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The Augmentation Hypothesis for Improvement of Antidepressant Therapy

Is Pindolol a Suitable Candidate for Testing the Ability of 5HT$_{1A}$ Receptor Antagonists to Enhance SSRI Efficacy and Onset Latency?

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Abstract

The development of selective serotonin reuptake inhibitors (SSRIs) provided a major advancement in the treatment of depression. However, these drugs suffer from a variety of drawbacks, most notably a delay in the onset of efficacy. One hypothesis suggests that this delay in efficacy is due to a paradoxical decrease in serotonergic (5-HT) neuronal impulse flow and release, following activation of inhibitory presynaptic 5-HT$_{1A}$ autoreceptors, following acute administration of SSRIs. According to the hypothesis, efficacy is seen only when this impulse flow is restored following desensitization of 5-HT$_{1A}$ autoreceptors and coincident increases in postsynaptic 5-HT levels are achieved. Clinical proof of this principal has been suggested in studies that found a significant augmenting effect when the β-adrenergic/5-HT$_{1A}$ receptor antagonist, pindolol, was coadministered with SSRI treatment. In this article, we review preclinical electrophysiological and microdialysis studies that have examined this desensitization hypothesis. We further discuss clinical studies that utilized pindolol as a test of this hypothesis in depressed patients and examine preclinical studies that challenge the notion that the beneficial effect of pindolol is due to functional antagonism of the 5-HT$_{1A}$ autoreceptors.

Index Entries: 5-HT$_{1A}$ receptor; serotonin; depression; dorsal raphe nucleus; pindolol; fluoxetine; WAY-100635.

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Introduction

Selective Serotonin Reuptake Inhibitors (SSRIs)

Antidepressant therapy, the treatment of major depression by pharmaceutical agents with demonstrated antidepressant activity, has been a feature of psychiatric treatment regimens since the 1950s. In the last 15 years, however, the field has been revolutionized by the introduction of the selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine, paroxetine, sertraline, and citalopram (for review, *see 1*). These compounds are rationally designed molecules that rely upon data implicating serotonin (5-HT), and possibly other monoamine neurotransmitters, in the etiology and treatment of depression, and modulation of 5-HT in its treatment. The logic is straightforward; 5-HT release and reception at central sites appears to be involved in affect, and may be significantly suppressed in many depressed patients. Several earlier treatment directions had a serotonergic component, so a general hypothesis emerged that enhancement of some or all aspects of 5-HT-mediated neurotransmission may be beneficial with respect to antidepressant therapy *(2)*. Because at the time of the development of SSRIs (and to the present for the most part), the specific postsynaptic 5-HT receptors mediating these effects had not been unequivocally identified, or specific agonists had not been discovered for receptors believed to be involved, inhibition of 5-HT reuptake provided a mechanism whereby serotonergic transmission could be effectively enhanced at all targets for this important neurotransmitter. Inhibition of 5-HT reuptake results in a longer synaptic dwell time for the 5-HT released by serotonergic neurons, effectively increasing the amount and duration of 5-HT available for interaction with 5-HT receptors.

The success of these compounds underscores both the importance of 5-HT in depression and the enormous benefit of rational drug design; these compounds are arguably the most successful psychiatric drug therapies to date. Nevertheless, they are fraught with side-effects (notably sleep disturbances and sexual dysfunction), they have an apparent significant delay in the onset of therapeutic benefit, and there are significant numbers of patients that are refractory to SSRI treatment *(3,4)*. The desire to improve upon the speed of therapeutic onset and to increase the proportion of patient response prompted the search for a hypothesis to explain the drawbacks of SSRI monotherapy and ultimately a mechanism for improvement.

Presynaptic 5-HT$_{1A}$ Receptor-Mediated Inhibition of 5-HT Release and Delayed Onset of SSRI Action

