Controversies in the Diagnosis and Treatment of Severe Depression

This section of The Journal of Clinical Psychiatry *summarizes a meeting on the topic of severe depression that was held at Lake Mohonk in New Paltz, New York, on May 3, 1996. The conference was sponsored by N.V. Organon of Oss in The Netherlands, and provided an opportunity to discuss the new antidepressant mirtazapine. The meeting was also timed to coincide with the American Psychiatric Association annual meeting in New York, N.Y. Invited speakers included Robert M. A. Hirschfeld, M.D., Titus H. Harris Distinguished Professor and Chair of the Department of Psychiatry and Behavioral Sciences, University of Texas Medical Branch, Galveston, Texas; Siegfried Kasper, M.D., Professor and Chairman of the Department of General Psychiatry, University of Vienna in Austria; Claude de Montigny, M.D., Ph.D., F.R.C.P.(C), Director, Neurobiological Psychiatry Unit, McGill University, Montreal, Canada; Elliott Richelson, M.D., Professor of Psychiatry and Pharmacology, Mayo Clinic, Jacksonville, Florida; and Lars F. Gram, M.D., Professor of Clinical Pharmacology, Institute of Medical Biology, Odense University in Denmark. Other participants were F. Artigas, Ph.D., Barcelona, Spain; M. Fava, M.D., Boston, Massachusetts; L. Grunhaus, M.D., Tel-Hashomer, Israel; Y. Lecrubier, M.D., Paris, France; S. A. Montgomery, M.D., London, England; F. M. Quitkin, M.D., New York, N.Y.; S. M. Stahl, M.D., Ph.D., San Diego, California; and R. Pinder, Ph.D., D.Sc., N.V. Organon, Oss, The Netherlands.*

Severe depression is a frequently diagnosed disorder and a major health problem in the United States and Europe. An international panel of experts met recently in New Paltz, New York, to discuss whether severe depression constitutes a distinct form of depression and to review effective treatments for the disorder. In his opening remarks, Roger Pinder, Ph.D., D.Sc., Medical Director CNS at N.V. Organon, said, "Severe depression is a major topic for discussion at the present time. There is a feeling, with some evidence, that patients with this disorder respond less well to SSRIs, suggesting that severe depression may be better served by using drugs like the tricyclic antidepressants or drugs that have a dual mechanism of action."

Diagnosing Severely Depressed Patients in Clinical Trials and in Clinical Settings

Confusion over what constitutes severe depression continues to invite debate on the subject, according to Robert M. A. Hirschfeld, M.D. In an informative review of the subject, he said that at least five clinical definitions of severe depression can be used that are different from DSM-IV and ICD-10 classifications (Table 1). Some evidence indicates that patients differ in their response to antidepressants, he said, and the most marked differences are seen in hospitalized patients and those with biological forms of depression, particularly melancholia. Additional definitions of severe depression include the use of threshold scores on the Hamilton Rating Scale for Depression (HAM-D) or the Montgomery-Åsberg Depression Rating Scale (MADRS). A number of studies have also included the need for hospitalization as an indication of severe depression, but this criterion may vary between families and countries, he said. A particular constellation of symptoms, some of which are regarded as more biological and more severe, is an acceptable way of defining severe depression. Another classic practice is the inclusion of psychotic features, such as delusions or hallucinations. Finally, a particularly good technique for the assessment of overall severity of illness is the Global Assessment Scale (GAS) that combines information on psychological, social, and occupational function with the symptoms presented by the patient. This scale was developed by the NIMH Psychobiology of Depression Collaborative Study and used in the DSM-IV.

Dr. Hirschfeld then presented data to illustrate these clinical definitions in detail, starting with several studies using the presence of certain depressive symptoms to define severe depression. A study of hospitalized patients with major depression who took paroxetine versus imipramine[1] showed a reduction of HAM-D scores to below 15 during the first 6 weeks of treatment. Nearly half of the patients (divided almost equally between the treatment groups) dropped out of the study primarily due

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Hirschfeld RA. Diagnosing severely depressed patients in clinical trials and in clinical settings, pp 552–554. In: Controversies in the Diagnosis and Treatment of Severe Depression. J Clin Psychiatry 1996;57:552–559

