The Pharmacologic Rationale for the Clinical Use of Antidepressants

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This section of The Journal of Clinical Psychiatry *reports on an expert meeting held on May 2–3, 1997, in Aruba. The meeting was supported by an unrestricted educational grant by NV Organon.* *Members of the expert panel were Trond Aarre, M.D., Nordfjordeid, Norway; Otto Benkert, M.D., Professor of Psychiatry, Johannes Guttenberg-Universität, Mainz, Germany; Jonathan R. T. Davidson, M.D., Professor of Psychiatry, Duke University Medical Center, Durham, N.C., U.S.A.; Elias Eriksson, Ph.D., Professor of Pharmacology, Göteborg University, Göteborg, Sweden; Siegfried Kasper, M.D., Professor of Psychiatry, University of Vienna, Austria; John Kogeorgos, M.D., M.R.C.Psych., Professor of Psychiatry, Aghia Olga Hospital, Athens, Greece; Charlotte Kremer, M.D., International Medical Adviser CNS Drugs, NV Organon, Oss, The Netherlands; Stuart Montgomery, M.D., Professor of Psychiatry, Department of Pharmacology, Imperial College School of Medicine at St. Mary's, London, U.K.; Andrew Nierenberg, M.D., Associate Professor of Psychiatry, Massachusetts General Hospital, Boston, Mass., U.S.A.; Philip Ninan, M.D., Emory Clinic, Atlanta, Ga., U.S.A.; Arthur Prange, M.D., UNC School of Medicine, Chapel Hill, N.C., U.S.A.; Elliott Richelson, M.D., Consultant and Donald C. and Lucy J. Dayton Professor, Mayo Medical School, Jacksonville, Fla., U.S.A.; Michael E. Thase, M.D., Professor of Psychiatry, Western Psychiatric Institute and Clinic, Pittsburgh, Pa., U.S.A.; and Andrew Winokur, M.D., Ph.D., Director of Psychopharmacology, Dartmouth-Hitchcock Medical Centre, Lebanon, N.H., U.S.A.*

Mirtazapine is the latest in a line of drugs that have recently been introduced for the treatment of depression. It is now available worldwide and has been used in more than 170,000 patients (May 1997). The novelty of this drug over other antidepressants lies particularly in its unique mechanism of action.

Mirtazapine inhibits neither the reuptake of norepinephrine (NE), serotonin (5-HT), or dopamine (DA) nor the activity of monoamine oxidase, thereby clearly being distinguished from the tricyclic antidepressants (TCAs), newer reuptake inhibitors of either serotonin and/or norepinephrine (SSRI/SNRI), and the monoamine oxidase inhibitors (MAOIs). Its pharmacologic profile is characterized by a potent and direct antagonism of α_2-adrenergic autoreceptors and heteroreceptors and the 5-HT_2 and 5-HT_3 receptors, resulting in an enhancement of both noradrenergic and 5-HT_1-mediated serotonergic neurotransmission. Mirtazapine is usually described as a noradrenergic and specific serotonergic antidepressant or NaSSA.

The expert panel reviewed the role of mirtazapine in major depression, considering new trial results indicating superior efficacy over the serotonin selective reuptake inhibitor (SSRI) fluoxetine in patients with high baseline HAM-D scores. It was argued by many of the participants that these results, taken with similar studies involving other dual action antidepressants, suggest superior efficacy of such drugs over more selective compounds, particularly in the treatment of the more severe forms of depression.[1,2]

In addition, the expert panel suggested that mirtazapine's unique pharmacologic profile, good tolerability, and its lack of pharmacokinetic interactions with other drugs had important implications in considering its clinical role in the treatment of depression and other disorders.

The Pharmacology of Mirtazapine

Mirtazapine is a dual action antidepressant drug which enhances neurotransmission of both NE and 5-HT without influencing monoamine uptake in any way. Moreover, its action on the serotonergic system is specific, which has important beneficial implications for this drug's side effect profile. These two characteristics give rise to mirtazapine's qualification as a NaSSA.

