## Mixed Depression and Anxiety: Serotonin<sub>1A</sub> Receptors as a Common Pharmacologic Link

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Although depressive and anxious symptoms frequently coexist, most studies tend to dichotomize anxiety disorders from depression. Consequently, pharmacologic agents are designated as antidepressants or anxiolytics. A number of developments are reversing this trend. One is changes in conceptualization of generalized anxiety disorder (GAD) and major depressive disorder to recognize the frequent existence of simultaneous symptoms of anxiety and depression in patients with related affective and anxiety disorders. A second is the increasing recognition that subsyndromal symptoms of anxiety and depression frequently exist that do not reach thresholds for GAD or depression but that may decompensate to overt anxiety disorder or depression. A third is the discovery of partial agonists for serotonin<sub>1A</sub> receptor subtypes that have promising efficacy in mixed depression and anxiety.

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umerous studies have shown the frequent coexistence of depressive and anxious symptoms in patients seen in clinical practice.<sup>1-6</sup> Although early research and psychopharmacologic treatment studies have tended to dichotomize anxiety disorders from depression, emphasizing one end of the spectrum or the other, recent developments are now reversing this trend. Some of these developments arise from long-term outcome studies that document the interaction between symptoms of anxiety and depression within individuals over time.7-25 Other recent observations linking anxiety and depression have been possible due to the development of novel pharmacologic probes and treatments, particularly those that have advanced our understanding of the neurotransmitter serotonin and its multiple receptor subtypes.<sup>6,26-37</sup> Such findings underscore long-standing observations from clinical practice that classical anxiolytics can treat symptoms of depression and that classical antidepressants can treat symptoms of anxiety, especially in patients in whom these symptoms coexist.

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#### THREE POINTS OF VIEW ON ANXIETY AND DEPRESSION

The three predominant points of view on how symptoms of anxiety and depression are related (the traditional, the comorbid, and the mixture/subsyndromal points of view) have been well described in previous reviews and will be discussed here only in brief.<sup>1,6</sup>

The **traditional point of view**<sup>1.2</sup> is that anxiety and depression are discrete entities, as are their treatments, i.e., the traditional anxiolytics and antidepressants (Figure 1). The introduction of these concepts into clinical practice during the 1960s and 1970s led to the treatment of generalized anxiety disorder (GAD) with benzodiazepines and major depressive disorder with tricyclic antidepressants. This was the era of dichotomizing anxiety from depression and was most useful not only for defining discrete diagnostic groups for early clinical studies of novel therapeutic agents, but also for rigorously defining subjects for drug development research and regulation.

This style of thinking has evolved in recent years with further subcategorization of anxiety and of depression. These multiple subtypes of anxiety include panic disorder, obsessive-compulsive disorder, social phobia, agoraphobia, and posttraumatic stress disorder, while multiple subtypes of depression include dysthymia, brief intermittent depression, "double" depression, and recurrent depression.

As the anxiety disorders and the affective disorders have become subcategorized, and as clinical experience with anxiolytics and antidepressants has increased, the conceptually sharp distinctions between these drugs have begun to erode. This has led not only to the use of benzodiazepines to treat—in some cases—symptoms of

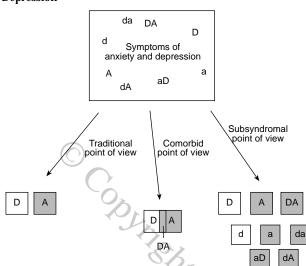


Figure 1. Three Points of View on Symptoms of Anxiety and Depression\*

\*The traditional point of view suggests that generalized symptoms of anxiety and depression can be dichotomized into one syndrome known as major depressive disorder (D) and another known as generalized anxiety disorder (A). The comorbid point of view suggests a third category, namely the presence of both anxiety and depression (DA). Finally, the subsyndromal point of view considers that depression and anxiety can also be present to a degree that is greater than normal, but less than that required for a full diagnostic syndrome of depression or anxiety. Thus, anxiety (a) and depression (d) and mixed anxiety depression (da) can be subsyndromal. Furthermore, full syndromal and subsyndromal mixtures can also occur (eg, aD and dA).

depression, but more profoundly to the use of classical antidepressants to treat subcategories of anxiety disorders,<sup>38</sup> in particular panic disorder, obsessive-compulsive disorder, and social phobia.