Table 1. Clinical Definitions of Severe Depression

Depressive symptoms	17-item HAM-D score ≥ 25 MADRS score ≥ 30
Hospitalization	
Symptom constellation	Melancholia Vital depression Timeless depression
Psychotic features	Delusions Hallucinations
Overall symptomatology and functional impairment	Global Assessment Scale < 50

to adverse events. An interesting dose-response effect was reflected by a correlation between a greater reduction in HAM-D scores and a higher blood level of paroxetine. A study by Ottevanger[2] measured HAM-D scores in hospitalized patients taking fluvoxamine, imipramine, and placebo; both active drugs lowered the HAM-D scores to about 15 during the first 6 weeks of treatment. A score that plateaus at 10 to 15 is an indication that the patient has not fully recovered and probably continues to meet the criteria for dysthymia, Dr. Hirschfeld said. A study by Bowden and colleagues[3] compared fluoxetine and desipramine in the treatment of moderate to severe depression in a mix of hospitalized patients and outpatients. They found that the severity of depression, as measured by HAM-D ≥ 25, was not a predictor of outcome for patients taking either drug.

Two studies of hospitalized patients by the Danish University Antidepressant Group (DUAG) compared clomipramine, a tricyclic antidepressant (TCA), to citalopram[4] and paroxetine,[5] serotonin selective reuptake inhibitors (SSRIs). Both studies showed a superior response to clomipramine, as assessed by response rates and decrease in HAM-D scores.

In the ensuing panel discussion, the point was made that hospitalization of depressed patients is a problematic measure of severity because of the variety of criteria used in different situations and/or countries. A suggestion was also made that patients in the DUAG studies might have been characterized less by severe depression than by other features of depression, such as treatment-resistance or obsessiveness.

In considering a constellation of symptoms, Dr. Hirschfeld said that Roose and colleagues[6] did a retrospective study of efficacy between fluoxetine and nortriptyline in elderly, melancholic patients with severe cardiac disease. In a nonrandomized study, 67% of the patients responded to nortriptyline compared with only 23% of patients who responded to fluoxetine. In a more recent study,[7] these findings have been supported by results of a comparison between venlafaxine and fluoxetine in a small number of hospitalized patients with melancholic depression. In that study, venlafaxine, a drug with dual action, also showed a superior response compared with fluoxetine, an SSRI. Dr. Hirschfeld extrapolated that these findings suggested a possible difference in response of patients to various classes of antidepressants and that different definitions of severity define somewhat different groups of depression.

In the assessment of patient outcome by use of HAM-D scores, a 50% reduction in the score is worthwhile, but the patient's level of function may still be equivocal. Most clinicians would like to see a HAM-D score of less than 5; this score indicates a better response to treatment, even though the patient may not be well, he said.

In a discussion of the use of psychotic features to define severe depression, Dr. Hirschfeld cited a study[8] that compared perphenazine with amitriptyline. These agents were given alone, and in combination, to patients with delusional depression. The combination treatment, using an antidepressant and an antipsychotic, was better than taking either drug alone, when measured by scores on the HAM-D and the Brief Psychiatric Rating Scale (BPRS).

Another study,[9] conducted in patients with psychotic depression, compared three treatment options: fluoxetine and perphenazine versus amitriptyline and perphenazine versus amoxapine alone. The three treatments showed similar efficacy and prompted Dr. Hirschfeld to reconfirm the usefulness of an antipsychotic when treating delusional depression.

Although the use of functional impairment, as measured by the GAS, is a valid way to classify severely depressed patients, no data are presently available that correlate this measurement with patient response to antidepressant medications.

Any discussion of the treatment of severe depression should include electroconvulsive treatment (ECT), Dr. Hirschfeld said. Even though ECT does not provide a long-lasting effect, it is safe and effective and should always be considered for treatment-resistant patients or those who have medical problems that preclude medication use.

In conclusion, Dr. Hirschfeld said that an increase in drug dosages is sometimes indicated for extended periods of time to elicit a therapeutic response in some patients. Although overall efficacy of SSRIs is generally comparable to TCAs, there are some exceptions, he said. "There is a strong place for medications other than the SSRIs for severe depression. Venlafaxine is one such drug, and I am also excited about the prospect of using mirtazapine in these patients."