Roger M. Pinder, Ph.D., D.Sc., Medical Director CNS, NV Organon, explained that mirtazapine is a potent antagonist ($pK_i = 7.7$) of both the α_2 autoreceptors—the receptors located on noradrenergic terminals by which NE controls its own release—and the α_2 heteroreceptors—the receptors located on the serotonergic terminals by which NE controls the release of 5-HT.[3] This antagonism explains how mirtazapine enhances both noradrenergic and serotonergic neurotransmission.

Considering the noradrenergic system, Dr. Pinder said that mirtazapine

has a disinhibiting effect on the α_2 autoreceptors, thereby enhancing noradrenergic neurotransmission. This has been clearly demonstrated in vivo: electrophysiologic studies in the locus ceruleus show that whereas clonidine, an α_2 agonist, switches off or alleviates noradrenergic firing, mirtazapine reverses this effect, thus raising the rate of firing. Furthermore, the direct antagonism of α_2 autoreceptors probably accounts for the ability of acutely administered mirtazapine to increase the extracellular concentration of dihydroxyphenylacetic acid (DOPAC), a surrogate marker for NE, in the hippocampus as measured using in vivo microdialysis.[3,4]

However, it is well established that noradrenergic cell bodies also project onto serotonergic cell bodies and control the firing of the 5-HT system.[5,6] These noradrenergic terminals have α_2 autoreceptors that inhibit the release of NE onto α_1 adrenoceptors on the 5-HT cell body. The stimulation of these receptors facilitates the firing of the serotonergic neuron. Thus, by blocking α_2 autoreceptors, mirtazapine enhances the release of NE in the raphe nucleus, which activates α_1 adrenoceptors to increase the firing rate of serotonergic soma.

Mirtazapine has little affinity for α_1-adrenoceptors,[3,4] in contrast to other antidepressants that increase noradrenergic release such as the selective noradrenergic reuptake inhibitors (e.g., desipramine, maprotiline) or mianserin. These drugs are potent α_1-adrenoceptor antagonists, whose action prevents further enhancement of serotonergic neurotransmission by increased NE. Drugs such as desipramine and maprotiline also lack mirtazapine's α_2-adrenoceptor antagonism.[7,8]

Enhancement of serotonergic neurotransmission by mirtazapine was demonstrated in electrophysiologic studies. The resting rate of firing of the dorsal raphe neurons instantly rises as a result of acute exposure to mirtazapine and its noradrenergic facilitating action on the cell bodies.[9] Furthermore, chemical lesioning of noradrenergic neurons prevents this effect, indicating that the increase in serotonin cell firing in the presence of mirtazapine is dependent on the noradrenergic system.

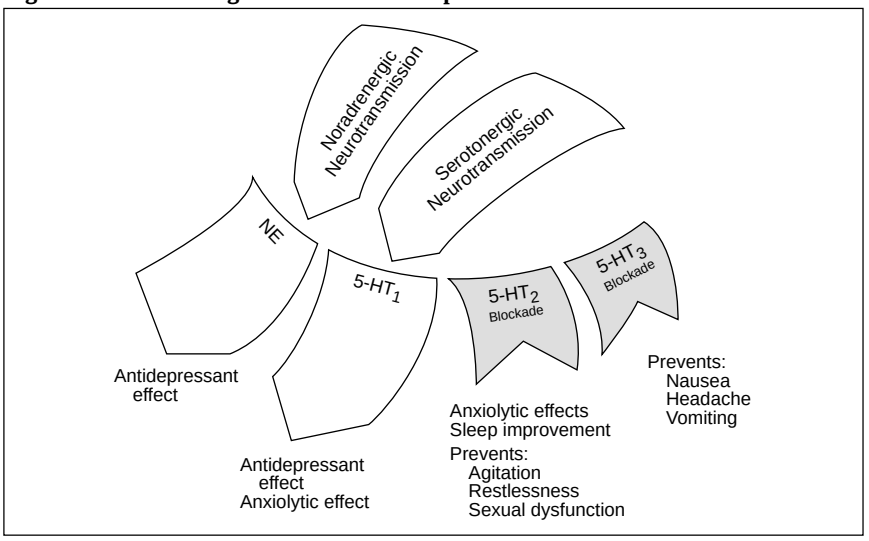
In addition, under physiologic circumstances the release of 5-HT is tonically inhibited by NE acting on α_2 heteroreceptors located on the serotonergic terminals.[10] However, by direct blockade of these α_2 heteroreceptors, mirtazapine has a disinhibitory action, thereby further facilitating 5-HT release.

