interesting to emphasize that paroxetine, more often associated with discontinuation symptoms, is the most potent serotonin reuptake inhibitor. However, among the SSRIs, paroxetine has the highest affinity for the muscarinic receptor in the human brain. This high affinity is comparable to imipramine's affinity, and only approximately half of clomipramine's affinity.[27]

The differences among SSRIs in the onset, frequency, intensity, and duration of the discontinuation syndrome might be further explained by each compound's pharmacokinetic profile.[28] Some of the clinically relevant pharmacokinetic parameters are the half-lives and the presence or absence of an active metabolite as shown in Table 1. In fact, the largest databases[22,23] suggest that a compound with a short half-life and absence of an active metabolite is more often associated with discontinuation symptoms of

Table 1. Pharmacokinetic Parameters of Selective Serotonin Reuptake Inhibitors[a]

Compound	Half-Life (h)	Active Metabolite and Its Half-Life
Fluoxetine	144	Norfluoxetine (7–15 d)
Citalopram	33	None[b]
Sertraline	26	*N*-Desmethylsertraline (66 h)
Paroxetine	21	None[b]
Fluvoxamine	15	None[b]

[a]Reprinted, with permission, from Calil et al.[17]
[b]No clinically active metabolites in terms of serotonin-uptake inhibition.

SSRIs. However, these pharmacokinetic parameters in isolation do not completely explain the discontinuation symptom differences among the SSRIs. They mainly explain the symptoms in terms of their frequency.

More recently, prospectively controlled studies were conducted to examine the effects of abrupt and brief interruption of long-term treatment with SSRIs.[29,30] A double-blind placebo substitution for 5 to 8 days in 242 patients receiving maintenance therapy with fluoxetine, sertraline, or paroxetine for 4 to 24 months was associated with the emergence of new symptoms mainly in patients treated with paroxetine, less in those with sertraline, and very few in the fluoxetine group.[29] Michelson et al.[30] systematically assessed symptoms and their effects on daily functioning after a 5-day interruption of SSRI therapy and subsequent continuation of the active treatment under double-blind and order-randomized conditions. The daily progression of new signs/symptoms associated with placebo substitution again showed that patients on paroxetine treatment developed symptoms statistically significantly earlier (on the second day) and of more intensity than those receiving sertraline, whereas patients on fluoxetine had no change at any time point. Also, statistically significant increases in functional impairment at work, in relationships, in social activities, and overall were reported by patients treated with paroxetine, whereas those patients treated with sertraline reported only deterioration in overall functioning. Patients treated with fluoxetine, however, reported no change in any area of functioning following the placebo substitution. These data are relevant in cases of missed doses and/or poor compliance, especially during therapy with the short half-life SSRIs, not uncommon in clinical practice. However, these data favoring fluoxetine must be interpreted with caution because fluoxetine's long half-life might have delayed the appearance of discontinuation symptoms. Thus, to overcome such limitation, another study followed patients randomized to placebo (N = 96), or to continued treatment with fluoxetine (N = 299) for 6 weeks, after an initial 12 weeks of fluoxetine treatment. There were no differences in reports of new or worsened adverse events in both groups after randomization nor in patient discontinuation related to adverse events. The abrupt interruption of fluoxetine was well tolerated as only few patients reported mild, self-limited light-headedness or dizziness.[31]

The SSRI discontinuation symptoms have been referred to as "withdrawal symptoms" in many case reports, although the symptom complex differs from the classic withdrawal syndrome associated with psychoactive substances, whether they are used therapeutically (e.g., sedative, hypnotics-anxiolytics) or not (e.g., alcohol, amphetamines, cocaine). Antidepressants have not been associated with tolerance, dependence, or drug-seeking behaviors. Moreover, according to the present diagnostic criteria, a withdrawal syndrome is only 1 criterion, and thus insufficient for establishing antidepressant dependence.[32]

PREGNANCY EXPOSURE

Women have a higher lifetime prevalence (10% to 25%) of depression than men.[33] Consequently, their chance of receiving long-term antidepressant treatment is also high, even throughout their childbearing years. Thus, clinicians must often face the dilemma of counseling either women with unplanned pregnancy (approximately 50% of them[34]) about antidepressant treatment or women who are planning a pregnancy when maintenance antidepressant treatment is required. The assessment of risks/benefits should always consider both the woman's depression characteristics and the risks to the child. Briefly, the risks of prenatal exposure to psychotropic drugs include, among others, the potential of teratogenicity, neonatal toxicity, behavioral teratogenesis, and long-term behavioral consequences.

Preclinical studies showed that fluoxetine, like other antidepressants, lacks teratogenic effects.[1] Since randomized, placebo-controlled studies of pregnancy outcome following drug exposure are unethical, data are accumulated from case reports, retrospective evaluation, cohort or case-controlled studies, and epidemiologic surveys. These data, gathered over the last decade, have demonstrated that prenatal exposure to SSRI antidepressants is nonteratogenic and relatively safe.