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Treatment Options in Severe Depression

Mirtazapine has proven efficacy in treating severely depressed patients, according to Siegfried Kasper, M.D. Data from the clinical trial program[1] showed that mirtazapine was as effective as amitriptyline and clomipramine in the treatment of this group of patients. In addition to the overall efficacy of mirtazapine, Dr. Kasper stressed that reduction in Hamilton Rating Scale for Depression (HAM-D) scores and improvement of patients in different subgroups of depression were important considerations for use of the new agent.

In line with the concept that severe depression may respond better to drugs with a dual rather than a single mode of action,[2–4] mirtazapine is a noradrenergic and specific serotonergic antidepressant (NaSSA), said Dr. Kasper. It has a different mode of action from tricyclic antidepressants, serotonin selective reuptake inhibitors, and monamine oxidase inhibitors, because it increases noradrenergic and serotonergic neurotransmission via a blockade of the central α_2-autoreceptors and heteroreceptors. The increased release of serotonin, via increased cell firing of 5-HT neurons, stimulates only the 5-HT_1 type receptors, because 5-HT_2 and 5-HT_3 type receptors are specifically blocked by mirtazapine.[5–7]

Data presented by Dr. Kasper[1] included results of placebo-controlled studies (some of which used an active comparator drug) and comparative studies with other antidepressants of established efficacy, including amitriptyline, clomipramine, doxepin, and trazodone. Over 4500 patients worldwide were included in these studies. Participants had a *Diagnostic and Statistical Manual* (DSM-III) diagnosis of major depressive episode (single or recurrent) and a baseline 17-item HAM-D score of at least moderate depression (total score of 18–24). None of the patients included in the study had been treated with electroconvulsive therapy in the previous 3 months or had taken an antidepressant (≥ 150 mg of amitriptyline or equivalent for at least 6 weeks) in the month preceding the trial. The studies were double-blind, randomly assigned, flexible-dose comparisons of 5 to 6 weeks' duration.

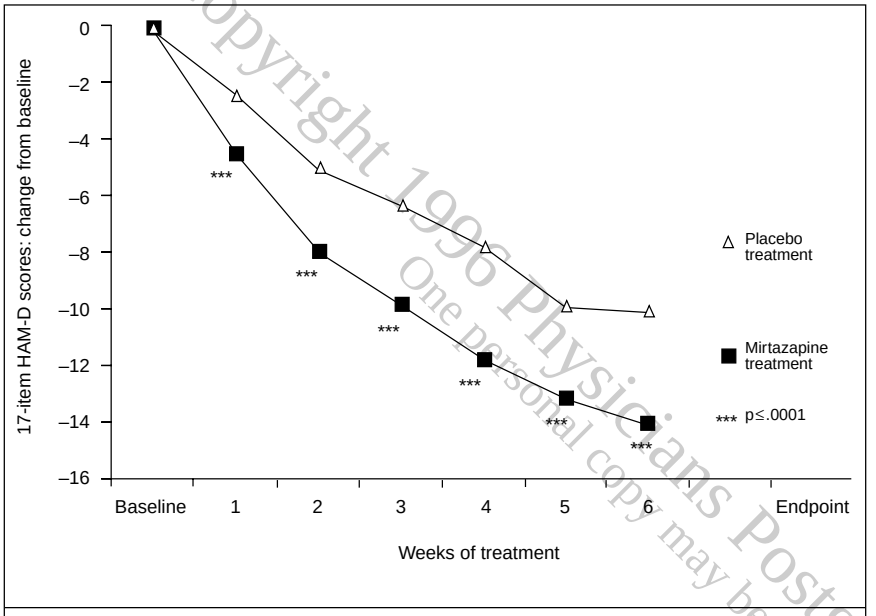
The statistical analysis was performed on an intent-to-treat basis, and included all patients for whom the baseline and at least one post-baseline assessment of the 17-item HAM-D scale were available. Efficacy analyses were performed for the individual studies and a meta-analysis was used to obtain pooled results. An endpoint analysis was performed for each study, both separately and for pooled results, with endpoint defined as the last available assessment of a patient within the time frame of the study (last observation carried forward analysis).

In the meta-analysis on the pooled data from five placebo-controlled studies, patients treated with mirtazapine experienced significantly greater improvement of depressive symptoms than did placebo-treated patients at all assessments from Week 1 to Week 6, and at endpoint (Figure 1). Dr. Kasper stressed that a significant reduction was also evident in the analysis of most HAM-D items: anxiety/somatization, cognitive disturbances, retardation depression, sleep disturbance, and melancholia (Figure 2).

