



Mechanism of action of the SPARI vilazodone: serotonin 1A partial agonist and reuptake inhibitor

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ISSUE:

Vilazodone is an antidepressant with a novel mechanism of pharmacologic action: serotonin partial agonist reuptake inhibitor (SPARI).

Take-Home Points

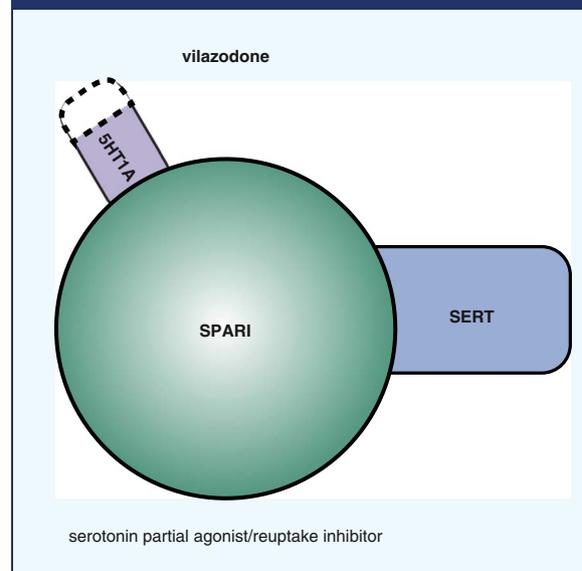
- Blocking the serotonin transporter (SERT) while simultaneously stimulating the serotonin 1A receptor produces pharmacologic synergy upon the serotonin system in preclinical models.
- In theory, combining these 2 mechanisms could not only yield antidepressant and anxiolytic actions, but rapid onset of these actions, fewer sexual side effects, and greater efficacy than either mechanism alone.
- So far, the combination of these two mechanisms—serotonin reuptake inhibition with serotonin 1A partial agonism or SPARI—has validated antidepressant actions in man, but the full potential of this combination remains to be proven in clinical trials.

The new antidepressant vilazodone, marketed in the U.S., combines serotonin transporter (SERT) inhibition with a second property: serotonin (5HT) 1A partial agonism.^{1–4} For this reason, vilazodone is called a serotonin partial agonist reuptake inhibitor (SPARI)^{1,5} (Figure 1). The combination of serotonin reuptake inhibition with 5HT1A partial agonism has long been known by clinicians to enhance the antidepressant properties and tolerability of serotonin selective reuptake inhibitors/serotonin norepinephrine reuptake inhibitors (SSRIs/SNRIs) in some patients. For example, SERT inhibition combined with 5HT1A partial agonism can also be achieved by adding

atypical antipsychotics with 5HT1A partial agonist actions such as quetiapine or aripiprazole to SSRIs/SNRIs.¹ 5HT1A partial agonist actions plus SERT inhibition can also be attained by augmenting SSRIs/SNRIs with the 5HT1A partial agonist buspirone.¹

Although these drug combinations achieve the same 2 actions that vilazodone does as a single molecule,

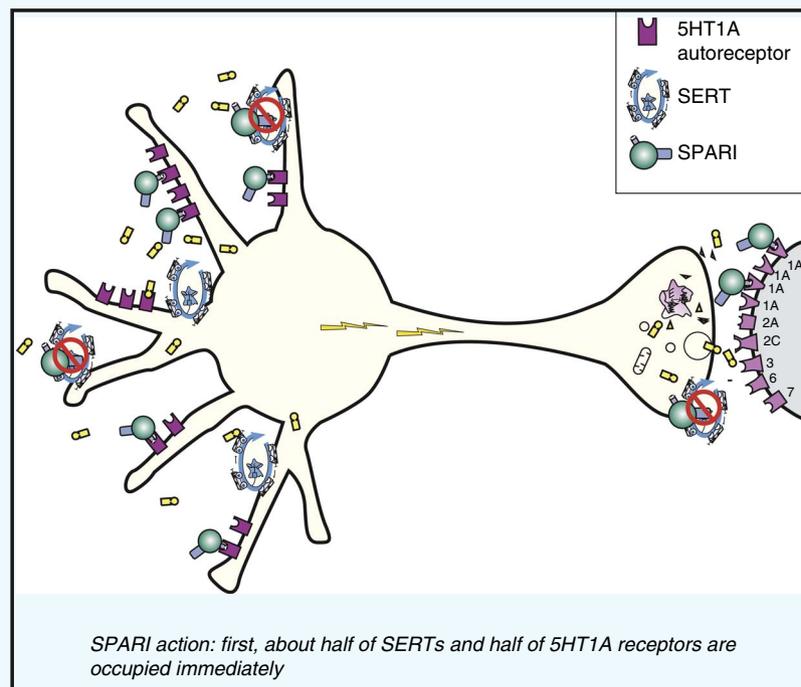
Figure 1. Serotonin partial agonist reuptake inhibitor (SPARI). Vilazodone is a partial agonist at the 5HT1A receptor and also inhibits serotonin reuptake. Its effects at 5HT1A receptors are equal to or more potent than its effects at serotonin transporters.





