Mechanism of Action of Trazodone: *a Multifunctional Drug*

Stephen M. Stahl, MD, PhD

NEW TREND IN PSYCHOPHARMACOLOGY

Multifunctional drugs are those with more than one therapeutic mechanism. Trazodone is a multifunctional drug with dose-dependent pharmacologic actions. That is, it has hypnotic actions at low doses due to blockade of 5-HT_{2A} receptors, as well as H_1 histamine receptors and α1 adrenergic receptors. Higher doses recruit the blockade of the serotonin transporter (SERT) and turn trazodone into an antidepressant. Although trazodone has traditionally been used as a low dose hypnotic, a new controlled release formulation that has the potential to improve the tolerability of high doses may provide an opportunity to revisit this multifunctional drug as an antidepressant as well.

INTRODUCTION

The concept of "multifunctional drugs" is rapidly taking hold in psychopharmacology.[1-4] Many drugs have more than one putative mechanism of therapeutic action and are multifunctional. By contrast, when an undesired pharmacologic action occurs at therapeutic doses, this is not a multifunctional drug but a "dirty drug." It is increasingly clear that most drugs with multifunctional therapeutic properties have different functions at different doses. Thus, the drug you get depends upon the dose you give. We have introduced the concept of multifunctional drugs in a previous article[1] and have applied this concept to the tricyclic antidepressant doxepin, which is a selective hypnotic/H_1 antagonist at very low doses and a multifunctional antidepressant at moderate to high doses.[5] Here we review another well known agent in psychopharmacology, trazodone, that is also a multifunctional drug: namely, it is a hypnotic at low doses and an antidepressant at high doses due to the manner in which different multifunctional binding properties apply at different doses.

OVERVIEW OF TRAZODONE PHARMACOLOGY

Trazodone is a good example of a dose dependent multifunctional drug in psychopharmacology. Low doses will only act via the most potent binding properties, but higher doses recruit additional pharmacologic actions and become

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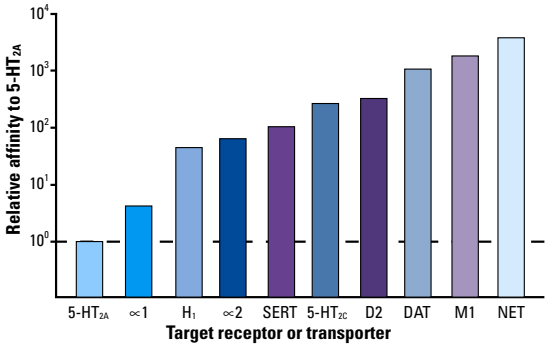
"multifunctional" with a different mixture of pharmacologic functions, depending upon how high a dose is given.

Trazodone's most potent binding property is 5-HT_{2A} antagonism. Its ability to block SERTs is 100 fold less potent than its ability to block 5-HT_{2A} receptors (Figures 1 and 2).[6-11] Since both of these actions are considered necessary for antidepressant efficacy, trazodone's multifunctional actions are sometimes categorized as "serotonin antagonist-reuptake inhibition" (SARI) (Figure 3A).[9] In order for trazodone to act as a multifunctional SARI, the effective antidepressant dose is pragmatically defined by trazodone's ability to target the weaker of these two binding properties, in this case, SERT blockade. This means in practice that in order for trazodone to act as a SARI, it must be administered at a dose that is ten to fifty fold higher than that necessary for blocking 5-HT_{2A} receptors (Figure 2).[6-11]

Other clinically relevant pharmacologic actions of trazodone are those at receptors where trazodone has moderate affinity, namely those with binding affinities between those it has for blocking 5-HT_{2A} receptors and SERT. These properties include blocking α1 adrenergic receptors and histamine H_1 receptors (Figures 1 and 2).[6-11] At the high doses necessary to block SERTs, actions of trazodone at other receptors with affinity in the range of SERT blockade might also be clinically relevant, such as blockade of α2 adrenergic receptors and 5-HT_{2C} receptors (Figure 1). When this happens, such actions may contribute to trazodone's antidepressant efficacy. 5-HT_{2C} antagonism is now known to be a property of several current antidepressants, including trazodone, mirtazapine, several tricyclic antidepressants, and the active metabolite of quetiapine, norquetiapine.[9,12] 5-HT_{2C} antagonism is also a property of several novel antidepressants including agomelatine.[9,12-15] α2 antagonism is a property of the known antidepressant mirtazapine.[9] Trazodone's actions at other monoamine transporters, such as the dopamine transporter (DAT) and the norepinephrine transporter (NET) are probably too weak to have clinical relevance (Figure 1).

Trazodone is converted into an active metabolite known as meta-chloro-phenyl piperazine (mCPP).[16-20] This agent has high affinity for a number of serotonin receptors, including $5HT_{2C}>5HT_3>5HT_{2A}>5HT_{1B}>5HT_{1A}>5HT_{1D}$, where it functions mostly as an agonist[18-20] in contrast to trazodone which acts as an antagonist at 5-HT_{2A} and 5-HT_{2C} receptors.[6-11] These pharma-

FIGURE 1.
Relative binding affinities of trazodone[3-11]



Shown are the affinities of trazodone for numerous neurotransmitter receptors and transporters. The most potent action is on 5-HT_{2A} receptors, where it functions as an antagonist. The horizontal line allows comparison of relative affinities of trazodone to other receptors and transporters for which it has lower affinity than for 5-HT_{2A} receptors.

5-HT_{2A}=serotonin 2A receptor; α1=α1 adrenergic receptor; H_1=histamine 1 receptor; α2=α2 adrenergic receptor; SERT=serotonin transporter; 5-HT_{2C}=serotonin 2C receptor; D2=dopamine 2 receptor; DAT=dopamine transporter; M1=muscarinic 1 cholinergic receptor; NET=norepinephrine transporter.