Serotonin neurons are largely localized within a small number of nuclei in the brainstem, notably the dorsal raphe nucleus (DRN). A prominent feature of their physiology is the presence of 5-HT autoreceptors that contribute to a feedback inhibitory loop for the regulation of this transmitter's release *(5)*. In the 1990s, several groups proposed that the initial period of SSRI treatment could be ineffective due to 5-HT autoreceptor activation in the presence of the drug, which could significantly reduce any potential immediate benefit of the SSRI by reducing impulse propagation of 5-HT neurons. The delay in drug action could reflect a desensitization of these receptors in the continued presence of elevated 5-HT at the autoreceptor *(see 6)*. Some data indicating that this desensitization occurs with prolonged SSRI treatment has been presented (*see* below). This suggested that a more rapid onset of action, and perhaps a greater proportion of responders, could result from the combination of a 5-HT$_{1A}$ autoreceptor antagonist with an SSRI, negating the need for autoreceptor desensitization. Of course if postsynaptic 5-HT$_{1A}$ receptors are also important for anti-depressant response, one must postulate that they are unaffected or sensitized by chronic SSRI treatment or any benefit of autoreceptor desensitization would be offset by desensitization of receptors participating in SSRI response.

This hypothesis (i.e., the augmentation hypothesis) has been explored preclinically, primarily using the β-adrenergic/5-HT_{1A} antagonist (±)pindolol and specific 5-HT_{1A} antagonists (e.g., WAY-100635) alone and in combination with fluoxetine or another SSRI. The hypothesis has also been repeatedly tested clinically using (±)pindolol and an SSRI. Because these initial data are the basis of several major drug-discovery efforts, we will review these data with the goal of assessing their applicability to the future of antidepressant therapy.

Preclinical Studies

Electrophysiological Studies

The hypothesis that presynaptic 5-HT_{1A} receptor blockade coincident with serotonin-reuptake inhibition will translate into a more rapid clinical therapeutic effect for SSRI drugs, the augmentation hypothesis, is based on several preclinical and clinical observations which were introduced previously. Two aspects of this hypothesis that have been tested using electrophysiological techniques are reviewed below. We first review studies that examined the hypothesis that presynaptic 5-HT_{1A} autoreceptors desensitize in the presence of chronic SSRI treatment. These studies demonstrate that 5-HT_{1A} autoreceptor desensitization occurs in the presence of chronic SSRI treatment. We next examine preclinical studies that tested the assumption that pindolol provides its beneficial clinical effects through functional 5-HT_{1A} antagonism. The results of these studies provide a more complex picture. Functional in vivo results are inconsistent with this hypothesis and suggest that pindolol acts as a 5-HT_{1A} autoreceptor agonist, whereas in vitro results suggest a partial agonist profile and indicate that the action of pindolol is dependent on the testing conditions. Because details of the postsynaptic consequences of the augmentation hypothesis have been reviewed elsewhere (*see*, e.g., *7*), they are not discussed in detail.

A key component of the augmentation hypothesis is the notion that the time-course of desensitization of presynaptic 5-HT_{1A} autoreceptors underlies the delay in efficacy of SSRI treatment; in this hypothesis, emergent SSRI efficacy requires that 5-HT_{1A} autoreceptors desensitize following chronic SSRI treatment. Acutely, SSRI treatment decreased midbrain 5-HT neuronal activity *(8–12)* due to an increase in 5-HT in the region of raphe cell bodies (*see*, e.g., *13*), which activates inhibitory somatodendritic 5-HT_{1A} receptors. The specificity of this effect was demonstrated by reversal or blockade using selective 5-HT_{1A} receptor antagonists *(9,11,14–16).* Chronic SSRI treatment (7–21 d) resulted in decreased sensitivity of 5-HT_{1A} autoreceptors measured both directly and indirectly. Desensitization was demonstrated directly by examination of DRN unit activity during chronic SSRI treatment *(17–19).* Using this method, chronic SSRI treatment typically decreased 5-HT DRN neuronal activity acutely and following 2 d of chronic treatment. By 7 d, this decrease was attenuated and at 14 d postchronic treatment no significant decrease in firing rate was observed *(17–20).* The desensitization following 14–21 d was accompanied by decreased sensitivity of 5-HT DRN unit activity to the nonselective 5-HT agonist, D-lysergic acid diethylamide (LSD), and the selective 5-HT_{1A} agonist, 8-OH-DPAT *(8,17,18,20).* Desensitization of presynaptic 5-HT_{1A} autoreceptors was also observed indirectly by measuring the effect of 5-HT afferent stimulation on hippocampal CA3 activity pre- and postchronic SSRI treatment *(21,22).* These latter studies showed that treatment with the 5-HT receptor antagonist, methiothepin, or chronic (but not acute) SSRI treatment increased the duration of suppression of hippocampal CA3 neuronal activity following electrical stimulation of ascending 5-HT pathways *(21,22).* Thus, current studies suggest that presynaptic 5-HT_{1A} autoreceptors are fully desensitized by 14 d of chronic SSRI treatment. This finding is consistent with the suggestion that reduced serotonergic impulse flow following acute SSRI treatment may delay a therapeutic effect that is dependent on postsynaptic

levels of 5-HT only attained following restoration of impulse flow (i.e., desensitization). It should be noted, however, that the results of microdialysis studies do not fully support this view (*see* discussion below and cf., *23,24*).