The effects of released 5-HT are mediated via multiple types of postsynaptic 5-HT receptors.[11] As mirtazapine has no affinity for the 5-HT_1 receptor, and is a potent antagonist of 5-$HT_{2A/2C}$ and 5-HT_3 receptors, the released 5-HT acts mainly through the 5-HT_{1A} receptors.[3] The net clinical effect is therefore an antidepressant effect without the typical SSRI adverse effects (Figure 1).

The manner in which mirtazapine enhances serotonergic neurotransmission is unique and may also produce a faster onset of action relative to many other antidepressants. Drugs like the SSRIs, which inhibit the reuptake of serotonin, produce an acute reduction in the serotonergic firing rate shortly after their administration. This is believed to be because the released 5-HT stimulates the presynaptic 5-HT_{1A} autoreceptors, whose role is to attenuate any abrupt increases in 5-HT release by decreasing both the firing rate of the 5-HT neurons and 5-HT synthesis.[12]

It is only after long-term exposure that the slow desensitization of the 5-HT_{1A} autoreceptor occurs, resulting in an increase in firing rate of these neurons and increased 5-HT release. Animal experiments with mirtazapine show that the serotonergic firing is not reduced acutely but rather increased in this manner which, said Dr. Pinder, suggests mirtazapine should have a faster onset of action than the SSRIs. He said there were hints that this was the case from existing data in clinical trials, although other ongoing work is expected to produce further support for this observation. Thus, concluded Dr. Pinder, mirtazapine not only enhances noradrenergic neurotransmission, but it also facilitates 5-HT_1-mediated serotonergic neurotransmission, resulting in a dual mechanism of action.

Figure 1. Pharmacologic Profile of Mirtazapine



Mirtazapine: The Clinical Trial Data

"Mirtazapine clearly shows superior efficacy over placebo and equivalent efficacy to 'gold standard' tricyclic antidepressants, even in severely depressed patients," said Professor Siegfried Kasper, Vienna, Austria, in an extensive review of the antidepressant's clinical trial program results. Mirtazapine is also efficacious in alleviating anxiety symptoms and sleep disturbances seen in depressed patients.

He also stressed mirtazapine's tolerability, explaining that its specificity on the serotonergic system and low affinity for other receptors leads to an absence of serotonergic and anticholinergic side effects.

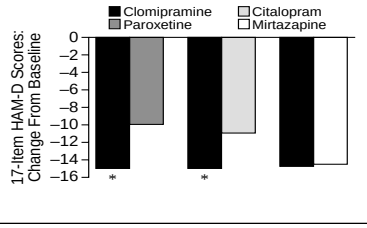
Professor Kasper said it was important to consider mirtazapine's efficacy in the treatment of severe depression independent of other results. He pointed out that clomipramine and amitriptyline, drugs used in mirtazapine's clinical trial program,[13,14] have proven efficacy in the treatment of severe depression. In addition, data from a meta-analysis of patients with a total HAM-D score (17-item) greater or equal to 25 showed that efficacy was equivalent in patients treated with either mirtazapine or amitriptyline.[15]