The efficacy of mirtazapine was then compared with that of amitriptyline in five double-blind studies, two of which were placebo-controlled. The studies were conducted in hospitalized patients and in outpatients who had a diagnosis of major depressive episode. The results revealed no difference between treatment groups in the overall improvement of depressive symptoms. The magnitude of improvement was equivalent for mirtazapine and amitriptyline in other important symptoms commonly associated with depression, as assessed by changes from baseline in the HAM-D scale.

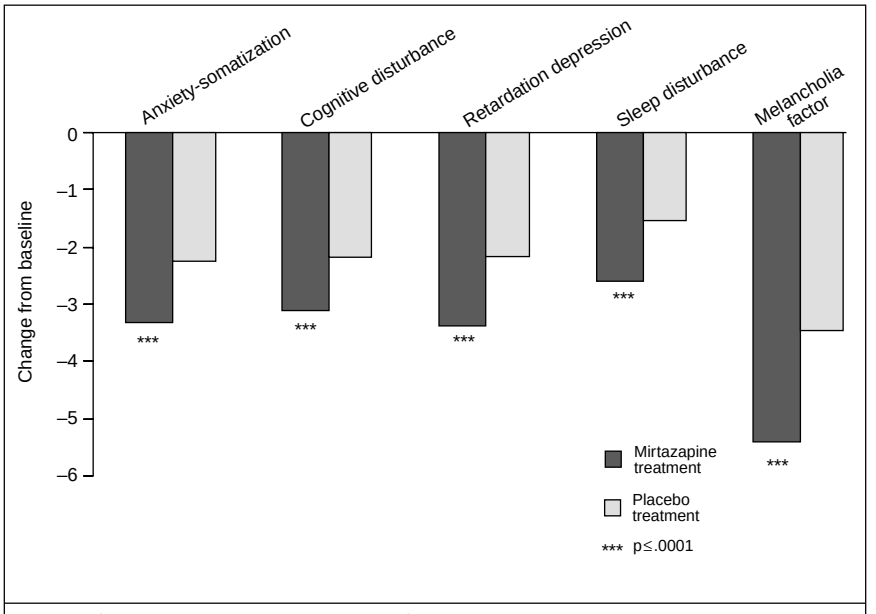
In the assessment of suicide risk, clinically relevant and statistically significant reductions from baseline were seen in patients treated with mirtazapine as compared to placebo. The magnitude of improvement was comparable to that of patients treated with amitriptyline.[8] Dr. Kasper added that these results are particularly important. In Germany, he said, some hospitals have banned the use of SSRIs because of the belief that the favorable side effect profile of these agents has been achieved at the expense of efficacy in

Figure 1. Changes From Baseline in Group Mean Scores on Hamilton Rating Scale for Depression (HAM-D): Mirtazapine Versus Placebo*



*From reference 1, with permission. Changes from baseline in group mean scores on the 17-item HAM-D during treatment with either mirtazapine (N = 249) or placebo (N = 246) according to observed case and endpoint analysis.

Figure 2. Changes From Baseline in Hamilton Rating Scale for Depression (HAM-D) During Treatment: Mirtazapine Versus Placebo*



*From reference 1, with permission. Changes from baseline in HAM-D during treatment with either mirtazapine (N = 249) or placebo (N = 246) according to endpoint analysis.

the treatment of severe or suicidal patients.

Equivalent response was noted in the response of severely depressed patients (a 17-item HAM-D score of ≥ 25) to mirtazapine as compared with either clomipramine or amitriptyline. At Week 6, all groups of patients showed a decrease in HAM-D scores ranging between 15.4 and 19.9 points. Dr. Kasper stressed that the results seen in trials comparing mirtazapine with clomipramine were particularly important because of the older drug's unsurpassed record in treating severe depression.

In conclusion, Dr. Kasper said: "There is no difference in efficacy between mirtazapine and either amitriptyline or clomipramine. Strong data sets show that the newer drug has an overall good efficacy in a whole range of patients, including those with severe depression. Efficacy of the drug is accompanied by a benign side effect profile and no reported cases of fatalities from overdosage."