According to the principal formulation of the augmentation hypothesis, a requirement for clinical augmentation of SSRI efficacy is a demonstration of functional 5-HT_{1A} receptor antagonism by the compound of interest. One of the few putative 5-HT_{1A} receptor antagonists that are approved for use in humans is the combined β-adrenergic/5-HT_{1A} receptor antagonist, pindolol. It has been reported that the addition of pindolol to antidepressant treatment produces beneficial clinical effects (*see* below) owing to pindolol's 5-HT_{1A} autoreceptor antagonist properties *(25).* The 5-HT_{1A} receptor antagonist properties of pindolol have been assessed in preclinical electrophysiological models. Contrary to the original prediction, current studies indicate that pindolol acts as a functional 5-HT_{1A} receptor agonist in vivo. Recent reports demonstrated that pindolol decreased the firing rate of putative 5-HT neurons recorded in the DRN *(26–34).* In each case, this suppression was reversed following administration of the selective 5-HT_{1A} antagonist, WAY-100635. Further, pindolol failed to antagonize the suppressive effect of SSRIs or the selective 5-HT_{1A} receptor agonist, 8-OH-DPAT, on 5-HT DRN neuronal activity *(28–30,32–34).* In an exception to these results it was reported that the suppressive effect of the nonspecific 5-HT receptor agonist, LSD, on DRN neurons was blocked by pindolol *(32).* Because pindolol did not block the suppressive effect of the selective 5-HT_{1A} receptor agonist 8-OH-DPAT in this same study, the authors proposed a feedback loop, where 8-OH-DPAT, but not LSD, acts at a postsynaptic 5-HT_{1A} site thereby exerting a negative influence on raphe activity. An alternative explanation suggested by Fornal et al. *(30)* is that this effect may be attributable to the activity of LSD at the α_2-adrenoceptor. In support of this latter explanation, pindolol inhibited the decrease in 5-HT DRN firing produced by the α_2-adrenoceptor agonist clonidine *(35).* Thus, the reversal of LSD-induced suppression of 5-HT DRN neuronal activity by pindolol cannot be conclusively ascribed to functional 5-HT_{1A} receptor antagonism. Collectively, in vivo electrophysiological evidence supports a functional 5-HT_{1A} receptor agonist role for pindolol. To the extent that this data extends to clinical studies, it contradicts the hypothesis that pindolol augments the antidepressive effect of SSRIs clinically through functional 5-HT_{1A} antagonist activity.

The properties of pindolol in in vitro electrophysiological models have been examined to a lesser degree. A single study demonstrated that pindolol decreased DRN neuronal activity, which was reversed by the selective 5-HT_{1A} receptor antagonist WAY-100635 *(34).* This study also demonstrated that pindolol reversed the suppressive effect of fluoxetine, indicative of a partial agonist profile for pindolol under these conditions. These findings are consistent with earlier studies demonstrating that pindolol reversed the suppressive effect of the 5-HT_{1A} receptor agonists, 5-carboxamidotyptamine (5-CT) and ipsapirone, in vitro *(36)* and displayed partial agonist activity in an in vitro functional G-protein activation assay *(37).* The results of the in vitro studies, taken with the previously discussed in vivo studies, indicate that pindolol may have differential functional activity dependent on test condition. Further research is needed to determine the processes that are responsible for these differences.

In summary, 5-HT DRN neurons are inhibited acutely following SSRI treatment and this effect is reversed or blocked by selective 5-HT_{1A} receptor antagonists. Further, presynaptic 5-HT_{1A} autoreceptors fully desensitize by 14 d postchronic SSRI treatment consistent with the hypothesis that the addition of a 5-HT_{1A} receptor antagonist to SSRI treatment should result in a large and rapid increase in terminal 5-HT that may translate into a rapid clinical effect. It should be noted, however, that *simultaneous* coadministration of the 5-HT_{1A} receptor antagonist, WAY-100635, with the SSRI, fluoxetine, failed to attenuate the acute suppressive effects

of fluoxetine on 5-HT DRN neurons in vivo *(16).* This latter finding should be considered when evaluating treatment regimens for 5-HT_{1A} receptor antagonist/SSRI clinical studies.