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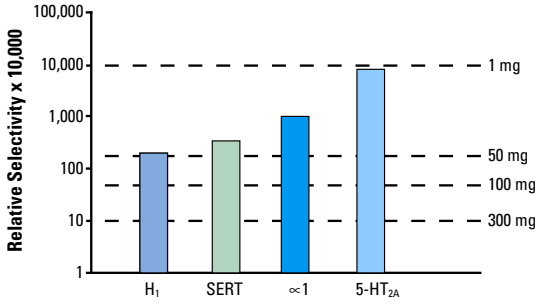
FIGURE 2.
Relative selectivities of trazodone at different doses[3-11]



Shown are the relative selectivities of trazodone for four key binding sites: the 5-HT_{2A} receptor, the α1 adrenergic receptor, SERT, and H_1. In contrast to Figure 1 which shows affinities, this shows relative selectivities, with the highest bars being the most selective actions of trazodone. For example, plasma trazodone concentrations after oral administration in humans,[21,22,40] predict that 1 mg of trazodone will occupy about half of 5-HT_{2A} receptors (ie, the top of the 5-HT_{2A} bar). The hypnotic dose of trazodone, ~50 mg, will fully saturate 5-HT_{2A} receptors, most of α1 adrenergic receptors, and about half of H_1 receptors and SERT. This is adequate for hypnotic dosing. However, it takes saturating doses for SERT (ie, about 300 mg) to attain antidepressant actions.

H_1=histamine 1 receptor; SERT=serotonin transporter; α1=α1 adrenergic receptor; 5-HT_{2A}=serotonin 2A receptor.

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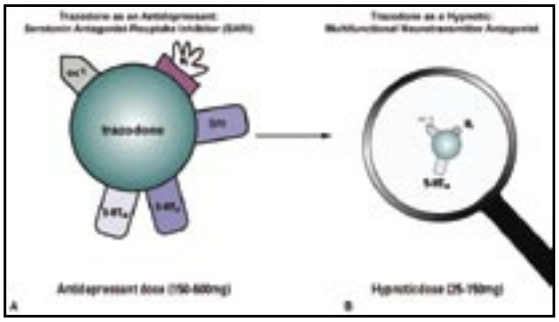
cologic actions of mCPP may contribute to the net pharmacologic effects of trazodone, and could theoretically mitigate trazodone's direct antagonist actions at 5-HT_{2A} and 5-HT_{2C} receptors. However, plasma and brain levels of mCPP appear to be less than 10% of those of trazodone itself.[21-22] Thus, the antagonist actions of trazodone are likely to overwhelm any effects of mCPP and block any agonist actions that mCPP may have at 5HT_{2A} and 5-HT_{2C} receptors.

FIGURE 3.
Trazodone as an antidepressant and as a hypnotic



A) High doses that recruit saturation of SERT at 150–600 mg of trazodone are required for antidepressant actions. At this high antidepressant dose, trazodone is a multifunctional serotonergic agent with antagonist actions at 5-HT_{2A} and 5-HT_{2C} receptors as well. Thus, its antidepressant actions are attributed to these serotonergic properties and trazodone is a multifunctional SARI. It is also an α1 and H_1 antagonist at these doses.

B) Lower doses of trazodone in the 25–150 mg range lose saturation of SERT, and thus lose antidepressant actions while retaining multifunction antagonist actions at 5-HT_{2A}, H_1 and α1 receptors, and hypnotic efficacy.

α1=α1 adrenergic receptor; H_1=histamine 1 receptor; SRI=serotonin reuptake inhibitor; 5-HT_{2C}=serotonin 2C receptor; 5-HT_{2A}=serotonin 2A receptor; SERT=serotonin transporter; SARI=serotonin antagonist-reuptake inhibitor.

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TABLE.
Possible Functions of Postsynaptic Serotonin Receptors

5HT$_{1A}$	*5HT$_{2A}$*	*5HT$_{2C}$*
Antidepressant Anxiolytic Pro-cognitive Hormone regulation	Sleep Sexual function Anxiety Regulation of dopamine release	Sleep Sexual function Anxiety Appetite, obesity Regulation of dopamine and norepinephrine release
None	Regulation of glutamate release	Regulation of glutamate release
Inhibition of cortical pyramidal neurons	Excitation of cortical pyramidal neurons	None

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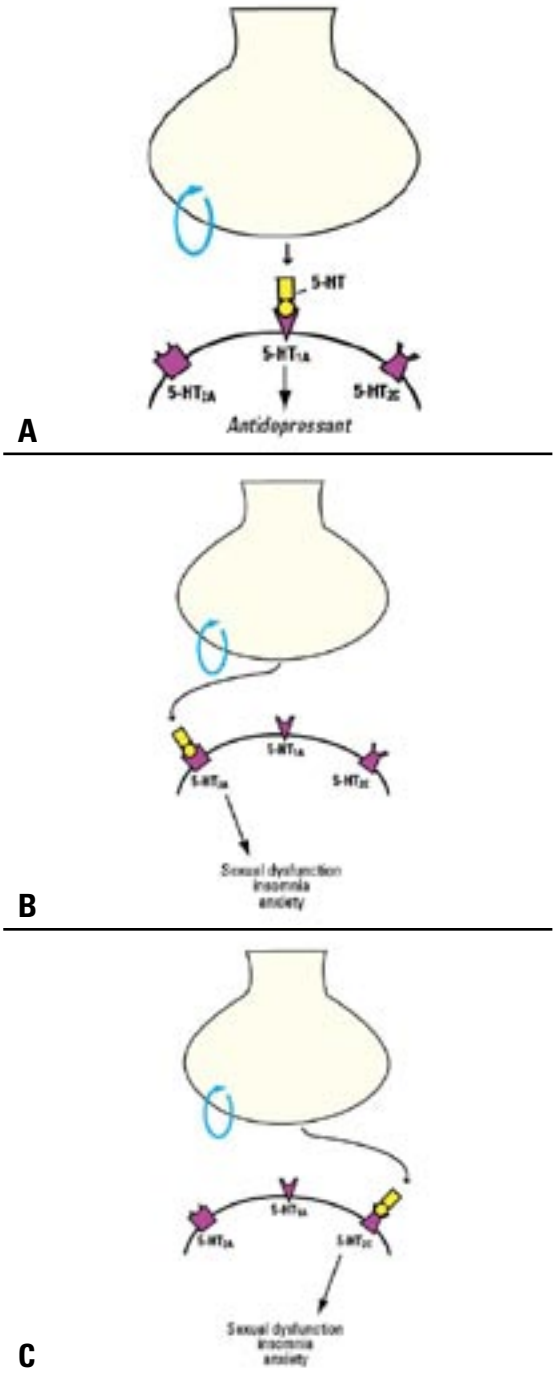
DIFFERENTIATION OF TRAZODONE FROM SSRIS/SNRIS