The efficacy of clomipramine is illustrated by work conducted by the Danish University Antidepressant Group (DUAG) showing clomipramine's superiority to citalopram[16] and paroxetine[17] (Figure 2). There is also some evidence suggesting that SSRIs may not be as effective as dual acting TCAs in the treatment of severely depressed patients.[18,19]

In terms of mirtazapine's side effect profile, sedation was observed in some patients treated with mirtazapine during the clinical trials. Professor Kasper said that, in his clinical experience, this appeared to be clearly related to the dose of mirtazapine used. In general, the higher doses (≥ 15 mg) were less frequently related to sedation, probably because of the greater noradrenergic input at these levels.[20]

During the clinical trial program, mirtazapine-treated patients reported half as much nausea, half as much headache (statistically significant), and no more agitation than those receiving placebo.[30] Although the trials were not set up specifically to address sexual dysfunction, there was no indication that mirtazapine caused this problem. The data show that on some measures fewer patients reported sexual dysfunction than those receiving placebo, a finding in line with mirtazapine's pharmacologic profile (blockade of 5-HT_2 receptors). Professor Kasper commented that in his personal experience sexual dysfunction was not reported with mirtazapine, and he encountered no problems with hypotension or cardiac changes.

Figure 2. Magnitude of Change During Treatment of Hospitalized Patients: Clomipramine Compared to Either Citalopram, Paroxetine, or Mirtazapine



Adapted from references 13, 16, and 17.
*p ≤ .05 citalopram or paroxetine vs clomipramine.

Table 1. Trial Design*

Inclusion criteria: major depressive episode (DSM-III-R), total 17-item HAM-D ≥ 21, item 1 ≥ 2
Number of patients: 133, recruited from the clinical population in the UK, Belgium, and The Netherlands
Length: 6 weeks plus extension up to 6 months
Rating scales: HAM-D, CGI, Visual Analogue Mood Rating Scale, Quality of Life and Enjoyment Scale
Weekly assessments at Weeks 1, 2, 3, 4, and 6
Dosage
Mirtazapine Weeks 1–4: 15–45 mg, with an optional increase from Week 5 and onward to 60 mg
Fluoxetine Weeks 1–4: 20 mg, with an optional increase from Week 5 and onward to 40 mg
Comedication: benzodiazepines allowed

*Abbreviations: CGI = Clinical Global Impressions, HAM-D = Hamilton Rating Scale for Depression.

Dual Action Versus Selective Drugs: Mirtazapine Versus Fluoxetine

Dr. Charlotte Kremer, International Medical Adviser CNS Drugs, NV Organon, presented results of a study comparing the efficacy and tolerability of mirtazapine and fluoxetine.[21]

Patients with a DSM-III-R diagnosis of a major depressive episode, 17-item HAM-D scores ≥ 21, and HAM-D item 1 (depressed mood item) scores ≥ 2 at baseline were recruited from clinical practice (mirtazapine, N = 66, 15–45 mg/day; fluoxetine, N = 67, 20–40 mg/day) (Table 1).

Statistical analysis performed at Weeks 1, 2, 3, 4, and 6 demonstrated statistically significant reductions from baseline in the total 17-item HAM-D scores at Weeks 3 and 4 in favor of mirtazapine. Although this trend was also seen at Week 6, the magnitude of difference did not reach significance at this timepoint (p = .054). However, the absolute difference of four points between the HAM-D score seen at endpoint is clinically relevant and is usually encountered in placebo-controlled studies only.[22]

Total percentage of dropouts was 26% for mirtazapine compared with 31% for fluoxetine. Dropout rates due to adverse events were 10% in the mirtazapine group compared with 13% in

the fluoxetine group. There were no statistically significant differences in percentages of patients complaining of adverse events; somnolence and dry mouth were reported more commonly in the mirtazapine group, and nausea and headache more commonly by patients receiving fluoxetine. However, a cluster analysis of serotonergic side effects, such as nausea, vomiting, and agitation, suggested that substantially more fluoxetine-treated patients reported such problems compared with mirtazapine-treated patients (39% versus 24%). One of 10 patients reported weight gain in the mirtazapine group, and weight loss was reported by 5% of the fluoxetine-treated patients. In conclusion, Dr. Kremer said that, in this group of patients with high baseline HAM-D scores, mirtazapine showed superior efficacy to the SSRI fluoxetine and equivalent tolerability.