A test of the augmentation hypothesis clinically requires the use of a compound with functional 5-HT_{1A} receptor antagonist properties. To date, pindolol is the only compound that has been used to test this hypothesis clinically. Preclinical studies revealed that pindolol has functional agonist activity at presynaptic 5-HT_{1A} autoreceptors in vivo, whereas the results of in vitro functional studies suggested a partial agonist profile. These differences suggest that pindolol may exhibit differential profiles under different conditions (i.e., in vivo vs in vitro).

Microdialysis Studies

According to the augmentation hypothesis, the capacity of SSRIs to increase extracellular 5-HT levels in regions critical for antidepressant action is initially constrained by autoreceptor activity, which inhibits firing of serotonergic neurons and terminal 5-HT release. Desensitization of these receptors, in turn, results in greater SSRI-induced increases in extracellular 5-HT in forebrain areas, which ultimately enables the delayed antidepressant response to SSRIs. Microdialysis allows for the direct assessment of drug effects on extracellular 5-HT levels in specific brain areas. Many aspects of the hypothesis are well-supported by microdialysis studies, but experiments specifically designed to assess the effects of chronic SSRI treatment on the responsiveness of 5-HT_{1A} receptors have produced conflicting and ambiguous findings.

Initial microdialysis studies assessed the effects of systemically administered 5-HT reuptake inhibitors and observed smaller and less potent effects of these compounds on serotonergic transmission than expected (for review, *see 39*). Many compounds including clomipramine, fluoxetine, fluvoxamine, and citalopram produced small increases in forebrain extracellular 5-HT (3 fold above baseline: *39–43*), or no increase in 5-HT levels *(44,45).* Typically, under the same conditions, larger increases were observed when 5-HT levels were measured in the raphe nuclei than other brain regions *(13,41,44).* These data suggested that increased 5-HT in the raphe nuclei constrained forebrain increases in 5-HT.

Direct evidence supporting the augmentation hypothesis came from studies assessing the effects of SSRIs applied locally in the brain. Application of SSRIs in forebrain areas produced larger increases in extracellular 5-HT than did systemic application *(44,46).* In contrast, local application of SSRIs in the raphe region decreased forebrain 5-HT release, and inhibited the effects of subsequent systemic dosing with SSRIs *(47,48).* Kreiss and Lucki *(49)* showed that local application of 8-OH-DPAT in the raphe nuclei decreased forebrain 5-HT concentrations, reinforcing the proposal that activation of 5-HT_{1A} autoreceptors mediates the constraints on forebrain 5-HT release.

Many studies have shown that 5-HT_{1A} receptor antagonists potentiate the increases in extracellular 5-HT produced by SSRIs in various brain regions. The selective 5-HT_{1A} receptor antagonists WAY-100635 and UH-301, as well as the β-adrenergic/5-HT_{1A} antagonists pindolol and propanolol, potentiate the effects of diverse SSRIs, such as fluoxetine, citalopram, fluvoxamine, and others *(16,41,43,50–53).* The effects of the 5-HT_{1A} antagonists are quite variable, ranging from 25–1900% potentiation relative to the SSRI alone, and one factor that seems to mitigate the variability in the magnitude of the potentiation is the sequence of the injections. In general, dosing with the 5-HT_{1A} antagonist after the SSRI produces a larger potentiation *(16,51,53)* than the reverse sequence *(16,43,50).* This observation may be of some concern when extrapolating to clinical studies in which the compounds are coadministered.