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The Pharmacologic Profile of Mirtazapine

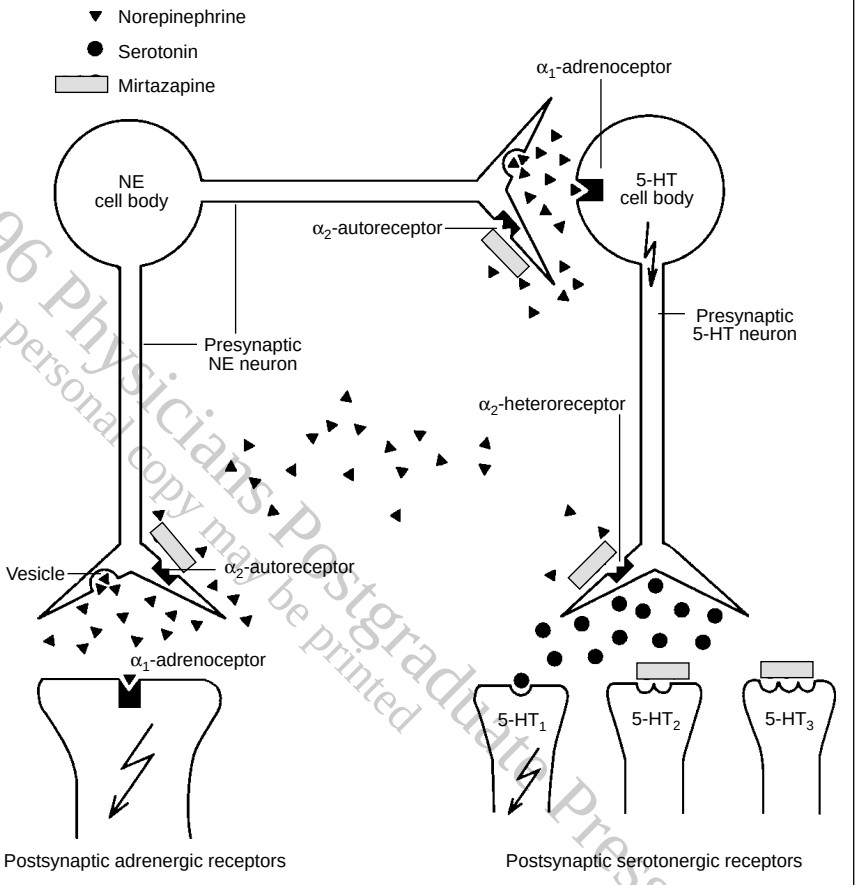
The only known common final effect of antidepressant treatments is an enhancement of 5-HT neurotransmission in the CNS upon their long-term administration, said Claude de Montigny, M.D., Ph.D. This has been well documented mainly by functional in vivo electrophysiologic studies, but also in several other paradigms such as microdialysis and behavioral models. There is mounting evidence that such a modification does occur in patients (as well as in healthy volunteers) undergoing antidepressant treatments. Furthermore, there is also conducive indications that this might be related to their therapeutic activity. The new antidepressant, mirtazapine, has a unique method of achieving this effect. Mirtazapine is a potent and direct α_2-adrenoceptor antagonist that enhances both noradrenergic and serotonergic transmission as a result of α_2 auto- and heteroreceptor blockade.[1] It is therefore described as a noradrenergic and specific serotonergic antidepressant, or NaSSA.

The effects of mirtazapine on noradrenergic and serotonergic neurotransmission have been widely studied in both in vivo and in vitro neurochemical, animal behavioral, and neurophysiologic studies.[1] Often the serotonin and norepinephrine systems are seen in parallel, but it should be emphasized that several important interactions occur between these two systems, he said. This concept becomes apparent when the pharmacology of mirtazapine is considered (Figure 1).