The Pharmacology of Antidepressants

Psychopharmacologists have yet to explain convincingly the lag time between the onset of antidepressant action and the onset of therapeutic efficacy, said Dr. Elliott Richelson, Jacksonville, Fla., in a review of the pharmacology of antidepressants (Table 2).

He said that while synaptic effects—along with many side effects—were observed within hours to days, onset of efficacy takes much longer and is probably related to changes in receptors, which in animal models occurred over periods of days to weeks.[24]

Such changes are thought to be due to a desensitization of receptors (loss of sensitivity to neurotransmitters) and down-regulation of receptors (biological destruction). Dr. Richelson said such phenomena could explain why in animals treated with an SSRI antidepressant, only relatively small initial increases in synaptic levels of serotonin were observed in the acute phase, whereas they became more robust with continued treatment.[25] Dr. Richelson emphasized that animal and clinical studies suggest that serotonin plays an important role in the mechanism of antidepressant action. This was first demonstrated 20 years ago by work by Shopsin and colleagues[26] and more recently by Delgado and colleagues[27] who found that depriving remitted patients of tryptophan—the amino-acid precursor of serotonin—leads to a relapse of depression. This was particularly pronounced among patients who had remitted during previous treatment with SSRI antidepressants. Work by Mann and colleagues[28] looking at the effect of fenfluramine on regional glucose metabolism in the brains of depressed patients also supports a hypofunction of the serotonergic system.

Despite an incomplete understanding of mechanisms underlying antidepressants' efficacy, Dr. Richelson said their acute synaptic effects had important implications for predicting adverse effect profiles of antidepressants (Table 3). Dr. Richelson then presented data from his laboratory obtained in experiments with human receptors in vitro.

In terms of norepinephrine reuptake inhibition, by far the most potent drugs are desipramine and protriptyline. The SSRIs had much lower potency, as did venlafaxine, while mirtazapine was virtually devoid of this action. The clinical consequences of such inhibition are tremor, tachycardia, and the augmentation of the pressor effect of some sympathomimetic drugs.

Paroxetine and sertraline show the most potent inhibition of serotonin reuptake, while mirtazapine was devoid of this action. The clinical consequences of 5-HT reuptake blockade are the well-recognized serotonergic side effects, which result from nonselective simulation of all 5-HT receptor subtypes and include gastrointestinal disturbances (appetite loss, nausea, vomiting, and diarrhea), headache, agitation, and sexual dysfunction.

Table 2. Pharmacologic Characteristics of the Ideal Antidepressant*

Rapid onset of action
Intermediate half-life
Defined therapeutic blood level
No side effects
Minimal drug interactions
Low toxicity associated with overdose
Broad spectrum of efficacy

*From reference 23.

Overall, the receptor binding profile of mirtazapine is that of low or very low affinity for α_1-adrenergic and muscarinic receptors, which explains the absence of adrenergic and anticholinergic side effects. Although this antidepressant has a relatively pronounced affinity for the histamine receptor, Dr. Richelson said, in practice at higher doses, this was less clinically relevant than expected, probably because its noradrenergic input from α_2-adrenergic receptor blockade counteracts this effect, in line with previous comments made during the course of the meeting.