The **comorbid point of view**<sup>1,2,8–10</sup> arises from the increasing recent recognition that anxiety frequently coexists with depression (Figure 1). This has proven to be particularly true in the newly evolving entities panic disorder and obsessive-compulsive disorder, in which a high incidence of current or past major depressive disorder is recognized. This depressive illness is not seen as being part of the anxiety disorder, but as a concomitant, comorbid illness occurring in a large subset of patients. In such cases, patients may be seen as having two illnesses that may therefore require treatment with two agents, one for the anxiety disorder and another for the depressive disorder.

The **mixture/subsyndromal point of view**<sup>1,2,8–10,39</sup> differs from the comorbid point of view in that the comorbid perspective recognizes that major depressive disorder can be a second illness in some patients with a specific type of anxiety disorder, whereas the mixture/subsyndromal view focuses on the fact that patients with a diagnosis of anxiety disorder can have concurrent symptoms of depression that do not, however, meet the criteria for a second diagnosis of major depressive disorder (Figure 1). Vice versa, patients with a diagnosis of depressive disorder can have simultaneous symptoms of anxiety and yet not have a second diagnosis of any subcategory of anxiety disorder. Thus, this point of view emphasizes the subsyndromal perspective that some patients have chronic symptoms of anxiety and depression, but may not always reach the level of severity required to make a diagnosis of an anxiety or affective disorder. Such subsyndromal symptoms are of interest because they may wax and wane and, in particular, decompensate under stress such that these individuals develop an overt full syndrome anxiety or depressive disorder. Investigators are interested in the subsyndromal category of mixed symptoms of anxiety and depression in an attempt to account for subjects with low levels of symptoms who might, nevertheless, be at higher lifetime risk for an anxiety or affective disorder than the general population.

Various combinations of anxiety and depression have also been recognized by psychopharmacologists, highlighting the fact that the clinical applications of classical anxiolytics and classical antidepressants overlap greatly. Indeed, newer agents based upon interactions with serotonin and its receptors are greatly expanding the theory that novel treatments for mixed disorders of anxiety and depression can reduce both symptoms of depression and symptoms of anxiety.

Such overlap was not emphasized during the original testing of the classical anxiolytics and classical antidepressants, perhaps in order to avoid confusing the traditional concepts of anxiety and depression, and of anxiolytics, and antidepressants. Today, as our concepts of anxiety and depression advance, diverge, and mix, so do our concepts of antidepressant and anxiolytic drugs. One could even ask: what is the modern definition of an antidepressant or an anxiolytic? Although there may not be a definite answer to this question, it is already clear that the modern concept of an "antidepressant" implies neither "merely an antidepressant" nor "not an anxiolytic."

### SEROTONIN<sub>14</sub> RECEPTORS AS A COMMON PHARMACOLOGIC LINK BETWEEN ANXIETY AND DEPRESSION

There are various contemporary theories linking the function of serotonin and its receptors to the actions of both anxiolytic and antidepressant drugs. The mechanisms discussed here are still evolving as hypotheses, and may be modified significantly as new knowledge unfolds rapidly in this area. However, these receptor-related mechanisms illustrate how a pharmacologic rationale can be applied to mixtures of psychiatric symptoms and to evolving psychiatric nosology of many closely related disorders, not only to develop theories explaining a common biological basis for related disorders, but also to simplify and improve treatments for such disorders.

The point of view suggesting that serotonin receptor function can link the mechanisms of both anxiolytic and

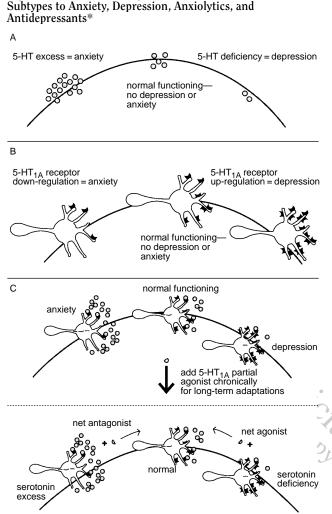


Figure 2. Theories Linking Serotonin and Its Receptor

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A. A simplified concept of how serotonin may be implicated in anxiety and depression. Anxiety may be associated with 5-HT excess and depression with 5-HT deficiency.