Mirtazapine interferes with noradrenergic transmission by selective blockade of pre- and postsynaptic α_2-adrenoceptors.[1] Noradrenergic neurotransmission is under the control of the presynaptic α_2-adrenoceptors (α_2-autoreceptors). Stimulation of these receptors by norepinephrine inhibits the release of norepinephrine. Mirtazapine increases the release of norepinephrine by a blockade of the α_2-autoreceptors and subsequently enhances noradrenergic transmission.[2–5] Because of mirtazapine's low affinity for α_1-adrenoceptors, the increased levels of norepinephrine lead to an enhancement of serotonergic cell firing. The increase of the firing rate of serotonergic neurons subsequently raises 5-HT release at the nerve terminal.[2–7]

In addition, blockade by mirtazapine of the α_2-heteroreceptors at the 5-HT nerve terminals prevents the inhibitory effect of norepinephrine on serotonin release, thereby increasing the release of 5-HT.[2–7] The effects of serotonin are mediated via several types of postsynaptic 5-HT receptors. Stimulation of 5-HT_1 type receptors is probably associated with antidepressant and anxiolytic effects, while stimulation of

Figure 1. Pharmacologic Profile of Mirtazapine*



*Adapted from reference 1, with permission. The noradrenergic system exerts a dual modulatory control of serotonergic transmission: an enhancing effect on serotonergic raphe neuron cell firing is mediated by α_1-adrenoceptors, and an inhibitory control on serotonin release is mediated by α_2-heteroreceptors. The net enhancing effect of mirtazapine on 5-HT release is mediated by 5-HT_{1A} receptors because 5-HT_2 and 5-HT_3 receptors are blocked by the compound.

5-HT_2 and 5-HT_3 type receptors is related to adverse effects. Stimulation of 5-HT_2 receptors is associated with insomnia, anxiety, agitation, and sexual dysfunction, whereas stimulation of 5-HT_3 receptors is associated with nausea.[8,9] Mirtazapine increases the release of serotonin, resulting in a net enhancement of neurotransmission via 5-HT_1 type receptors because it directly blocks 5-HT_2 and 5-HT_3 receptors. The blockade of these receptors prevents the development of adverse side effects.

Rats that are devoid of the noradrenergic system (because of pretreatment with the neurotoxin 6-OH dopamine) show no increase in the firing of serotonergic neurons when treated with mirtazapine. Yet, in control rats with a preserved norepinephrine system, mirtazapine significantly increases the firing activity of serotonin neurons, said Dr. de Montigny. "This provides a definite indication that mirtazapine is exerting this effect on the firing activity of serotonin neurons through its activity on the noradrenergic system."

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The Pharmacologic Rationale Behind Antidepressant Efficacy in Severe Depression

The pharmacologic rationale behind antidepressant efficacy in severe depression is still uncertain, said Elliott Richelson, M.D. Studies conducted over the years suggest a desensitization and down-regulation of certain receptors for catecholamines and serotonin.[1] Based on animal and clinical studies, there is also strong evidence of a serotonin role in the mechanism of antidepressant action.[2] Some of the best direct evidence of hypofunction of the serotonergic system in the brains of patients with major depression is the effect of fenfluramine on regional glucose metabolism, as demonstrated in a recent study by Mann and colleagues.[3]

Although psychopharmacologists are still unable to explain convincingly why clinical efficacy takes weeks—while changes at the synapse and drug side effects are seen within hours or days—receptor affinities are nevertheless important in understanding the clinical effects of different antidepressants, said Dr. Richelson. It is not enough to have knowledge of the affinities of drugs for a particular receptor without also having an understanding of the pharmacokinetics, he said. The acute synaptic effects of antidepressants can explain some of their adverse effects, their interactions with other drugs, and the reasons why some antidepressants are more likely than others to cause these adverse events. Antidepressants and electroconvulsive shock have common effects on a multitude of neurotransmitter receptors (Table 1).

Dr. Richelson then reviewed the pharmacologic properties of antidepressants, the possible clinical consequences of receptor blockade, and the receptor binding profile and effects of mirtazapine, a new antidepressant (Figure 1).

Histamine (H_1) Receptor

Possible clinical consequences of blockade: potentiation of CNS depressant drugs, sedation, drowsiness, and weight gain.

Mirtazapine shows H_1 antagonism, but to a significantly lower extent than does the tricyclic antidepressant doxepin. In addition, there are indications that the drug's antagonism at the α_2-receptors—that can lead to CNS arousal—counteracts the blockade of the H_1 receptor.

Muscarinic Cholinergic Receptor

Possible clinical consequences of blockade: blurred vision, dry mouth, constipation, urinary retention, and memory dysfunction.

Mirtazapine has a very low affinity for this receptor site. Dry mouth occurs in some patients; however, this may be a symptom of depression rather than an effect of mirtazapine. No other anticholinergic side effects have been observed.