Dosed properly for the treatment of depression (Figures 2 and 3), trazodone acting as a SARI blocks SERT just like the serotonin selective reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs). However, unlike SSRIs and SNRIs, trazodone simultaneously blocks 5-HT_{2A} receptors and to a lesser extent, 5-HT_{2C} receptors (Figure 1), a key differentiating feature with major clinical implications, especially in terms of tolerability.

There are over 14 known subtypes of serotonin receptors,[9] and when SERT is blocked, serotonin itself acts promiscuously to stimulate all of these receptors at any site where serotonin is increased. A good deal of preclinical evidence suggests that it is the agonist actions of serotonin specifically upon 5-HT_{1A} receptors that account for the therapeutic effects of SSRIs/SNRIs (Table; Figures 4A, 5, and 6).[9] Unfortunately, agonist actions of serotonin at other receptor subtypes are thought to be the cause of numerous side effects of blockers of SERT (Table; Figures 4B, 4C, 5, and 6). These potentially unwanted agonist actions at unwanted serotonin receptor subtypes may be the "cost of doing business" by SSRIs/SNRIs. Fortunately, over time, these other receptors often desensitize, at least in some patients, with tolerance developing to some of the side effects that their stimulation causes.

Insight into the specific consequences of stimulating or blocking various serotonin receptor subtypes comes from studies that link specific functions to each different receptor subtype (Table).[9] Thus, stimulating 5-HT_{1A} receptors theoretically leads to antidepressant effects (Figures 4A, 5, 6, and 7). Antidepressant actions of drugs that inhibit SERT are possibly mediated via presynaptic and postsynaptic 5-HT_{1A} receptors (Figures 4A and 5).[9] Hypothetically, presynaptic 5-HT_{1A} somatodendritic autoreceptors desensitize over time following the administration of a SERT inhibitor, leading to enhanced 5-HT release (Figure 5).[9] This eventually leads to the delivery of more serotonin into the synapse, with consequent antidepressant actions (Figure 5). It does not appear that postsynaptic

FIGURE 4.
The theoretical functions linked to 3 key serotonin receptors



Stimulating 5-HT_{1A} receptors is linked to antidepressant actions (A) whereas stimulation of 5-HT_{2A} receptors (B) and 5-HT_{2C} receptors (C) are linked to the side effects of sexual dysfundtion, insomnia and anxiety.

5-$HT_{1A/2A/2C}$=serotonin 1A, 2A, or 2C receptor.

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5-HT_{1A} receptors desensitize so antidepressant efficacy is generally sustained (Figure 5). However, antidepressant efficacy of SSRIs/SNRIs is lost over time in some patients, a phenomenon sometimes called "poop-out." Hypothetically, unwanted desensitization of post synaptic 5-HT_{1A} receptors could be linked to this loss of efficacy after long term drug administration.

Postsynaptic 5-HT_{2A} and 5-HT_{2C} receptors often desensitize as well in many patients after long term administration of SSRIs/SNRIs, hypothetically leading to abatement of some side effects linked to these receptors, especially anxiety (Figures 4B, 4C, and 5). Insomnia, on the other hand, is not as readily improved after long term treatment with SSRIs/SNRIs and in fact is the most common residual symptom after treatment with these agents.[9] Sexual dysfunction can wane with chronic administration of SSRIs/SNRIs but in many patients is a persistent problem.