B. In the anxious state, 5-HT<sub>1A</sub> somatodendritic autoreceptors may be down-regulated in an ineffectual attempt to compensate for excessive serotonin (left end of the spectrum). In the depressed state, 5-HT<sub>1A</sub> autoreceptors may be up-regulated in a similarly ineffectual attempt to compensate for deficient serotonin (right end of the spectrum). C. 5-HT<sub>1A</sub> partial agonists may have both anxiolytic and antidepressant actions. In the case of anxiety, an excess of serotonin and perhaps a down-regulation of 5-HT<sub>1A</sub> receptors will result in a 5-HT<sub>1A</sub> partial agonist having a net antagonist effect leading to a normalization of serotonin levels and receptors and a reduction in anxiety. In the case of 5-HT<sub>1A</sub> receptors will cause a 5-HT<sub>1A</sub> receptors in a perhaps an up-regulation of 5-HT<sub>1A</sub> receptors and a reduction in anxiety. In the case of depression, a deficiency of serotonin and perhaps an up-regulation of 5-HT<sub>1A</sub> receptors will cause a 5-HT<sub>1A</sub> partial agonist to be perceived as a net agonist, leading to a normalization of serotonin levels and receptors and a reduction in depression.

antidepressant actions is developing from knowledge of how drugs affect receptors acutely, and how these acute effects can be converted by the neuron into an adaptive neurobiological effect that is therapeutic to the patient. However, the exact role of serotonin in anxiety and depression remains elusive and these theories are as yet unproved. Nevertheless, explanations for delayed therapeutic drug effects are increasingly being sought by implicating delayed neurobiological mechanisms.

#### Serotonin Excess in Anxiety?

A general role for serotonin in anxiety has long been suspected as, for the most part, pharmacologic manipulations that enhance serotonin also enhance anxiety whereas pharmacologic manipulations that reduce serotonin also reduce anxiety.<sup>6</sup> This is essentially the opposite of depression in which pharmacologic manipulations that enhance serotonin often reduce depression.<sup>6</sup> Such early conceptions of the role of serotonin in anxiety as a "serotonin excess syndrome" and in depression as a "serotonin deficiency syndrome" are naive oversimplifications and very imprecise, although they do have some heuristic value (Figure 2). The actual role of serotonin in the actions of anxiolytic and antidepressant agents is indeed likely to be far more complex.

## Serotonin Receptor Adaptations as Mediators of Anxiety?

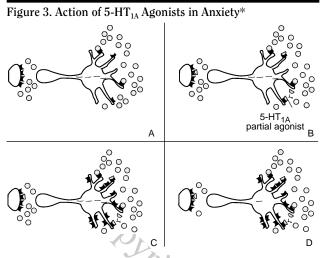
A corollary to the hypothesis of serotonin excess in anxiety is that 5-HT receptors adapt to this excess of 5-HT. Thus, the excessive serotonin state of anxiety could theoretically be accompanied by a down-regulation of 5-HT<sub>IA</sub> receptors in order to counter this excess by preventing excessive neuronal impulse flow (Figure 3).

This is the opposite of the hypothesis for depression, where the deficiency of 5-HT might be expected to cause the 5-HT<sub>1A</sub> receptors to up-regulate in a similarly unsuccessful attempt to enhance neuronal impulse flow in the 5-HT neuron (Figure 4).

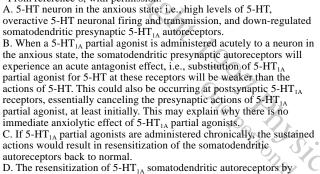
# Partial Agonists Both for Serotonin Excess and for Serotonin Deficiency?

The biochemical pharmacology of partial agonists endows them with properties such that these agents can function either as agonists or as antagonists, depending upon the amount of endogenous ligand present. In the case of serotonin neurons and their functioning in anxiety and depression, when serotonin is absent (depression), a partial serotonin agonist will be a net agonist (Figure 4). When serotonin is present in excess (anxiety), the same partial agonist will, however, be a net antagonist (Figure 3). Thus, a partial serotonin agonist would theoretically boost deficient serotonergic activity, yet block excessive serotonergic activity.

