"Dopamine-Dependent" Side Effects of Selective Serotonin Reuptake Inhibitors: A Clinical Review

Cristian Damsa, M.D.; Anja Bumb, M.D.; Francesco Bianchi-Demicheli, M.D.; Pierre Vidailhet, M.D.; Robert Sterck, M.D.; Antonio Andreoli, M.D.; and Stefan Beyenburg, M.D.

Objective: Neurophysiologic findings indicate an inhibition of dopaminergic neurotransmission by selective serotonin reuptake inhibitors (SSRIs). This article highlights the relationships between changes in dopaminergic neurotransmission induced by SSRIs and the occurrence of certain side effects such as hyperprolactinemia, extrapyramidal symptoms, sexual and cognitive dysfunction, galactorrhea, mammary hypertrophy, and, more rarely, gynecomastia.

Data Sources and Selection: A systematic search of the literature in English, French, and German from 1980 to 2004 was performed in MEDLINE, EMBASE, and the Cochrane Library using the keywords *SSRI*, *dopamine*, *serotonin*, *side effects*, *antidepressants*, *citalopram*, *escitalopram*, *sertraline*, *paroxetine*, *fluoxetine*, *fluvoxamine*, and *nefazodone*. References cited in all trials were searched iteratively to identify missing studies. All studies concerning inhibition of dopaminergic neurotransmission by SSRIs and SSRI-related side effects were considered. We retained 62 significant articles debating the subject.

Data Extraction and Synthesis: We critically reviewed the studies, depending on the methodologies (case reports, clinical reports, randomized studies), and assessed the pertinence of "dopamine-dependent" SSRI-related side effects. The analytic review of these articles suggests that some specific SSRI-related side effects be classified as dopamine-dependent.

Conclusions: At a clinical level, it could be useful to underline dopamine-dependent characteristics of some SSRI-related side effects. This approach would allow clinicians the opportunity to search other dopamine-dependent side effects systematically. At a pharmacologic level, this approach could stimulate the development of molecules with a "corrective" function on dopamine-dependent side effects of SSRIs by facilitating dopaminergic neurotransmission.

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Received Dec. 16, 2003; accepted March 15, 2004. *From the Department of Psychiatry, University of Geneva, Geneva, Switzerland (Drs. Damsa, Bianchi-Demicheli, and Andreoli); the Department of Neurosciences, Centre Hospitalier de Luxembourg, Luxembourg (Drs. Bumb and Beyenburg); the Fédération des Services de Psychiatrie d'Adultes, Hôpital Civil 1, Strasbourg Cedex, France (Dr. Vidailhet); and the Department of Psychiatry, Jolimont Hospital, La Louvière, Belgium (Dr. Sterck).*

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Corresponding author and reprints: Cristian Damsa, M.D., 25 rue Goetz-Monin, 1205 Geneva, Switzerland (e-mail: c.damsa@bluewin.ch).

With the increasing use of selective serotonin reuptake inhibitors (SSRIs), treating physicians are faced with uncommon side effects, some of which were incompletely documented at the time of the launch of these medications. SSRIs can induce hyperprolactinemia, extrapyramidal symptoms, sexual and cognitive dysfunction, galactorrhea, and mammary hypertrophy, as well as gynecomastia. On the basis of several clinical reports and neurophysiologic data about the inhibition of dopaminergic neurotransmission by SSRIs, this article proposes to classify all of these SSRI-related side effects under the term *dopamine-dependent* side effects (Table 1).

A systematic search of the literature in English, French, and German from 1980 to 2004 was performed in MEDLINE, EMBASE, and the Cochrane Library using the keywords *SSRI*, *dopamine*, *serotonin*, *side effects*, *antidepressants*, *citalopram*, *escitalopram*, *sertraline*, *paroxetine*, *fluoxetine*, *fluvoxamine*, and *nefazodone*. References cited in all trials were searched iteratively to identify missing studies. All studies concerning inhibition of dopaminergic neurotransmission by SSRIs and SSRI-related side effects were considered. We retained 62 significant articles debating the subject.

HYPERPROLACTINEMIA

Several publications[1,2] identified the serotonergic drugs as one cause of hyperprolactinemia; SSRIs were sometimes considered one of the most frequent iatrogenic

Table 1. Dopamine-Dependent Side Effects of SSRIs

Side Effect
Hyperprolactinemia
Extrapyramidal symptoms
Sexual dysfunction
Cognitive dysfunction
Galactorrhea
Mammary hypertrophy
Gynecomastia

Abbreviation: SSRI = selective serotonin reuptake inhibitor.

causes of hyperprolactinemia.[3] All SSRIs were identified as a possible cause of hyperprolactinemia: paroxetine,[3,4–6] fluoxetine,[7–9] fluvoxamine,[3,10–13] citalopram,[14,15] and sertraline,[3,16,17] although 50 mg of sertraline for 3 weeks was not found to induce hyperprolactinemia in normal controls.[18]