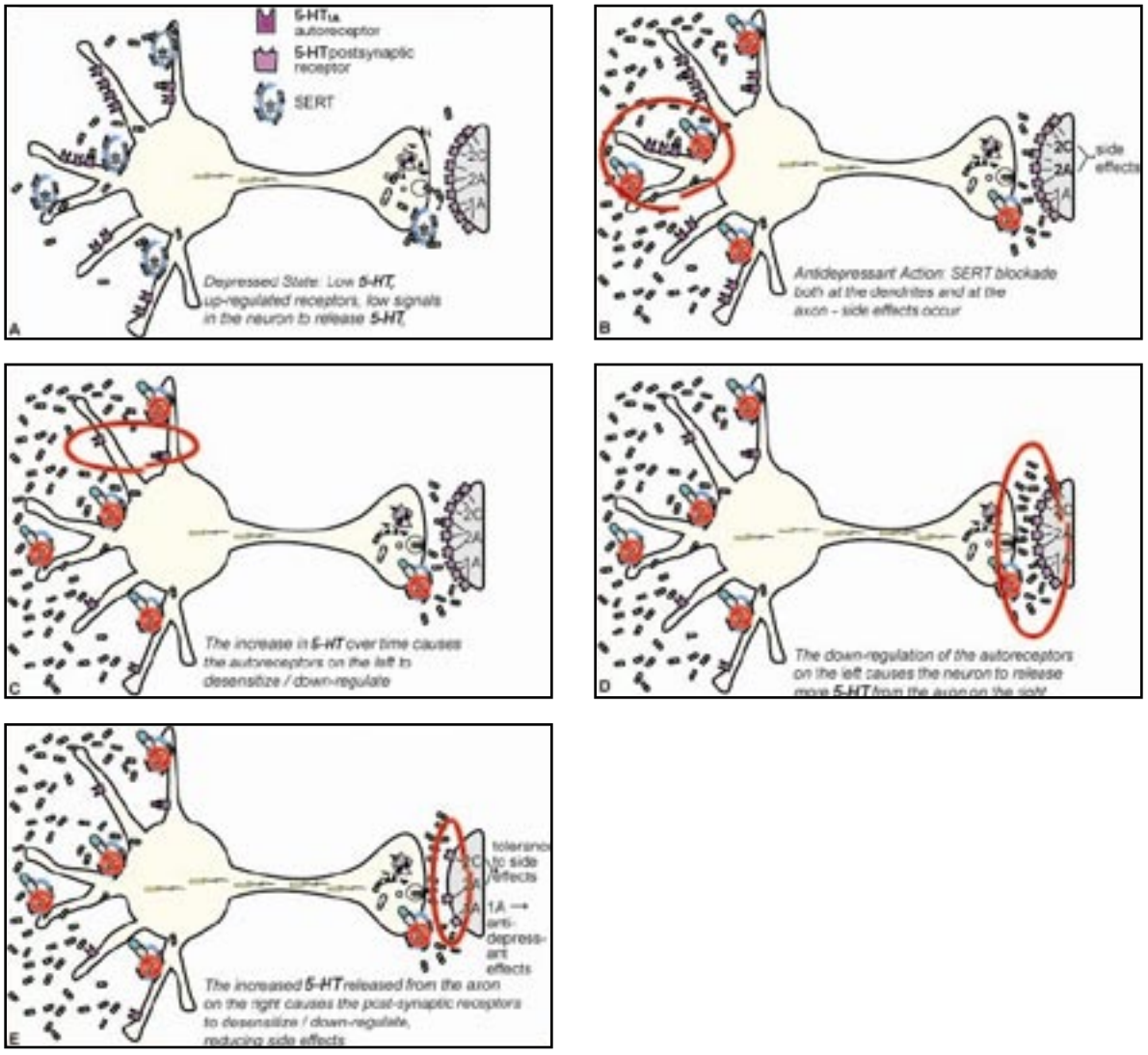
In summary, by raising serotonin at all serotonin receptors and in all brain areas, SERT inhibitors such as SSRIs and SNRIs simultaneously cause antidepressant actions by stimulating 5-HT_{1A} receptors, but side effects by stimulating 5-HT_{2A} and 5-HT_{2C} receptors (Figures 4 and 6). However, when SERT inhibition is combined with 5-$HT_{2A/2C}$ inhibition, this leads to antidepressant actions without sexual dysfunction, anxiety, or insomnia (Figure 7). Simultaneous blocking of 5-HT_{2A} and 5-HT_{2C} receptors with the SARI trazodone when SSRIs/SNRIs are administered can also potentially treat the insomnia and anxiety associated with depression itself as well as prevent that caused by SERT inhibition. Clinical experience has long validated the improved tolerability of SSRIs/SNRIs by simultaneously blocking 5-HT_{2A}/5-HT_{2C} receptors, and may account for why low dose trazodone is one of the most frequently prescribed concomitant agents along with an SSRI/SNRI.[9]

MECHANISM OF TRAZODONE AS A LOW DOSE HYPNOTIC

Trazodone is approved as a high dose antidepressant but is more commonly used "off label" as a low dose hypnotic.[9,23] In fact, prescribing low dose trazodone as a hypnotic may be the most frequent off label use of a drug in all of psychopharmacology.[23] Off label use does not mean that such prescribing is a bad thing, despite what some formularies or critics say. It just means that the Food and Drug Administration has not approved

this therapeutic use. The FDA regulates the sale of medicine, not the practice of medicine, and does not proscribe the use of trazodone as a hypnotic. The practice of medicine is set instead by community standards of care, experts, and guidelines, and in clinical practice trazodone has

FIGURE 5.
Mechanism of action of antidepressants that block SERT (SSRIs, SNRIs)



A. Prior to treatment, in the depressed state, serotonin levels may be low and serotonin receptors may be upregulated.

B. When SERT inhibitors are first given, they block SERTs everywhere, but have the greatest amount of serotonin release on the left, in the somatodendritic area. On the right, the increased serotonin in the synapse only causes side effects at 5-HT_{2A} and 5-HT_{2C} receptors, but not yet therapeutic effects at 5-HT_{1A} receptors.

C. With time, the 5-HT_{1A} receptors on the left down regulate.

D. The down regulation of these 5-HT_{1A} somatodendritic autoreceptors on the left now leads to a disinhibited serotonin neuron, with increased neuronal impulse flow and increased serotonin release in the synapse on the right. Side effects continue but antidepressant effects are just beginning.

E. This increased synaptic serotonin on the right finally has antidepressant actions theoretically via post synaptic 5-HT_{1A} receptors and if the 5-HT_{2A} and 5-HT_{2C} receptors down regulate, the side effects that they mediate may begin to show tolerance.

SSRI=selective serotonin reuptake inhibitor; SNRI=serotonin norepinephrine reuptake inhibitor; 5-$HT_{1A/2A/2C}$=serotonin 1A, 2A, or 2C receptor; SERT=serotonin transporter.

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become accepted as perhaps the most popular hypnotic in the United States.[23]

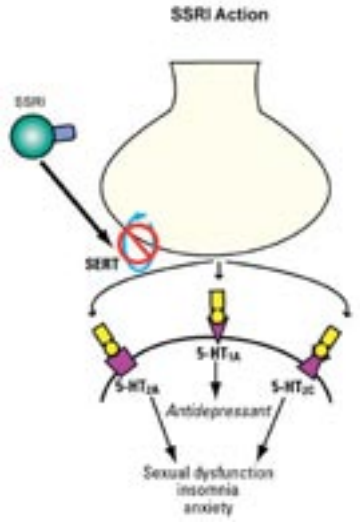
Since trazodone is most potent in blocking 5-HT_{2A} receptors, one might think that this action alone could account for its low dose hypnotic efficacy. Indeed, the selective 5-HT_{2A} antagonist eplivanserin has been shown to have therapeutic actions on sleep maintenance and the approval of eplivanserin for this use is pending in several markets at the present time.[24] However, eplivanserin does not appear to have robust actions in causing sleep onset.[24] By contrast, trazodone does promote sleep onset as well as sleep maintenance, but at doses considerably higher than those necessary to saturate 5-HT_{2A} receptors.