To the extent that a surfeit of serotonin is linked to anxiety, this theory predicts that a serotonin partial agonist should be an anxiolytic. To the extent that serotonin deficiency is linked to depression, this theory predicts that a serotonin partial agonist should also be an antidepressant. Using an analogy with light switches, a room will be dark when agonist (serotonin) is missing and the light switch is off. This can serve as a metaphor for depression, when se-



\*From reference 6, with permission.



b) The resensitization of 5-H $_{1A}$  solutioned in a diffecterior by chronic administration of 5-H $_{1A}$  partial agonists allows the neuron to slow down its neuronal impulse flow and to diminish its release of serotonin. Theoretically, this would be associated with a normalization of function and a reduction in the symptoms of anxiety.

rotonin is depleted. A room will be brightly lit when it is full of serotonin agonist and the light switch is fully on. This serves as a metaphor for anxiety, associated with excessive serotonin activity. If partial agonists act like a rheostat, they would turn the lights on partially, but not fully. Each partial agonist has its own degree of partiality built into the molecule and will light the room to a certain extent, no matter what dose is used, depending only on its intrinsic partial agonist properties. Adding a partial serotonin agonist to the dark (depressed) room, where there is no serotonin, will turn the lights up (presumed antidepressant action), but only as far as the partial serotonin agonist works on the serotonin receptor rheostat. In contrast, adding a partial serotonin agonist to the fully lit (anxiety) room will have the effect of turning the lights down to the level of lower brightness on the serotonin rheostat. This is a net antagonistic effect relative to the fully lighted room and a presumed anxiolytic action. Thus, after adding partial serotonin agonist to the dark (depressed) room and to the brightly lit (anxiety) room, both rooms will be equally lit. The degree of brightness corresponds to being partially turned on as dictated by the properties of the partial agonist. However, in the dark

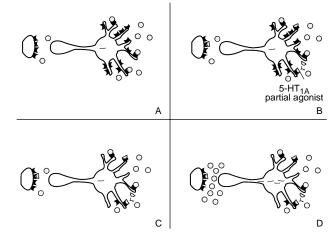


Figure 4. Action of 5-HT<sub>14</sub> Agonists in Depression\*

\*From reference 6, with permission.

A. In the depressed state, 5-HT<sub>1A</sub> somatodendritic autoreceptors may be up-regulated in a futile attempt to compensate for deficient serotonin neurotransmitter.

B. When a 5-HT<sub>1A</sub> partial agonist is administered acutely to a neuron in the depressed state, the somatodendritic presynaptic autoreceptors will experience an acute agonist effect, i.e., substitution of 5-HT<sub>1A</sub> partial agonist for 5-HT at these receptors will overcome the deficiency of 5-HT at these receptors. This could also be occurring at postsynaptic 5-HT<sub>1A</sub> partial agonist, at least initially. This may explain why there is no immediate antidepressant effect of 5-HT<sub>1A</sub> partial agonists. C. If 5-HT<sub>1A</sub> partial agonists are administered chronically, the sustained actions would cause a resensitization (i.e., down-regulation) of the somatodendritic autoreceptors back to normal.

D. The down-regulation of  $5\text{-HT}_{1A}$  somatodendritic autoreceptors by chronic administration of  $5\text{-HT}_{1A}$  partial agonists allows the neuron to turn its neuronal impulse flow back on and to increase its release of 5-HT. Theoretically, this would be associated with a normalization of function and a reduction in the symptoms of depression.

room, the partial agonist has acted as a net agonist, whereas in the brightly lit room, the partial agonist has acted as a net antagonist.

The presence of an agonist and an antagonist in the same molecule is a relatively new dimension in therapeutics. Using the serotonin example, this concept has led to suggestions that serotonin partial agonists could treat not only states that are theoretically deficient in serotonin (such as depression), but also states that theoretically have an excess of serotonin (such as anxiety). To some extent, this has been demonstrated for the marketed serotonin<sub>1A</sub> partial agonist buspirone.40,41 Investigators in some countries are, however, somewhat skeptical as yet about how powerful the anxiolytic effects of buspirone are compared with those of the benzodiazepines. Several other  $5-HT_{1A}$ compounds have shown promising efficacy, both in major depression and in GAD. Such agents may be particularly useful in mixed states of anxiety and depression. However, which degree of partiality is optimal is not yet established. In the case of serotonin agonists, an entire potency series of partial agonists, with a spectrum of partiality, is currently in clinical testing and may subsequently yield the answer to this question.

