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# LETTER TO THE EDITOR

# Fluoxetine and Raynaud's phenomenon: friend or foe?

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**Keywords** fluoxetine, Raynaud's phenomenon, systemic sclerosis

## Tables of Links

| TARGETS | |
|---|---|
| **G protein-coupled receptors** [2] | **Enzymes** [4] |
| 5-$HT_{2A}$ receptor | Adenylate cyclase |
| 5-$HT_{2B}$ receptor | eNOS |
| 5-$HT_{1B}$ receptor | Nitric oxide (NO)-sensitive (soluble) guanylyl cyclase |
| 5-$HT_{7}$ receptor | |
| CGRP receptor | |
| **Voltage-gated ion channels** [3] | |
| Calcium-activated potassium channels | |
| Voltage-gated calcium channels | |

| LIGANDS |
|---|
| Fluoxetine |
| Nifedipine |

These Tables list key protein targets and ligands in this article which are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [1], and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 [2–4].

Whether fluoxetine, a selective serotonin reuptake inhibitor, is an effective treatment for Raynaud's phenomenon (RP) has been debated for about 20 years. Based on one positive efficacy trial [5] and some preliminary observations [6], fluoxetine is recommended in RP secondary to systemic sclerosis (SSc), after failure of calcium channel blockers [7]. However, when one looks closely at the available evidence, the lack of a homogeneous effect of fluoxetine in RP patients is obvious.

The crossover study comparing the efficacy of nifedipine and fluoxetine in 56 patients with primary or secondary RP showed a significant improvement in the Raynaud's condition score (RCS) [4.35 (0.39) *vs.* 2.3 (0.35); $P = 0.0002$] and daily frequency of attacks [2.98 (0.31) *vs.* 1.7 (0.25);



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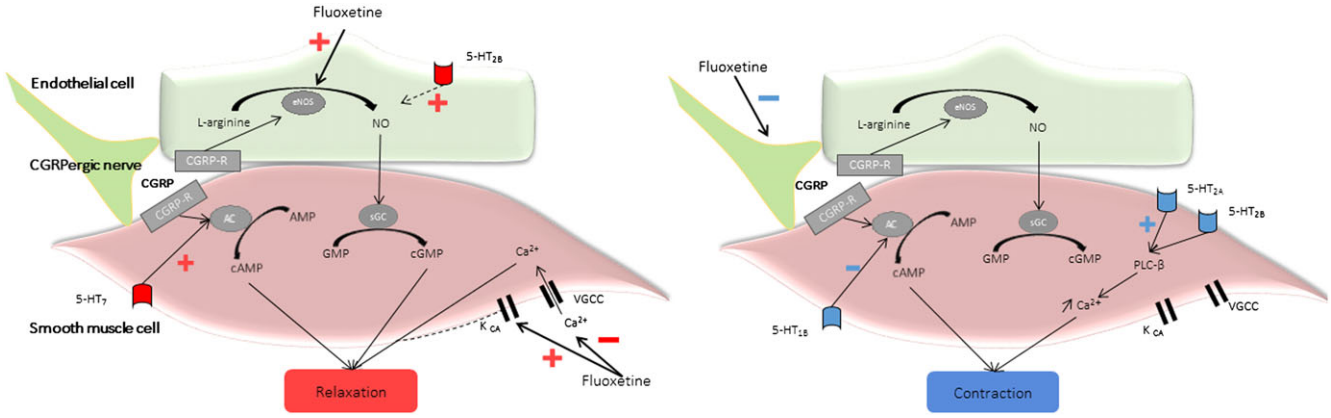


## Figure 1

Co-existing vasodilator–vasoconstrictor pharmacodynamic effects of fluoxetine. AC, adenylyl cyclase; AMP, adenosine monophosphate; cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; CGRP, calcitonin gene-related peptide; eNOS, endothelial NO synthase; GMP, guanosine monophosphate; Kca, calcium-sensitive potassium channel; NO, nitric oxide; PLCβ, phospholipase C beta; R-CGRP, calcitonin gene-related peptide receptor; sGC, soluble guanylate cyclase; VGCC, voltage-gated calcium channels

$P$ = 0.003] [4]. However, when looked at more carefully, subgroup analysis showed a significant benefit for RCS and the frequency of attacks in primary RP, while only RCS was significantly improved in patients with secondary RP. Likewise, the secondary criterion of percentage of rewarming after cold challenge was positive in primary RP [33.4% (±7.5%) *vs*. 58.8% (±8.7%); $P$ = 0.03] but negative in secondary RP [31.6% (±6.4%) *vs*. 31.2% (±8.2%); $P$ = 0.97]. Furthermore, we could hypothesize that the antidepressant activity of fluoxetine may have a significant impact on a subjective measurement of self-reported outcomes such as RCS. Owing to the discovery of thrombocyte dysfunction correlated with an increase in intraplatelet serotonin in RP, the antiaggregant effect of fluoxetine was hypothesized to be the main mechanism [8]. However, later studies using antithrombotic drugs were disappointing and evidence of their benefit in RP is now limited [9].

The involvement of the serotoninergic pathway in vascular tone is complex; serotonin causes direct vasoconstriction through $5HT_{2A}$, $5HT_{2B}$ and $5HT_{1B}$ receptors [10]. Experimental data also suggest that serotonin released from adrenergic nerves inhibits calcitonin gene-related peptide-containing nerve-dependent vasodilation [11]. By contrast, vasodilation is mediated through $5HT_7$ and $5HT_{2B}$ receptors, located on smooth muscle cells and on the endothelium, respectively [10]. Endothelium-dependent vasodilation would be secondary to increased nitric oxide (NO) bioavailability, through enhanced endothelial NO synthase activity [11, 12]. Mechanisms underlying direct activity on smooth muscle cells may involve activation of calcium-sensitive potassium channels [13] and inhibition of voltage-gated calcium channels [12] (Figure 1).

Whether fluoxetine increases, through the reduction in serotonin reuptake into platelets, or decreases, through the sequestration of serotonin at the intestinal level, the plasma serotonin concentration is still controversial [14]. However, this probably has a limited impact, considering that vasomodulation mediated by fluoxetine is not dependent on plasma serotonin concentration [15].

In light of the clinical discrepancies described above, we raise the hypothesis that in SSc, endothelial dysfunction could explain the reduced vasodilator effect of fluoxetine, and could even switch the balance between vasoconstriction and vasodilation.

We therefore believe that there is insufficient scientific evidence to recommend fluoxetine as a treatment in SSc-related RP. A well-designed, double-blinded clinical trial that properly stratifies patients according to RP aetiology would address this question.

## Competing Interests

All authors have completed the Unified Competing Interest form and declare no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

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