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Figure 2. Mechanism of action of the SPARI vilazodone, part 1. When the SPARI vilazodone is administered, about half of serotonin transporters (SERTs) and half of serotonin 5HT1A receptors are occupied immediately.



these drug combinations are not identical to the actions of the single agent vilazodone. That is, atypical antipsychotics have many additional pharmacologic actions, some desirable and others not.¹ Bupropion and its active metabolite 6-hydroxy-bupropion are weaker 5HT1A partial agonists than vilazodone and are estimated to occupy fewer 5HT1A receptors for a shorter time at clinically administered doses than does vilazodone.^{1,6} Bupropion and 6-hydroxybupropion also bind to 5HT1A receptors with lower affinity than 5HT itself, whereas vilazodone binds to 5HT1A receptors with higher affinity than 5HT, suggesting that addition of bupropion to an SSRI/SNRI likely results in 5HT1A receptor occupancy that occurs more robustly in states of low 5HT levels and not as robustly in states of high 5HT levels, whereas vilazodone binds to 5HT1A receptors even in the presence of 5HT. Another difference between bupropion plus a SSRI/SNRI versus vilazodone is that when bupropion augments a SSRI, the bupropion is generally dosed so that about 10–20% of 5HT1A receptors are occupied and the SSRI is dosed so that about 80% of SERTs are blocked.¹ On

the other hand, human neuroimaging studies suggest that vilazodone is dosed so that about 50% of both SERTs and 5HT1A receptors are occupied (Figure 2).⁶ Whether this accounts for clinically significant differences between the administration of vilazodone monotherapy versus the augmentation of SSRIs/SNRIs with bupropion or atypical antipsychotics is not known, but could account for the apparently lesser incidence of sexual dysfunction with vilazodone than with either SSRIs alone or with the augmentation SSRIs with bupropion. It is also not known whether the enhanced efficacy of bupropion or atypical antipsychotics combined with SSRIs/SNRIs for depression, which has been demonstrated in clinical trials for patients who fail SSRI monotherapy, will also apply to vilazodone, as appropriate clinical trials to determine this have not yet been conducted.

In animal models, adding 5HT1A partial agonism to SSRIs causes more immediate and robust elevations of brain 5HT levels than SSRIs do alone.^{2–4} This is thought to be due to the fact that 5HT1A partial agonists are a type of “artificial serotonin” selective especially for



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Figure 3. Mechanism of action of the SPARI vilazodone, part 2. Blockade of the serotonin transporter (SERT) causes serotonin to increase initially in the somatodendritic area of the serotonin neuron, on the left (red circle).

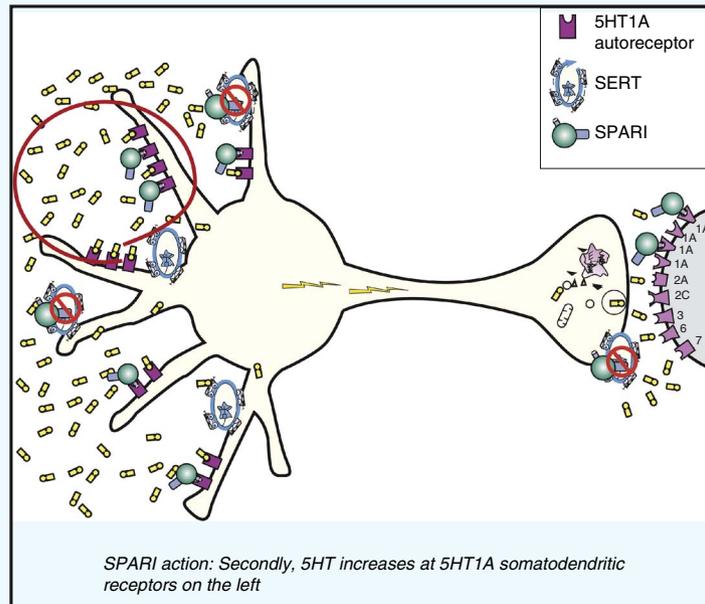


Figure 4. Mechanism of action of the SPARI vilazodone, part 3. The consequence of serotonin increasing in the somatodendritic area of the serotonin neuron (see Figure 3) is that the somatodendritic 5HT1A autoreceptors desensitize or down-regulate (red circle).