Roughly half of brain 5-HT_{2A} receptors are blocked by 1 mg of trazodone (ie, at Kd; see Figure 2, top dotted line), and essentially all 5-HT_{2A} receptors are saturated at 10 mg of trazodone (ie, at 10x Kd), but the clinically effective hypnotic doses of trazodone are in the 25–100 mg range (Figure 2, second from the top dotted line). Thus, it appears that doses higher than those that cause selective 5-HT_{2A} antagonist actions are necessary for the hypnotic actions of trazodone. The receptor binding profile of trazodone shows that increasing the dose beyond saturation of 5-HT_{2A} receptors recruits additional pharmacologic actions, specifically blockade of α1 adrenergic receptors and H_1 histamine receptors as well. This makes low dose trazodone a multifunctional drug with 5-HT_{2A}, α1 adrenergic and H_1 histamine antagonist properties (Figure 3B).

Such a profile should indeed create an effective hypnotic on theoretical grounds, since arousal mechanisms are known to involve the actions of several neurotransmitter systems in addition to serotonin, including norepinephrine, dopamine, acetylcholine, and histamine.[5,9,25] Blocking several of these systems simultaneously can impair arousal and induce sleep. In fact, selective blockade of the histamine system alone can be enough for robust hypnotic actions as was discussed in a companion article in this series on multifunctional drugs with H_1 antihistamine properties.[5] Adding additional antagonist actions at α1 adrenergic and 5-HT_{2A} receptors should enhance this sleep inducing effect of H_1 blockade.[5,9,25]

Thus, the hypnotic dose of trazodone is sufficient to saturate all 5-HT_{2A} receptors (>10x Kd),

FIGURE 6.
SSRI/SNRI action



SERT inhibition by SSRI/SNRI action at the presynaptic neuron increases 5-HT at all receptors, with 5-HT_{1A} mediated antidepressant actions but 5-HT_{2A} and 5-HT_{2C} mediated sexual dysfunction, insomnia and anxiety.

SSRI=selective serotonin reuptake inhibitor; 5-$HT_{1A/2A/2C}$=serotonin 1A, 2A, or 2C receptor; SERT=serotonin transporter.

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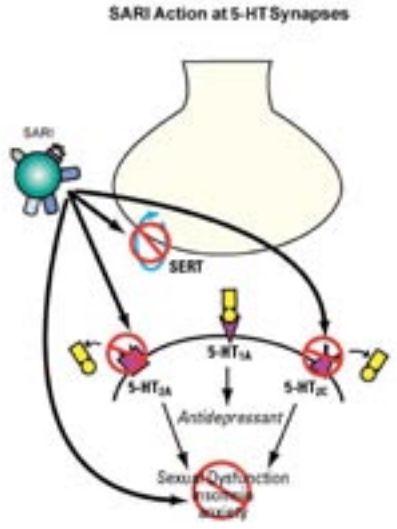
FIGURE 7.
SARI action



SERT inhibition by SARI action at the presynaptic neuron increases 5-HT only at 5-HT_{1A} receptors, where it leads to antidepressant actions, but SARI action also blocks 5-HT actions at 5-HT_{2A} and 5-HT_{2C} receptors, failing to cause sexual dysfunction, insomnia, or anxiety. In fact these blocking actions at 5-HT_{2A} and 5-HT_{2C} receptors can improve insomnia and anxiety, and theoretically can exert antidepressant actions of their own.

SARI=serotonin antagonist-reuptake inhibitor; 5-$HT_{1A/2A/2C}$=serotonin 1A, 2A, or 2C receptor; SERT=serotonin transporter.

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and to block half or more of H_1, and α1 receptors (~1x Kd for these receptors) (Figure 2). Blocking half of these receptors definitely contributes to hypnotic activity.[26] While SERT is also blocked by about 50% at hypnotic doses of trazodone (ie, at 1x Kd for SERT in Figure 2), this is not sufficient for antidepressant actions. In fact, many studies have shown that the SSRIs/SNRIs must be dosed so that SERT is nearly completely saturated in order to attain antidepressant actions in depressed patients.[9] Hypnotic doses are insufficient for this degree of action at SERT, which is why they are too low for antidepressant effects.

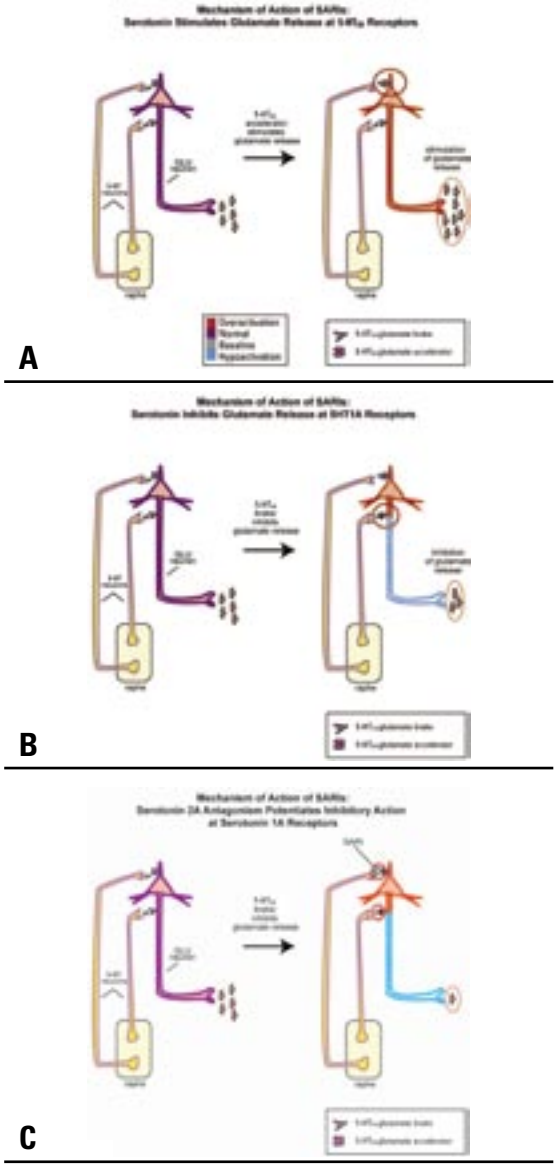
In summary, 5-HT_{2A} antagonism plus H_1 antihistamine and α1 adrenergic antagonism theoretically explain the therapeutic actions of trazodone as a hypnotic in the 25–150 mg dose range (Figures 2 and 3B). Combine this with the fact that trazodone does not cause dependence and has a relatively short half life, and in many ways, you have an ideal hypnotic agent.