Another autoreceptor that could contribute to the constraints on increased 5-HT levels are the terminal 5-HT_{1B} autoreceptors, which regulate 5-HT release. Antagonists of 5-HT_{1B} receptors potentiate the increase in 5-HT produced by SSRIs *(54–56).* Furthermore, combining antagonists of both 5-HT_{1A} and 5-HT_{1B} receptors with

SSRI produces greater effects than antagonists of either receptor alone *(55,56).* This observation may be important for unbiased consideration of the effects of pindolol. In microdialysis studies, pindolol reliably potentiates SSRI effects, and this effect has been attributed to 5-HT_{1A} receptor blockade *(14,51,57).* However, pindolol also has relatively high affinity for rat 5-HT_{1B} receptors, where it reportedly functions as an antagonist *(58),* and the 5-HT_{1B} receptor activity may mediate these effects of pindolol. Dawson and Nguyen *(45)* reported that pindolol potentiated the effects of WAY-100635 and fluoxetine but not GR-127935 (a 5-HT_{1B} antagonist) and fluoxetine. This finding indicates that pindolol functions as a 5-HT_{1B} antagonist and does not function as a 5-HT_{1A} antagonist in vivo to potentiate the effects of fluoxetine. It should be noted that, relative to rat 5-HT_{1B} receptors, pindolol binds with low affinity to the homologous human 5-HT_{1B} receptor *(59,60).* Nonetheless, the diminished support for a role for 5-HT_{1A} autoreceptor antagonism in the experimental augmentation of forebrain 5-HT levels produced by pindolol coadministration suggests that pindolol may provide its beneficial clinical effects via a mechanism distinct from its activity at 5-HT_{1A} autoreceptors as well.

As discussed earlier, electrophysiology studies found that 5-HT_{1A} receptors desensitize following chronic administration, consistent with the hypothesis that desensitization of these receptors underlies the delayed therapeutic effect of SSRI treatment. Microdialysis studies have also addressed the effects of chronic dosing with SSRIs on basal and evoked 5-HT levels in various brain areas including the striatum, cortex, and hippocampus. In these studies an SSRI is typically administered for a period of 14 d or more and some combination of the following four endpoints is examined: 1) effects on basal 5-HT, 2) effects on evoked 5-HT, 3) effects of a 5-HT_{1A} agonist (8 OH-DPAT) on 5-HT levels, and 4) effects on the ability of a 5-HT_{1A} antagonist to potentiate SSRI effects on 5-HT levels. Interpretation of these endpoints is difficult, because it is dependent on the amount of drug present and the degree of functional uptake inhibition at the time that the endpoint is measured. The variables that must be factored into a determination of uptake inhibition include half-life of the compound, dosing regimen, duration of action of the compound, maximal effect of the compound, and brain region for dialysis.

An early study found that the SSRI fluvoxamine enhanced basal levels of 5-HT by a greater amount when dosed chronically than when dosed acutely *(61).* These investigators used a submaximal dose, arguing that this is the clinically relevant dose. However, by giving submaximal doses chronically, the possibility arises that plasma levels of fluvoxamine or an active metabolite accumulate *(62),* and therefore, the increased effects may not represent autoreceptor desensitization. Using an alternative design to address this question, several studies reported that chronic SSRI treatment increased basal extracellular 5-HT and that this effect corresponded to a reduced effect of 8-OH-DPAT *(63–65).* Because acute administration of 8-OH-DPAT lowers dialysate 5-HT concentrations in forebrain regions *(49,66,67),* a reduction of this effect during chronic SSRI treatment is consistent with desensitization of 5-HT_{1A} receptors. However, two caveats should be considered with the time profile in these studies. First, the use of the term basal is questionable, as no attempts were made in these studies to determine whether residual drug concentrations were present at the time of testing; rather than enhanced basal effects, these may represent prolonged evoked effects. Second, because extracellular 5-HT levels were enhanced at the time at which the dialysis experiment was performed, it is likely that 5-HT_{1A} receptors were occupied by 5-HT, thereby decreasing any additional effect that could be produced following 8-OH-DPAT treatment.

Additional studies reported that chronic SSRI treatment does not impact basal extracellular concentrations of 5-HT, and these studies report differing effects on 5-HT_{1A} receptor function. Several reports found that chronic SSRIs did not impact basal 5-HT concentra-

tions or the effects of 5-HT_{1A} agonist administration *(23,68–71).* Invernizzi et al. *(72)* and Dawson et al. *(57)* also found no effect on basal 5-HT levels following chronic SSRI treatment, however, they did report a potentiation of acute SSRI treatment effects and a reduced 8-OH-DPAT effect. Cremers et al. *(24),* observed that 48 h after chronic citalopram dosing, basal 5-HT levels were not increased, and subsequent acute dosing with citalopram did not produce potentiated effects, even though the effects of 8-OH-DPAT were decreased. This result is particularly interesting because the investigators ensured that plasma levels of citalopram were very low (<9 n*M*) at the time of the microdialysis experiment.