α_1-Adrenergic Receptor

Possible clinical consequences of blockade: potentiation of the antihypertensive effect of some drugs, postural hypotension, dizziness, and reflex tachycardia.

Mirtazapine has a very low α_1 blockade, and, consequently, shows no related side effects.

α_2-Adrenergic Receptor

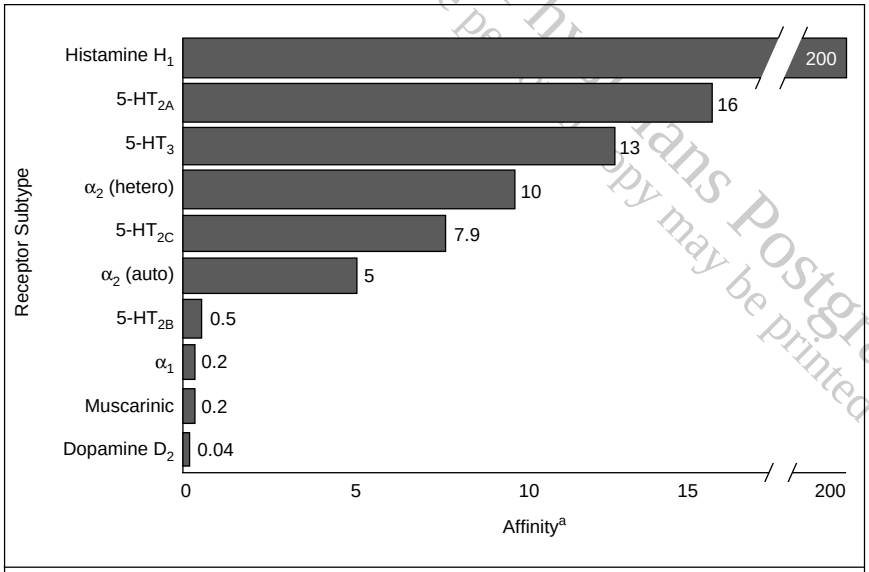
Possible clinical consequences of blockade: reduction in depressive symptoms.

Table 1. Common Effects of Antidepressants and Electroconvulsive Shock (ECS) on Neurotransmitter Receptors*

α_2-Adrenoceptors	Decreased
α_1-Adrenoceptors	Increased, ?ECS
β-Adrenoceptors	Decreased
5-HT_{2A} (postsynaptic)	Decreased, increased with ECS
5-HT_1 (somatodendritic autoreceptors)	Decreased
$GABA_B$	Increased
Dopamine autoreceptors	Decreased
NMDA/Glycine binding site	Decreased affinity

*Data from reference 5.

Figure 1. Receptor Binding Profile of Mirtazapine*



*Data adapted from reference 4.
[a]$10^{-7} \times 1/K_i$, where K_i = inhibitor constant in molarity.

Mirtazapine shows affinity for this receptor that is higher than that of any other antidepressant. The increase of both noradrenergic and serotonergic activity via α_2-autoreceptors and heteroreceptors, respectively, may explain its efficacy.

Dopamine (D_2) Receptor

Possible clinical consequences of blockade: extrapyramidal movement disorders, endocrine changes, and sexual dysfunction in males.

Mirtazapine has very low affinity for these receptors, and, consequently, shows no related side effects.

Serotonin 5-HT_2 Receptor

Possible clinical consequences of blockade: prophylaxis of migraine headache; reduction in anxiety, depression, and psychosis; reduction in sexual dysfunction; sleep improvement; and weight gain.

Mirtazapine's relatively high affinity for these receptors explains the lack of serotonergic side effects with this antidepressant, and its anxiolytic properties.

Serotonin 5-HT_3 Receptor

Possible clinical consequences of blockade: reduction in anxiety, reduction in psychosis, enhancement of memory, and antiemetic effect.

Mirtazapine's relatively high affinity for these receptors explains anxiolytic effects and the lack of nausea.