MECHANISM OF ACTION AS A HIGH DOSE ANTIDEPRESSANT

It takes high doses of 150–600 mg to turn trazodone into a powerful SERT inhibitor (Figures 1, 2, and 3A).[9,23] At these high doses, SERT is inhibited to the extent required of an antidepressant, ie, greater than 70% to 80% if not complete saturation. Put differently, high doses recruit the additional action of SERT inhibition to 5-HT_{2A} antagonism, adding yet another pharmacologic mechanism to the portfolio of multifunctional properties of trazodone once it reaches this dose.

There are now theoretical reasons to suggest how 5-HT_{2A} antagonists and 5-HT_{2C} antagonists can also have antidepressant actions as well as the enhanced tolerability actions described above. Such considerations even suggest the possibility that added together, SERT inhibition plus 5-$HT_{2A/2C}$ antagonism would have synergistic antidepressant actions.[27-38] One potential neurobiological substrate for antidepressant synergy between 5-HT_{2A} antagonism and SERT inhibition comes from the opposing actions of serotonin at prefrontal cortex pyramidal neurons (Figure 8).[9,36] When SSRIs/SNRIs lead to increased release of serotonin in the prefrontal cortex, this serotonin exerts contradictory actions at postsynaptic 5-HT_{1A} receptors and 5-HT_{2A} receptors (Figure 8).[9,36] That is, serotonin inhibits pyramidal neurons in the prefrontal cortex at 5-HT_{1A} receptors (Figure 8B) and

FIGURE 8.
Mechanism of action of SARIs



A pyramidal neuron in the prefrontal cortex releasing glutamate and receiving input from two serotonin neurons projecting from the raphe.

A. Normally, serotonin stimulates glutamate release at 5-HT_{2A} receptors on pyramidal neurons, and thus the 5-HT_{2A} receptor is sometimes called a serotonin accelerator, leading to stimulation of glutamate release from the pyramidal neuron on the far right.

B. Normally, serotonin inhibits glutamate release at 5-HT_{1A} receptors on pyramidal neurons and thus the 5-HT_{1A} receptor is sometimes called a serotonin brake, leading to inhibition of glutamate release from the pyramidal neuron on the far right.

C. In the case of a SARI, serotonin is increased at the 5-HT_{1A} receptor due to inhibition of the serotonin transporter SERT, but serotonin is blocked at the 5-HT_{2A} receptor due to direct actions of the drug. The net outcome is that the 5-HT_{2A} antagonism potentiates the inhibitory action of 5-HT_{1A} receptor stimulation and the inhibition of glutamate from pyramidal neurons is potentiated, on the far right.

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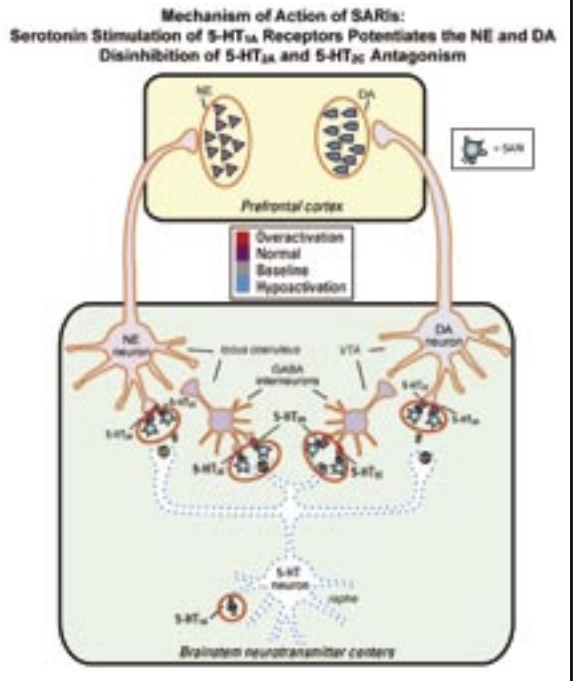
excites these same neurons at 5-HT_{2A} receptors (Figure 8A). The balance between these two actions determines whether there is net excitation or net inhibition of a pyramidal neuron by serotonin. Theoretically, therapeutic actions of serotonergic antidepressants may be linked to reduction of overactive cortical pyramidal neurons in depression[9] and thus antidepressants may act in part by inhibiting these prefrontal cortex pyramidal neurons, reducing the release of glutamate downstream.

Thus, when serotonin levels rise after SERT inhibition, 5-HT_{2A} receptors will excite pyramidal neurons and thus mitigate the theoretically desirable 5-HT_{1A} mediated inhibition of these neurons (Figure 8A and 8B). On the other hand, when 5-HT_{2A} receptors are blocked at the same time that 5HT1A receptors are activated, this potentiates rather than reduces the inhibition of cortical pyramidal neurons (Figure 8C), hypothetically mediating synergistic antidepressant effects.[9,27-30]

FIGURE 9.
Mechanism of action of SARIs as possible antidepressants by potentiating the release of dopamine and norepinephrine in prefrontal cortex



Noramlly, serotonin (at the bottom) regulates both NE and DA release. It does this via 5-HT_{2A} receptors and 5-HT_{2C} receptors that either directly or indirectly inhibit NE and DA release. If a SARI blocks this inhibition by 5-HT_{2A} and/or 5-HT_{2C} antagonism, this disinhibits the NE and DA neurons, resulting in potentiated release of these neurontransmitters in prefrontal cortex (red circles at the top).

SARIs=serotonin antagonist-reuptake inhibitors; 5-$HT_{1A/2A/2C}$=serotonin 1A, 2A, or 2C receptor; NE=norepinephrine; DA=dopamine.