A final approach assessed the ability of autoreceptor antagonists to potentiate the effects of SSRIs after chronic dosing with SSRIs. Three reports indicate that after chronic dosing with SSRIs, autoreceptor antagonists maintained their ability to potentiate SSRI effects *(50,73,74).* These data suggest that after chronic SSRI treatment, 5-HT_{1A} and 5-HT_{1B} receptors can still constrain increases in 5-HT concentrations produced by SSRIs, i.e., functional desensitization had not occurred. This may be the most convincing test of the desensitization hypothesis, as it enables the assessment of autoreceptor function in the presence of the SSRI and the associated elevated 5-HT concentration, thereby avoiding the issues with pharmacokinetics and duration of action that presumably impacted the results discussed earlier.

Addressing the augmentation hypothesis from a different perspective, a recent microdialysis report determined the effects of chronic coadministration of pindolol with fluoxetine *(57):* a paradigm similar to that employed in the clinic. These authors found that both chronic fluoxetine administration and chronic pindolol administration desensitized 5-HT_{1A} receptors. However, coadministration of pindolol with fluoxetine did not produce desensitization. These results suggest that pindolol can act as a 5-HT_{1A} agonist acutely, but may still act as an 5-HT_{1A} antagonist when dosed chronically in combination with an SSRI. This surprising profile may be due to a partial agonist property of pindolol at 5-HT_{1A} receptors, and provides further evidence that pindolol may not be an ideal drug for testing this hypothesis.

Collectively, the microdialysis data support the concept that autoreceptor activity acutely constrains the effects of SSRIs on dialysate 5-HT levels, but they do not provide strong support for the hypothesis that adaptive changes enable greater increases in extracellular 5-HT levels after chronic dosing. Subtle methodological differences appear to influence the results of these mechanism of action studies, so any conclusion remains ambiguous. Further, caution must be taken when extrapolating these microdialysis results to clinical observations. The acute effects suggest that autoreceptor antagonist co-administration may augment the enhancement of 5-HT levels by SSRIs, which could result in superior antidepressant activity. However, because SSRIs are given at submaximal doses in the clinic, coadministration of 5-HT_{1A} antagonists with SSRIs may simply mimic the effects of higher, possibly toxic, doses of SSRIs alone.

Clinical Studies

Clinical trials to date have focused on the effect of pindolol addition to standard antidepressant treatment on response latency and efficacy in both normal depressed and treatment-resistant depressed patient populations. Recent discussion of these data have suggested that anywhere from 3 out of 6 *(75),* upwards to 6 out of 7 *(76),* placebo-controlled studies support the augmentation hypothesis. Accordingly, in the following, we attempt an objective review of these studies. We conclude that approx 50% of adequately controlled trials demonstrate a beneficial effect of pindolol coadministration.

In general, open-label clinical trials support the suggestion that pindolol augments the effect of SSRI treatment and improves efficacy in treatment resistant patients (*see* Table 1).

Table 1
Open Label Clinical Studies of Pindolol/Antidepressant Drug Treatment

Authors (ref)	Pub. yr	Antidepressant treatment	Patient population	Effect on latency?	Effect on efficacy?
Artigas et al. *(92)*	1994	Paroxetine (untreated) or current therapy (Rx resistant)	Major depression treatment resistant and untreated	(+) 5 of 7 showed remission or partial remission at 1 wk	(+) 6 of 8 showed remission or partial in 1 wk (treatment resistant patients)
Blier and Bergeron *(25)*	1995	Paroxetine (untreated) or current therapy (Rx resistant)	Major depression treatment resistant and untreated	(+) 8 of 9 showed 50% decrease in HAM-D at 1–2 wks	(+) 10 of 17 showed 50% decrease in HAM-D at 1 wk; 12 of 17 by 2 wks (treatment resistant patients)
Dinan and Scott *(93)*	1996	Fluoxetine Sertraline Paroxetine	Major depression Treatment resistant	(–) 3 of 13 showed a relevant change by one wk	(–) 3 of 13 treatment resistant patients showed response at 3 wks
Vinar et al. *(94)*	1996	Ongoing SSRI treatment	Periodic/major depression	(+) 20 of 27 showed more rapid effect with combo treatment	(+) 5 of 7 treatment resistant patients showed improvement with combo
Bakish et al. *(95)*	1997	Nefazodone	Major depression	(+) 15 of 20 showed 50% decrease in HAM-D at 1 wk	(+) Remission rates greater for combo than nefazodone alone (40% vs. 9% at 1 wk; 90% vs. 30% at 5 wks)
Blier et al. *(96)*	1997	Buspirone Fluvoxamine	Major depression	(+; buspirone) 8 of 10 showed 50% decrease in HAM-D at 1 week (–; fluvoxamine) 0, 4 and 8 of 8 showed >50% decrease at 1, 2 and 3 wks	Not directly tested
Cardoni and Pisetsky *(97)*	1997	Paroxetine Fluoxetine Venlafaxine	Axis I major depression inpatients	(+) 5 of 8 showed significant improvement in 3 d	Not directly tested
Erfurth et al. *(98,99)*	1997 and 1998	Paroxetine	Severely depressed female inpatients	(–) No sig. hastening of response	Not directly tested
Shiah et al. *(100)*	1999	ECT	Major depression – antidepressant free	(+) 50% of combo patients responded to 6 ECT treatments versus 0% for placebo	(–) Combo treatment not better than ECT alone on absolute level of efficacy