The overall picture of mirtazapine, said Dr. Richelson, is that of low (or very low) affinity for α_1-adrenergic receptors and cholinergic muscarinic receptors; this explains the absence of adrenergic and anticholinergic side effects. The drug has a relatively pronounced affinity for the histamine H_1 receptor, and the resulting sedation can be of benefit to the many depressed patients, who are also anxious. However, as the dosage is increased, its effects on other receptors tend to counteract the sedation seen with mirtazapine. While Dr. Richelson emphasized that much remains to be understood about the function of different serotonin receptor subtypes, mirtazapine's blockade of 5-HT_2 and 5-HT_3 subtypes, in contrast to the serotonin selective reuptake inhibitors (SSRIs), could explain its lack of serotonergic side effects. In particular, he said, the sexual dysfunction seen with the SSRIs has not been observed with mirtazapine, probably because of its strong blockade of 5-HT_2 receptors. In addition, many of the SSRIs produce typical insomnia, but this is not the case with mirtazapine.

In the ensuing panel discussion, it was pointed out that mirtazapine has no clinically relevant effect on the P450 system, in contrast with several SSRIs.

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Role of Dual Action in Severe Melancholic Depression

Lars Gram, M.D., has long been an advocate of dual action antidepressants, and his studies form the basis for much of the current evidence supporting the higher efficacy of dual action antidepressants.

A study in the 1970s[1] analyzed the response of patients to imipramine in relation to the steady-state plasma concentrations of imipramine and the primary metabolite desipramine. These compounds inhibit reuptake of norepinephrine and serotonin, but their relative potencies are quite different. Imipramine has preferentially an inhibitory effect on serotonin reuptake, whereas the primary metabolite desipramine is largely an inhibitor of norepinephrine reuptake. The results of the study showed that low plasma levels of either imipramine or desipramine were associated with insufficient effect: high plasma levels of both compounds were necessary for a therapeutic response. This suggests that the different effects of imipramine (serotonergic) and of desipramine (noradrenergic) both are necessary for effective antidepressant action.

In recent years, drugs selectively yielding both serotonergic and adrenergic effect have been introduced (dual action). In vitro, the different drugs in this class have different relative potency with respect to the two effects. The in vitro potency studies have to be transferred to the clinical situation, but this transfer is extremely complicated. Furthermore, it is not known which is the most appropriate balance between adrenergic and serotonergic effect. Dutch psychiatrist Hermann van Praag has also suggested that a combined augmentation of serotonin and catecholamine in the central nervous system provide the best condition for antidepressant activity.[2]

Dr. Gram explained that the Danish University Antidepressant Group (DUAG) is a permanent multicenter study group that is composed of participants from several psychiatric departments in Denmark. The group has been conducting research for about 15 years. He then reviewed recent DUAG studies and other data in support of dual action antidepressants. Both studies presented investigated hospitalized patients, randomly assigned to a double-blind treatment regimen with a fixed dose of clomipramine (150 mg/day), a TCA, and either citalopram[3] (40 mg/day) or paroxetine[4] (30 mg/day), both of which are SSRIs. At endpoint, measured by the Hamilton Rating Scale for Depression (HAM-D), 28% of patients who took citalopram showed a complete response compared with 60% of patients who took clomipramine. In the second study, the response rates at endpoint were 22% for paroxetine and 57% for clomipramine. Although it was later suggested by panelists that the doses of SSRIs may have been too low, Dr. Gram said that they were within the manufacturer's standard recommendation for use. He also rejected any implication that the length of the trials was too short and said that the short duration could not explain the dramatic differences in response rates seen in both studies.

Further confirmation of the superiority of dual action antidepressants comes from the retrospective study by Roose and colleagues,[5] and the more recent French study[6] with fluoxetine and venlafaxine. Both studies investigated patients with melancholia and both groups showed a dramatic difference in response that favored dual action drugs, Dr. Gram said: "The DUAG patients appeared to be characterized by more depression, more retardation, and nihilistic delusions. Taken with the other findings, this suggests that patients with melancholia or endogenous depression have a better response to dual action drugs." Increasing numbers of clinicians are coming to a similar conclusion, he said. Although acknowledging that more work is needed in this particular field, Dr. Gram said that current data suggest that the SSRIs should be used only in nonmelancholic patients and the dual action drugs should be used in patients with endogenous or melancholic depression.

There was general agreement with Dr. Gram's viewpoint from the panel of experts. According to Stephen M. Stahl, M.D., Ph.D., "Severe depression is a heterogeneous group of illnesses. We need to know more about it. However, in the meantime, when it comes to treating these difficult types of depression, simultaneous use of two different pharmacologic mechanisms to treat the depression just makes sense."

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