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Another mechanism whereby 5-$HT_{2A/2C}$ antagonists could mediate antidepressant effects is by raising the levels of the neurotransmitters dopamine and norepinephrine in the prefrontal cortex.[4,9,12,15,31-35] This mechanism has been postulated to explain in part the antidepressant actions of some atypical antipsychotics with 5-HT_{2A} antagonist properties,[2,9,12,28] as well as the antidepressant properties of the 5-HT_{2C} antagonists agomelatine and quetiapine (via its active metabolite norquetiapine).[4,9,12] 5-HT_{2A} and 5-HT_{2C} receptors regulate the release of dopamine and norepinephrine in the cortex, generally inhibiting the release of these neurotransmitters, sometimes via an inhibitory GABA-ergic interneuron.[31-38] When this inhibition is blocked by a 5-$HT_{2A/2C}$ antagonist such as the SARI trazodone, this disinhibits both dopamine and norepinephrine release in prefrontal cortex, potentially mediating antidepressant effects (Figure 9).[9]

These various pharmacological mechanisms which suggest the way in which 5-$HT_{2A/2C}$ antagonists could be antidepressants in themselves, and especially the possibility that these mechanisms could exert synergistic antidepressant actions along with simultaneous SERT inhibition are still just theoretical considerations. No clinical trials prove that adding 5-$HT_{2A/2C}$ antagonism to SSRI/SNRI action potentiates antidepressant effects in depressed patients. Nevertheless, this notion is consistent with observations that atypical antipsychotics, which have 5-HT_{2A} antagonist effects as a prominent property, do potentiate the actions of SSRIs/SNRIs in certain depressed patients,[9,23] especially those who have treatment resistant depression,[23] and the observation that several agents with 5-HT_{2C} antagonist actions are approved antidepressants.[4,9,12]

PHARMACOKINETICS OF TRAZODONE: *COMPARING IMMEDIATE RELEASE AND SUSTAINED RELEASE FORMULATIONS*

If high doses recruit the critical SERT inhibition to make trazodone an antidepressant, and high doses also recruit 5-HT_{2C} antagonism, which combined with 5-HT_{2A} antagonism has multiple theoretical mechanisms by which the antidepressant actions and tolerability of SERT inhibition could be enhanced, why don't clini-

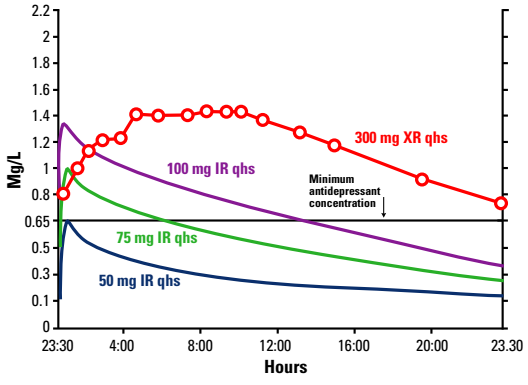
cians just raise the dose and turn trazodone into an antidepressant? Why instead is trazodone much more commonly prescribed at low doses simultaneously with an SSRI/SNRI than it is prescribed as a monotherapy at high doses?

Part of the answer to this question is that trazodone has been a generic drug during the era of extensive promotional activities of SSRIs/SNRIs. However, there is a major clinical reason why trazodone is not used more frequently as a high dose monotherapy for the treatment of depression: it is often too sedating during the day when given in antidepressant doses.

Traditional trazodone exists as a short acting "immediate release" (IR) formulation that rapidly generates peak drug levels, which rapidly decline (Figure 10).[16,17,21,22,39] Figure 10 shows steady state levels of trazodone IR at 50, 75, and 100 mg dosing at qhs after 9 days, calculated by pharmacokinetic modeling.[39] Rapidly rising peak levels between 0.65 and 1.3 mg/L[39] are associated with robust hypnotic actions, that do not apparently show tolerance over time and do not often show any "hangover" sedation the next morning.[23] Rapid, unsustained plasma levels are ideal for a hypnotic and pulsatile drug delivery is a desired property so that it does not cause tolerance.[9] No wonder trazodone IR is an excellent hypnotic.

Also shown in Figure 10 is the minimum concentration of trazodone which several studies have suggested is required for antidepressant action (the line at 0.65 mg/L).[21,22,40] Hypnotic doses briefly if ever reach these levels. That is why hypnotic doses are not adequate for antidepressant dosing. For comparison purposes, the plasma drug levels are shown when a new once a day formulation, trazodone extended release (XR) is given at a dose of 300 mg qhs (Figures 10 and 11).[39] Firstly, the manner of drug delivery for the XR formulation is slowly rising and slowly falling, with sustained levels above the minimum antidepressant concentration and with peak plasma trazodone levels in the same range generated by only 100 mg of trazodone IR.[39] Thus, trazodone XR at 300 mg should provide sufficient and constant blood levels of trazodone for antidepressant actions, yet might theoretically be no more sedating than 100 mg of trazodone IR. Furthermore, the sustained blood levels generated by trazodone XR are theoretically ideal for

FIGURE 10.
Trazodone IR vs trazodone XR given once nightly[39]



Shown here are steady state estimates of the plasma trazodone levels from the hypnotic dosing of 50, 75, or 100 mg qhs of IR trazodone given for 9 days. Peak drug concentrations are reached rapidly with a similarly rapid fall off over the night. The minimum levels estimated for antidepressant actions of trazodone[21,22,40] are reached transiently if at all by hypnotic dosing. By contrast, 300 mg of trazodone XR given once nightly generates plasma trazodone levels that rise slowly and never fall below minimum antidepressant concentrations.[39] Peak levels of trazodone XR at 300 mg are about the same as the peak levels of 100 mg of trazodone IR.

IR=immediate release; XR=extended release.