These studies are of limited value, however, when critically evaluating the effectiveness of pindolol coadministration due to several factors, including a high placebo-response rate inherent in depression clinical trials (mean of 30–40%; see *77*), experimenter and subject bias, and the use of historical data for comparison of the rapidity of onset (i.e., the lack of a treatment group receiving antidepressants alone).

Double-blind, placebo-controlled studies, by contrast, are a more valuable method for evaluating treatment response in depressed patients *(78,79).* Ten studies have examined the effect of pindolol coadministration on latency and/or efficacy measures under these conditions (Table 2). Eight of these directly addressed latency measures. Of these, three studies showed no acceleration with pindolol coadministration *(80–82),* whereas an additional three studies demonstrated a positive effect *(83–85).* The results of the remaining two studies are ambiguous *(86,87).* In one of these latter studies *(86),* a significant effect was reported with pindolol coadministration, however, when stringent conditions were used for analysis (i.e., only patients with a sustained response were used in the analysis), no acceleration was detected. The remaining study by Tome et al. *(87)* involved two test centers. One center reported a significant effect of pindolol coadministration whereas there was no effect observed at the second center. A subsequent covariance analysis of the pooled population found a significant effect of coadministration at d 4 and 7 of treatment. Given the equivocal results of these latter studies, we conclude that 50% of placebo-controlled studies are supportive of a role of pindolol coadministration in decreasing the latency of onset for SSRI antidepressant treatment.

When assessing efficacy as the primary endpoint, the results of double-blind placebo-control trials are also equivocal. Thus, of nine studies that have directly addressed this issue, four have failed to demonstrate an advantage of pindolol coadministration *(80,81,84,88),* whereas four did show an advantage *(82,83,86,89).* Similar to above, the study of Tome et al. *(87)* showed an increase in overall efficacy at one center but not at a second. Again, these studies indicate that 50% of published reports found a beneficial effect of pindolol coadministration on efficacy.

In summary, clinical trials that have examined the effect of pindolol/SSRI cotherapy on antidepressant latency or efficacy are presently equivocal. Approximately 50% of controlled studies fail to find a beneficial effect of pindolol addition. The successful augmentation observed in the remaining studies suggests:1) that pindolol can enhance antidepressant action in some instances, and 2) that an unidentified and therefore uncontrolled component of pindolol may account for the lack of reliability in these studies. One obvious possibility is that pindolol is not the appropriate drug to adequately test the augmentation hypothesis. As reviewed earlier, the action of pindolol preclinically and in some clinical markers of 5-HT_{1A} activity (*see,* e.g., *90*) suggests a partial agonist profile. Because the functional activity of partial agonists are dependent upon many factors, including receptor reserve and endogenous neurotransmitter levels, it is possible that the usefulness of pindolol could be limited. A recent study showed that the binding potential of 5-HT_{1A} receptors to the 5-HT_{1A} receptor antagonist, [^{11}C]WAY-100635, was reduced in depressed patients compared with normal controls *(38).* These alterations in receptor function of depressed patients may ultimately dictate patient populations that could benefit from pindolol/SSRI augmentation therapy. By contrast, SSRI coadministration with a functional 5-HT_{1A} antagonist may provide more robust and reliable clinical effects. These issues require further clinical evaluation, preferably with specific and potent 5-HT_{1A} receptor antagonist/SSRI combinations. Another possibility suggested by recent receptor occupancy studies using positron emission tomography (PET), is that the dose of pindolol currently used in clinical studies may be insufficient to fully occupy presynaptic 5-HT_{1A} autoreceptors in man *(91).* A higher clinical dose of pindolol might therefore result in a more consistent response. It should be restated, however, that