# Do Partial Agonists Work as Anxiolytics by Causing Serotonin Receptor Adaptations?

According to the theory of serotonin dysfunction in anxiety, the adaptations of the 5-HT<sub>1A</sub> somatodendritic autoreceptors are incapable of overcoming the excess in 5-HT and cannot correct the state of anxiety (Figure 2B). However, 5-HT<sub>1A</sub> partial agonists may act upon serotonin receptors and assist the neuron in correcting not only the hypothesized imbalances in serotonin, but also the hypothesized dysregulation of its receptors (Figure 3). These actions of the 5-HT<sub>1A</sub> partial agonists cause delayed adaptations in 5-HT<sub>1A</sub> receptors, which may also explain the delay in onset of anxiolytic effects of these drugs. In contrast, the benzodiazepines act almost immediately, thus suggesting that it is their acute changes in chloride conductance, and not delayed receptor adaptation, that account for their immediate therapeutic effects.

In terms of serotonin receptors, presynaptic somatodendritic 5-HT<sub>1A</sub> autoreceptors may be down-regulated in the anxious state (Figure 3), and serotonin may be in excess at these receptors (Figures 2 and 3). The down-regulated receptors are unable, however, to compensate adequately for the excessive amount of 5-HT available, and the patient is therefore anxious. Neuronal cell firing may be increased and 5-HT release augmented (Figure 3A).

When a 5-HT<sub>1A</sub> agonist is given acutely to an anxious patient, it competes with serotonin for the 5-HT<sub>1A</sub> receptors (Figure 3B). Instead of maximal stimulation of 5-HT<sub>1A</sub> receptors by excess serotonin, the addition of a 5-HT<sub>1A</sub> partial agonist causes a net reduction in the action at these receptors as the partial agonist is acting at these receptors in a partial and weaker manner than serotonin itself.<sup>6,42-55</sup> It might be predicted that such an action would cause a sudden reduction in anxiety. However, this does not occur. There is a simultaneous acute replacement of 5-HT by 5-HT<sub>1A</sub> agonist postsynaptically, and the net effect seen at the postsynaptic neuron at first is no change in net 5-HT activity at postsynaptic 5-HT<sub>1A</sub> receptors (Figure 3B).

However, if the 5-HT<sub>1A</sub> receptor partial agonist continues to exert net antagonistic actions with chronic treatment, this theoretically causes 5-HT<sub>1A</sub> somatodendritic receptors to return to a normal state (Figure 3B). This readaptation of somatodendritic autoreceptors in turn restores the ability of the 5-HT neuron to abolish its 5-HT neuronal impulse flow<sup>42–55</sup> and thereby causes relief of anxiety (Figure 3B). Interestingly, it does not appear that chronic drug treatment alters the sensitivity of postsynaptic 5-HT<sub>1A</sub> receptors.

### Can 5-HT<sub>IA</sub> Agonists Also Act as Antidepressants by Causing Mirror Image Adaptations in Serotonin Receptors?

In the case of  $5\text{-HT}_{1A}$  partial agonists given for treatment of depression, their actions can be conceived as mirror images of their actions in anxiety<sup>6,42–55</sup> (Figures 2, 3,

4A–B). It is interesting to note that these postulated 5-HT<sub>1A</sub> partial agonist effects in depression<sup>6,42–55</sup> are virtually the same as the actions suggested for serotonin selective reuptake inhibitors (SSRIs) in depression.<sup>6,56–64</sup>

Thus, in the depressed state, presynaptic somatodendritic 5-HT<sub>1A</sub> autoreceptors may be up-regulated (Figure 4) and serotonin may be deficient at these receptors (Figure 2). As already discussed, this is the mirror image of the status of these receptors proposed for anxiety. Upregulated receptors are unable to compensate adequately for the reduced amount of 5-HT available, and the patient is therefore depressed. Neuronal cell firing is diminished, and 5-HT release is decreased from such neurons.