The implication of SSRIs in hypothalamic stimulation of release of prolactin (the dopamine holds opposite effect[3]) is supported by the observation that serotonergic agents, such as *d*-fenfluramine, also increase the prolactin level,[19] whereas metergoline, a serotonergic antagonist, was successfully used to stop lactation by prolactin drop-off in postpartum women to avoid breastfeeding.[20] The increase of prolactin level induced by *d*-fenfluramine was well recognized,[21–23] most likely a result of a direct postsynaptic action on the 5-HT_{2C} receptors[24]; therefore, several studies used this test to evaluate the central serotonergic function.[25,26]

Two mechanisms were considered to explain the prolactin release induced by the serotonergic system: the presynaptic inhibition of dopamine discharge by the serotonergic receptors (mechanism considered as the most probable by Egberts et al.[12]) or the direct stimulation of the hypothalamic postsynaptic serotonergic receptors.[17] In healthy volunteers, pindolol, a 5-HT_{1A} antagonist, decreased basal prolactinemia, and ritanserin, a 5-HT_2/5-HT_{1C} antagonist, blocked the increase of prolactinemia induced by *d*-fenfluramine.[27] Rittenhouse et al.[28] suggest that the activation of the receptors 5-HT_2/5-HT_{1C} can increase prolactinemia. The subtypes of the serotonergic receptors involved in the basal secretion of prolactin are not well elucidated.[4]

EXTRAPYRAMIDAL EFFECTS

Serotonergic inhibition of the dopaminergic system is revealed also by extrapyramidal effects of SSRIs,[12,29,30] such as bradykinesia, rigidity, akathisia, and even acute dystonia. Many publications point to a role of SSRIs in the occurrence of extrapyramidal effects.[31–36] Moreover, fluoxetine can cause a clinical picture that looks like neuroleptic malignant syndrome, supporting the hypothesis that some side effects of SSRIs may be dopamine-dependent.[37]

SEXUAL DISORDERS

Several mechanisms of action were proposed to explain sexual disorders caused by SSRIs (dopaminergic inhibition, hyperprolactinemia, anticholinergic effects, inhibition of nitric oxide synthetase).[3] The role of SSRI-induced dopaminergic inhibition in sexual disorders is supported by the evidence that dopaminergic agonists can diminish ejaculatory dysfunction secondary to SSRIs.[3,38,39] Three types of substances were utilized to prevent SSRI-induced sexual adverse events: antagonists of serotonergic receptors, antagonists of adrenergic α_2 receptors, and dopaminergic agents. Unfortunately, most clinical attempts have considerable methodological problems, e.g., the absence of a double-blind study design or a limited number of participants.[40] A recent placebo-controlled trial found bupropion as a possible "antidote" for SSRI-induced sexual dysfunction.[41]

The incidence of sexual disorders during paroxetine treatment seems to be higher than that for other SSRIs.[3,11,42,43] This observation could be associated with the relative selectivity on dopaminergic reuptake of paroxetine among SSRIs, combined with the fact that paroxetine is the most potent SSRI at blocking the human serotonin transporter. According to these findings, Rosen et al.[3] suggest that citalopram, the most selective of the SSRIs, could be associated with an elevated risk for sexual disorders compared with sertraline. However, long-term results from clinical studies are lacking.

COGNITIVE DYSFUNCTION

Attention disorders were found by Schmitt et al.[44] in 21 healthy volunteers. The subjects completed 3 treatment periods of 2 weeks' duration in which sertraline (50 mg, days 1–7; 100 mg, days 8–14), paroxetine (20 mg, days 1–7; 40 mg, days 8–14), and placebo were administered. Vigilance (Mackworth Clock Test), selective attention (Stroop test, dichotic listening), and divided attention (dichotic listening) were assessed at baseline and on days 7 and 14 of each treatment period. Selective and divided attention were unaffected by SSRI treatment, but administration of paroxetine (day 14) impaired vigilance performance at each investigated dose. The decrease of attentiveness was identified by the Mackworth Clock Test (prolonged response time and reduced validity of answers), without modifications of selective or distributive attention (Stroop test, color of words). Sertraline did not produce a significant decline in vigilance performance, presumably due to its concomitant effects on dopamine activity, counteracting the negative effects of serotonin on dopamine neurotransmission.[44] It was concluded that a serotonergically mediated reduction of dopamine activity plays an important role in the reduction of human vigilance following SSRI administration.[44] These data were

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confirmed in part by the study of Van Laar et al.,[45] who observed a reaction speed decrease at day 1 with paroxetine versus placebo, as well as a discreet increase of error rate in visual selective attention task on day 8.