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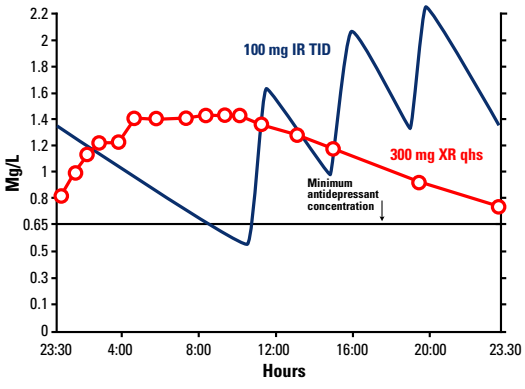
FIGURE 11.
Comparison of antidepressant dosing of trazodone IR and trazodone XR[39]



Trazodone IR given as 100 mg three times a day at steady state after 9 days generates a saw tooth pattern of plasma drug levels that often greatly surpass the minimum antidepressant concentration necessary for trazodone, yet do not sustain drug levels above this concentration all night long. This generates more than needed amounts of trazodone during some hours of the day with possible side effects such as sedation, while less than needed amounts of trazodone during some hours of the day with possible reduction in antidepressant efficacy. By contrast, the same amount of trazodone given once a day as a 300 mg XR formulation at night generates a smoothly rising pattern of plasma drug levels, always sustained above the minimum antidepressant concentration, and with much lower peak levels compared to the same total daily dose of trazodone IR.

IR=immediate release; XR=extended release.

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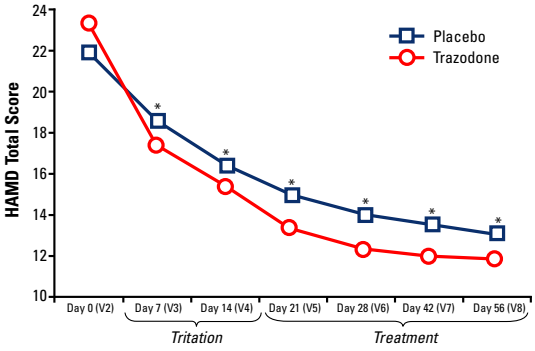
causing tolerance to the side effect of sedation, as opposed to short term pulsatile delivery with trazodone IR where no tolerance to the therapeutic effect of sedation would be desired.

Quantification of the pharmacokinetics of trazodone IR administered in the antidepressant dose of 300 mg per day as 100 mg TID is shown in Figure 11.[39] In this case, 100 mg TID of trazodone IR creates a saw tooth pattern of plasma trazodone concentrations, with levels generally far higher than the minimum antidepressant concentration for most of the day, yet with plasma drug levels nevertheless falling overnight to below the minimum required antidepressant concentration prior to the morning dose.[39] These very high levels of trazodone during some parts of the day from antidepressant dosing surpass by two to three fold those levels generated by hypotic dosing (compare peaks of trazodone IR in Figures 10 and 11). No wonder trazodone IR given as 100 mg TID can have unacceptable daytime sedation in some patients. Add to this the inconvenience of multiple daytime dosing, and it is understandable why the acceptability of trazodone IR in doses adequate for antidepressant efficacy has been limited.

FIGURE 12.
Trazodone XR vs placebo in a randomized double blind placebo controlled study of major depressive disorder[41]



412 patients were randomized, 406 received at least 1 dose of study medication, with 202 patients in the trazodone XR group and 204 in the placebo group. A total of 105 of the 412 patients prematurely discontinued the study. A two week titration period to trazodone 150, 225, 300, or 375 mg daily versus placebo was followed by 42 days of treatment at the titrated dose. At the end of the two week titration period the mean maximum daily dosage was 310 mg for the trazodone XR group and 355 mg for the placebo group. There was a significantly greater improvement in the mean HAM-D 17 total score in the trazodone XR group compared with placebo by the first week of the double blind phase (day 7 of titration) which was maintained thoughout the trial (P<.005, LOCF).

IR=immediate release; XR=extended release; HAM-D=Hamilton Rating Scale for Depression; LOCF=last observation carried forward.

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The plasma drug levels of trazodone XR given as 300 mg qhs, are also shown in Figure 11, just as they were in Figure 10 for comparison purposes.[39] Trazodone XR attempts to thread the needle with blood levels sustained above the minimum antidepressant concentration yet without the pulsatile drug delivery with unnecessarily high trazodone plasma levels in a saw tooth pattern characteristic of trazodone IR given three times a day (Figure 11). The pharmacokinetic profile of trazdone XR suggests that it should have fewer peak dose side effects, yet comparable antidepressant efficacy, to the proven antidepressant dosing of 100 mg of trazodone IR TID.

In fact, this new formulation of trazodone XR has been tested in depressed patients with a surprisingly low incidence of sedation (Figure 12).[41] Since no head to head comparisons of the tolerability of trazodone IR with trazodone XR have been performed to date, it will take use in clinical practice settings to determine whether the tolerability of trazodone XR is a significant improvement, particularly for daytime sedation, over trazodone IR. Nevertheless, trazodone XR has been studied against placebo with statistically significant efficacy[41] (Figure 12) and has now been submitted for approved by the FDA for marketing in the US. The XR strategy may provide the best option for raising the dose of trazodone sufficiently to become an antidepressant while retaining adequate tolerability in terms of low degrees of daytime sedation compared to trazodone IR. Trazodone XR also has a low incidence of anxiety, insomnia, and sexual dysfunction,[41] so it can create another option for depressed patients on SSRIs/SNRIs who are unable to tolerate those medications due to such side effects.

CONCLUSION

Trazodone is an old friend in psychopharmacology, now seen as a multifunctional drug with pharmacologic actions at low doses making it a hypnotic and additional multifunctional pharmacologic actions at high doses making it an antidepressant. The IR formulation of trazodone is preferred for hypnotic use, whereas the new controlled release formulation of trazodone XR may be preferred for antidepressant use. Trazodone XR should theoretically allow adequate dose escalation to administer high doses for antidepressant action while avoiding sedation of the immediate release formulation. As an antidepressant, trazodone should be as effective

as SSRIs/SNRIs,[42,43] yet have a low incidence of anxiety, insomnia and sexual dysfunction, the properties expected for a multifunctional SARI.

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