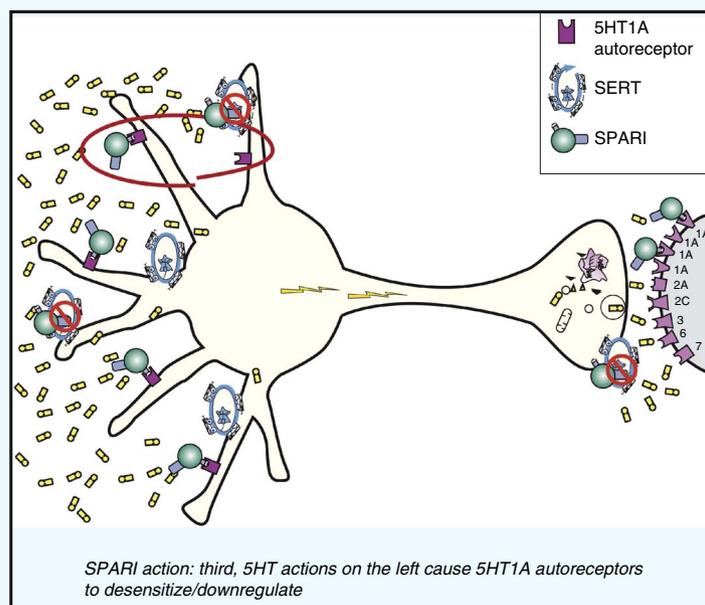
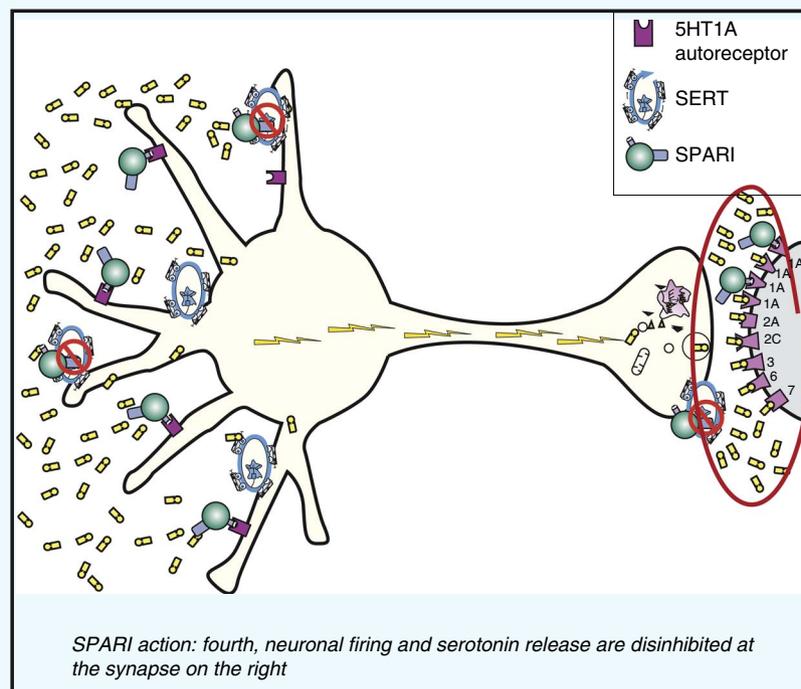




Figure 5. Mechanism of action of the SPARI vilazodone, part 4. Once the somatodendritic receptors down-regulate, as depicted in Figure 4, there is no longer inhibition of impulse flow in the serotonin neuron. Thus, neuronal impulse flow is turned on. The consequence of this is release of serotonin in the axon terminal on the right (red circle).



presynaptic somatodendritic 5HT_{1A} autoreceptors, and that 5HT_{1A} partial agonist action occurs immediately after the drug is given (Figure 3).¹⁻⁴ Thus, 5HT_{1A} immediate partial agonist actions are theoretically additive or synergistic with simultaneous SERT inhibition, since this leads to faster and more robust actions at 5HT_{1A} somatodendritic autoreceptors than with SERT inhibition alone, including their down-regulation (Figure 4). This hypothetically causes faster and more robust elevation of synaptic 5HT than possible is with SSRIs alone (Figure 5).

Theoretically, SPARI actions could lead to faster antidepressant onset if rapid elevation of 5HT is linked to rapid antidepressant onset. However, clinical studies do not support this,⁷⁻⁹ because the rapid increase in serotonin is not well tolerated due especially to gastrointestinal side effects. In addition, dose titration must be slowed down in order to attain full dosing, which would also slow down any potential rapid antidepressant onset.^{1,7-9} SPARI actions could hypothetically lead to more antidepressant efficacy than selective SERT inhibition, as suggested by

bupirone or atypical antipsychotic augmentation of SSRIs/SNRIs, but this has not been demonstrated yet in head-to-head trials of vilazodone against an SSRI. Finally, SPARI actions could theoretically lead to lesser sexual dysfunction, due to lesser degrees of SERT inhibition than SSRIs. Low sexual dysfunction is shown for vilazodone in placebo controlled trials,⁷⁻⁹ but has not proven to be less than SSRIs yet in head-to-head trials.

Thus, there are many theoretical advantages to the SPARI combined mechanism, but proof of that advantage over current antidepressants or well-known combinations of 2 agents to achieve the same pharmacologic actions is still awaited.

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