GALACTORRHEA

Egberts et al.[12] found that SSRIs were associated with an 8 times higher risk for galactorrhea as compared with other antidepressants. Several SSRIs are suspected to induce galactorrhea: paroxetine,[12,29] sertraline,[17,46] fluvoxamine,[12,47,48] and fluoxetine.[7,12,49] There is no clear correlation between prolactin level and galactorrhea.[12]

MAMMARY HYPERTROPHY AND GYNECOMASTIA

SSRIs can be associated with mammary hypertrophy in women.[5,50,51] Amsterdam et al.[5] found different degrees of mammary hypertrophy in 39% of 59 women treated for at least a month with an SSRI (paroxetine, fluoxetine, sertraline) or with venlafaxine. Despite the high percentage of patients who developed mammary hypertrophy while receiving treatment with paroxetine, there were no statistically significant differences between the different drugs.[5] Mammary hypertrophies were unrelated to age, state of menopause, and duration of the antidepressant treatment.

We recently reported a patient in whom paroxetine monotherapy was probably the key factor in triggering gynecomastia.[52] Benazzi[53] described another case of gynecomastia in a patient taking fluoxetine; however, the patient was concomitantly treated with risperidone. These 2 observations are supported by the occurrence of gynecomastia caused by the 5-HT_{1A} agonist tandospirone.[54] There is no clear relation between prolactin levels and gynecomastia or mammary hypertrophy. Controlled studies are necessary to clarify these particular side effects of SSRIs. Another study[55] evaluating the possible association between antidepressant therapy and breast cancer did not find any significant correlations, even if the results concerning SSRIs are not completely reassuring (the estimated relative risk was 1.8 for a recent use of an SSRI, at the limit of the statistical significance).

DISCUSSION

Data suggest that SSRIs can inhibit dopaminergic neurotransmission not only by their effects on dopamine secretion or recapture or on dopaminergic receptors, but also indirectly through serotonergic mediation.[3,9,12,33,56] Complex changes of dopaminergic neurotransmission (mostly antidopaminergic effects) have been described with SSRIs.[4,57,58]

The dopamine-dependent side effects of SSRIs could evoke some mild side effects of antipsychotic drugs. These side effects could be explained not only by dopaminergic inhibition by SSRIs but also by the complex interactions that exist between serotonin and neurotransmitters other than dopamine, as well as the direct action of the SSRIs through serotonergic receptors (that could also provoke side effects such as hyperprolactinemia or sexual dysfunction). We feel that it could be a relevant alleviation of the clinical context to keep in mind that SSRIs may inhibit dopaminergic neurotransmission, although SSRIs have no antipsychotic effects (sometimes they can provoke aggravation of psychotic symptoms) and, vice versa, some antipsychotics can worsen depression.[59] It is very likely that the level of reduction of dopaminergic neurotransmission by SSRIs is not sufficient to induce an antipsychotic effect (blocking dopamine receptors is more effective than inhibiting release of dopamine).

The clinical observation of dopamine-dependent side effects of SSRIs could be complicated by interactions with other drugs susceptible to modifying the dopaminergic secretion or able to provoke the same similar adverse events through different mechanisms. A recent review article[60] highlights drug interactions specific to each SSRI at the level of the cytochrome P450 (CYP) isozymes: fluvoxamine (inhibits CYP1A2 and CYP2C19 and moderately inhibits CYP2C9, CYP2D6, and CYP3A4), fluoxetine and paroxetine (inhibit CYP2D6), sertraline (moderately inhibits CYP2D6), and citalopram (mildly affects the major isoforms of CYP). Thus, pharmacokinetic and pharmacodynamic considerations also play a role when analyzing different clinical effects of SSRIs.[60]

Nefazodone, a serotonin antagonist reuptake inhibitor, seems to not provoke dopamine-dependent side effects, meaning the selective blockade of serotonergic receptors. Furthermore, a pilot randomized trial suggests that nefazodone could even improve extrapyramidal symptoms in depressed Parkinson's disease patients.[61]

There is no evidence of a possible difference in dopamine-dependent side effects of escitalopram and citalopram. The dopaminergic inhibition by SSRIs could also obstruct recovery from depression. A clinical report suggests an interest in dopaminergic agonists such as bupropion for fluoxetine-resistant major depressive disorder,[62] but this finding needs confirmation in large double-blind studies.

The occurrence of a dopamine-dependent side effect should initiate a systematic search for other dopamine-dependent effects to improve compliance and to avoid clinical deterioration. At a pharmacologic level, this approach could stimulate the development of molecules with "corrective" effects on the SSRIs' dopamine-dependent side effects by facilitating dopaminergic neurotransmission.

Drug names: bupropion (Wellbutrin and others), citalopram (Celexa), escitalopram (Lexapro), fluoxetine (Prozac and others), nefazodone (Serzone and others), paroxetine (Paxil and others), pindolol (Visken), risperidone (Risperdal), sertraline (Zoloft), venlafaxine (Effexor).

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