Table 2
Placebo-Controlled Trials of Pindolol/Antidepressant Drug Treatments

Authors (ref)	Pub. yr	Antidepressant treatment	Patient population	Effect on latency?	Effect on efficacy?
Maes *et al. (89)*	1996	Trazodone	Major depression Treatment resistant and untreated populations	Not directly tested	(+) 72.5% remission with combo vs 20% with trazodone alone after 4 wks
Berman *et al. (80,101)*	1997 and 1999	Fluoxetine	Major depression	(–) No differences between combo and FLX alone groups	(–) No differences between combo and FLX alone groups
Moreno *et al. (81)*	1997	Fluoxetine, 80% Desipramine, 10% Bupropion, 10%	Major depression – treatment resistant	(–) No differences between combo and antidepressant alone groups at wk 1 or wk 2	(–) No differences between combo and antidepressant alone groups at end of trial (2 wks)
Perez *et al. (86)*	1997	Fluoxetine	Major depression	(?) Time to improvement decreased with combo, but not sig. when "stringent conditions"[a] were used	(+) More responders with combo treatment (75% vs 59%)
Tome *et al. (87,102,103)*	1997	Paroxetine	Major depression	(?) Time to improvement decreased with combo at 1 center but not at 2nd[b]	(?) Better effectiveness of combo at 1 center only
Zanardi *et al. (83)*	1997	Paroxetine	Untreated major depression	(+) Combo treatment produced sig. higher response rate at 1–2 wks	(+) Combo treatment produced better response rate and lower lower HAM-D scores at study completion (4 wks)
Zanardi *et al. (84)*	1998	Fluvoxamine	Psychotic depression	(+) Combo treatment produced sig. higher response rate than fluvoxamine alone at wk 3 and 4	(–) No differences between combo and fluvoxamine alone groups at end of study (6 wks)
Bordet *et al. (85)*	1998	Paroxetine	Major depression	(+) Lower HAM-D scores at d 5 and 10 and more improved patients at d 10 with combo treatment	Not directly tested
Maes *et al. (82)*	1999	Fluoxetine	Major depression – treatment resistant	(–) No sig. accelerator effect with combo treatment[c]	(+) Better response rate with combo treatment (60% vs 9%)
Perez *et al. (88)*	1999	Clomipramine Fluoxetine Fluvoxamine Paroxetine	Major depression – treatment resistant	Not directly tested	(–) No differences with combination treatment

[a] Stringent conditions used only patients with a sustained response for analysis.

[b] Covariate analysis of pooled population found a sig. accelerator effect for pindolol on a secondary efficacy variable at two time points (i.e., days 4 and 7).

[c] Although pindolol + fluoxetine did not show a sig. accelerator effect, mianserin (5-HT2A/C - a2 receptor antagonist) + fluoxetine treatment did.

pindolol exhibits functional agonist activity at higher preclinical doses.

Summary

In this brief review, we have examined preclinical and clinical evidence pertaining to the antidepressant augmentation hypothesis and to the specific use of pindolol/SSRI co-administration as an adequate test of this hypothesis. There is a significant body of preclinical data supporting the idea that antidepressant efficacy could be enhanced and onset latency perhaps decreased if somato-dendritic 5-HT autoreceptors are acutely antagonized. By eliminating this negative feedback loop, a more rapid, in fact immediate enhancement of 5-HT release in areas such as the forebrain should be and often are observed. Timing of the coadministration may be critical, however, and may reduce the desirability of incorporation of both 5-HT_{1A} antagonism and SSRI activity in a single molecule. Use of pindolol, a drug with a wide spectrum of pharmacological interactions and a less than clear profile of 5-HT receptor interaction, may contribute to the equivocal results seen in the clinic. Only by clinical evaluation of coadministration of SSRIs with potent and specific 5-HT_{1A} receptor antagonists will the full potential of dual therapy be evaluated with sufficient rigor.

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