Goldstein and Sundell[35] reviewed the safety of SSRIs during pregnancy. They included prospectively ascertained pregnancy outcomes reported by 4 cohort-controlled and 5 survey studies. All of the reviewed studies indicated that in utero exposure to SSRIs, mainly during the first trimester of pregnancy, a period of well-known maximum vulnerability to structural and neurochemical abnormalities of the central nervous system, does not significantly increase the risks of spontaneous abortion or major malformation. Furthermore, the birth weight, prematurity rates, and postnatal complications do not differ from the control incidence values of major birth defects. Only 1 of these 4 cohort-controlled studies assessed the offspring's long-term neurobehavioral development.[36] Three groups of women exposed to fluoxetine (N = 67), TCAs (N = 92), or a nonteratogen,

Table 2. Pregnancy Outcomes Following Exposure to Selective Serotonin Reuptake Inhibitors

Data Source	Fluoxetine	Sertraline	Paroxetine	Fluvoxamine	Citalopram
Goldstein and Sundell[35]	1088	152	102	88	...
Ericson et al[44]	15	32	118	...	364
Total	1103	184	220	88	364

such as analgesics, antibiotics, and dental x-ray (N = 84, nondepressed), were compared. Children were assessed for up to 86 months of age. Language and behavior development did not differ among the children born to the 3 groups of women, as there were no differences in their birth weight, heights, head circumferences, and perinatal complications. An interesting observation of the review by Goldstein and Sundell[35] was the fact that pregnancy outcome data with fluoxetine (N > 1000) far exceeded those on the use of all other SSRIs (N = 342; Table 2).

Wisner et al.[41] reviewed the pharmacologic treatment of depression during pregnancy. They analyzed 4 prospectively controlled studies[40,43] along 5 different domains of reproductive toxicity. In conclusion, although data are from a small number of patients and do not distinguish antidepressant effects from illness effects (depression also affects offspring development), this new information provides a valuable tool in the management of depression during pregnancy.

A meta-analysis[41] of prospectively controlled and uncontrolled epidemiologic studies examined the safety of fluoxetine during the first trimester of pregnancy. A power analysis indicated that 26 other controlled studies similar in size to those examined[38,39,42,43] would be necessary to reverse the lack of association of fluoxetine exposure during early pregnancy and measurable teratogenic effects in humans.[41]

The pregnancy exposure database has been further enlarged with another prospective study[44] of delivery outcome following the use of antidepressants during early pregnancy, i.e., before the end of week 16. Data from the Swedish Medical Birth Registry for the years 1995–1997 recorded 969 pregnant women using antidepressants. Among them, 531 used only an SSRI, 431 used only other antidepressants (mostly a TCA), and 15 received both. The number of pregnancies exposed to each SSRI is shown in Table 2. The delivery outcome was supplemented with information from the Registry of Congenital Malformations. Several variables were examined and the observed number of each was compared with the expected number, calculated from all births (N = 281,728 babies) in the population, after stratification for maternal age, parity, and smoking habits. No increase in congenital abnormalities was observed during the perinatal period, even though women using antidepressants were older and smoked more often than other women. The frequency of multiple births was lower than expected, especially in the women who had used SSRIs. Gestational duration was shorter than in the general population, but it did not influence the babies' survival and was similar for all antidepressants. The newborns were heavier than expected, especially in the group receiving TCAs and other antidepressants.[44]

The most important finding from this large Swedish study is replication of data from different sources showing that use of antidepressants in early pregnancy does not seem to significantly increase the risk for babies born from mothers exposed during the perinatal period. In addition, although most women in Sweden were using TCAs and citalopram, the total number of prospectively ascertained outcomes from pregnancy exposure to antidepressants is still larger for fluoxetine than any other SSRI (Table 2).

Nevertheless, further data on neurobehavioral development are needed as well as on the effects of having a depressed mother who is untreated. There are few data reporting that children born from depressed mothers have more pediatric events in the subsequent years and reduced educational levels up to 5 years, which are conceivably examples of behavioral teratogenicity.[37] In addition, depressed women probably do not get adequate prenatal care or diet, among other factors. In fact, depressed women smoke more cigarettes than the general population[44] and consume more alcohol as well.[36]

SUMMARY

Fluoxetine's safety profile, especially during long-term treatment, includes features such as low adverse events and dropout rates compared with TCAs and other SSRIs; established safety in overdose; low rate of mild discontinuation symptoms following treatment interruption in comparison to other SSRIs; and lack of teratogenic effects in prospectively ascertained pregnancy outcomes as assessed by both the postnatal period and neurobehavioral development. These characteristics of fluoxetine are extremely important to patients undergoing continuation and maintenance treatment. These patients may now benefit from another breakthrough in antidepressant therapy, the newly available fluoxetine once-a-week formulation, which offers several advantages.

Drug names: citalopram (Celexa), fluoxetine (Prozac), fluvoxamine (Luvox), paroxetine (Paxil), sertraline (Zoloft), venlafaxine (Effexor).

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