In the case of the SSRIs, the drug is acting indirectly on the 5-HT<sub>1A</sub> receptor but directly at the reuptake pump to increase serotonin. It is this increased serotonin that, in turn, acts directly on 5-HT<sub>1A</sub> somatodendritic autoreceptors.<sup>6,56-64</sup> In the case of a 5-HT<sub>1A</sub> partial agonist, however, the drug acts directly as a "substitute" for serotonin at the 5-HT<sub>1A</sub> receptor.<sup>6,42-55</sup>

The postulated deficiency of serotonin in depression means that the direct agonist actions of  $5\text{-HT}_{1A}$  partial agonists at up-regulated somatodendritic autoreceptors (Figure 4B) might first decrease neuronal impulse flow, as would be expected from the function of this receptor. Indeed, this has been demonstrated with  $5\text{-HT}_{1A}$  agonists in experimental animals.<sup>42–55</sup> While this effect might be predicted to make depression worse, it appears that 5-HT impulse flow may already be so deficient in depressed patients that this effect is not observed, either with SSRIs or with  $5\text{-HT}_{1A}$ partial agonists. In addition, there is a simultaneous acute postsynaptic replacement of 5-HT by  $5\text{-HT}_{1A}$  agonist and thus, the net initial effect at the postsynaptic neuron is essentially unchanged in terms of 5-HT activity (Figure 4B).

However, maintaining stimulation of 5-HT<sub>1A</sub> somatodendritic autoreceptors with chronic 5-HT<sub>1A</sub> partial agonist treatment leads to functional down-regulation of these receptors (Figure 4B), and neuronal impulse flow is theoretically turned on (Figure 4B). In experimental animals, the acute suppression of neuronal impulse flow caused by a 5-HT<sub>1A</sub> agonist is lost upon chronic treatment as the autoreceptors are desensitized.<sup>42–55</sup> This could theoretically cause a delayed increase in serotonin release at the synapse and possibly down-regulation of postsynaptic 5-HT<sub>2A</sub> receptors, as seen with SSRI treatment.

Interestingly, only the presynaptic somatodendritic  $5\text{-HT}_{1A}$  autoreceptors, and not the postsynaptic  $5\text{-HT}_{1A}$  receptors, appear to be desensitized by chronic treatment with  $5\text{-HT}_{1A}$  partial agonists.<sup>42–55</sup> The  $5\text{-HT}_{1A}$  agonist is also competing postsynaptically for 5-HT, and this somewhat mitigates the effects of increased 5-HT release from enhanced neuronal impulse flow. However, the net action of increased 5-HT release overcomes this effect, resulting in a boost in 5-HT at postsynaptic receptors and relief of depression.

This theory therefore supports the notion of a pharmacologic cascading mechanism by which both 5-HT<sub>1A</sub> agonists, as well as SSRIs, may exert their therapeutic actions in depression. Hypothetically, this mechanism consists of a down-regulation of somatodendritic 5-HT<sub>1A</sub> autoreceptors, which thus restores neuronal impulse traffic in the 5-HT neurons and perhaps causes an increase in 5-HT release in axon terminal synapses with subsequent postsynaptic 5-HT<sub>2</sub> receptor down-regulation.<sup>6,42-64</sup> The 5-HT<sub>1A</sub> agonists act directly at the somatodendritic autoreceptor while the SSRIs cause 5-HT levels to increase so that 5-HT itself down-regulates the somatodendritic autoreceptor.

### CONCLUSIONS

These hypothetical mechanisms of action of serotonin<sub>IA</sub> partial agonists on serotonin receptors in anxiety—and the mirror image corollary for depression—are still theories. Nevertheless, they show how pharmacologic rationale can evolve from knowledge of how drugs affect receptors acutely to how those acute effects could be transposed by the neuron into some type of adaptive neurobiological effect that is therapeutic to the patient. Although the exact role of serotonin in anxiety and depression remains elusive and these theories are as yet unproved, they provide interesting hypotheses that generate significant research efforts into elucidating the exact role of serotonin receptor subtypes, not only in the biological basis of anxiety and depression, but also as potential mediators of the mechanism of action of anxiolytic and antidepressant drugs.

Drug name: buspirone (BuSpar)

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