Mirtazapine is unique among antidepressants for its blockade of 5-HT_3 receptors, which is thought to have a beneficial effect especially on emesis and also on anxiety and agitation. Mirtazapine also shows antagonism of the 5-HT_2 receptor, as does nefazodone. This receptor blockade may reduce or prevent sexual side effects and improve sleep. Dr. Richelson said that although much remains to be understood about the function of different serotonin receptor subtypes, these serotonin receptor blocking actions clearly appear to be related to mirtazapine's lack of serotonergic side effects and its good tolerability.

Table 3. Pharmacologic Properties of Antidepressants and Their Possible Clinical Consequences*

Property	Possible Clinical Consequences
Blockade of NE uptake at nerve endings	Tremors Tachycardia Erectile and ejaculatory dysfunction Blockade of antihypertensive effect of guanethidine and guanadrel Augmentation of pressor effect of sympathomimetic drugs
Blockade of 5-HT uptake at nerve endings	Gastrointestinal disturbances Increase or decrease in anxiety (dose dependent) Sexual dysfunction Extrapyramidal side effects Interactions with L-tryptophan, MAOIs, and fenfluramine
Blockade of DA uptake at nerve endings	Psychomotor activation Antiparkinsonian effect Aggravation of psychosis
Blockade of H_1 receptors	Potentiation of central depressant drugs Sedation, drowsiness Weight gain Hypotension
Blockade of muscarinic receptors	Blurred vision Dry mouth Sinus tachycardia Constipation Urinary retention Memory dysfunction
Blockade of α_1-adrenergic receptors	Potentiation of the antihypertensive effect of prazosin, terazosin, doxazosin, and labetalol Postural hypotension, dizziness Reflex tachycardia
Blockade of dopamine D_2 receptors	Extrapyramidal movement disorders Endocrine changes Sexual dysfunction (males)

*From reference 23, with permission.

Table 4. Patients for Whom Mirtazapine May Be Particularly Relevant

More severe forms of depression
Long-term treatment
Intolerance to SSRIs/venlafaxine
Melancholia
Depression with accompanying somatic illness
Elderly patients

Which Depressed Patients May Benefit the Most From Mirtazapine?

There is a growing recognition, especially widespread within Europe, that SSRIs are not as efficacious in more severely depressed patients as drugs that enhance both noradrenergic and serotonergic neurotransmission. Results from mirtazapine's clinical trial program and the recent mirtazapine-fluoxetine study combined with results obtained with other dual-acting antidepressants strongly support this notion. Mirtazapine's combination of strong efficacy and good tolerability, especially the absence of serotonergic side effects, was seen to offer particular benefit to these groups of depressed patients (Table 4).

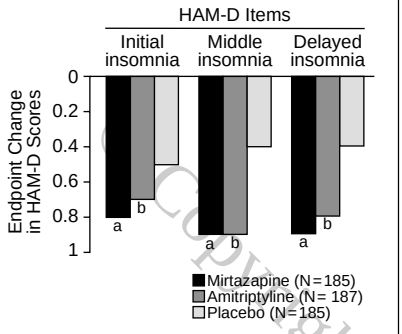
Professor Kasper summed up the European view: "We are trying to reduce the usage of TCAs in Europe, but, at the same time, we are aware that they are one of the best options in the acute treatment of severe depression. A patient who is perceived to be best treated with a TCA, as opposed to an SSRI, would be better off on mirtazapine."

Mirtazapine was also judged to be important in the consideration of long-term antidepressant treatment. Dr. Thase suggested that mirtazapine's advantages over amitriptyline in the long-term treatment of depression[29] were not solely related to its superior tolerability. He outlined increasing concern that reuptake inhibitors, in particular SSRIs but also TCAs, "wear out" or lose efficacy, adding that this may be related to accommodative changes at the level of the synaptic receptors. Hence, he believed that mirtazapine's unique mechanism of action, which is unlikely to be associated with such a "wear-out" effect, offers a convincing argument for use in patients requiring long-term treatment.

Moving on to consider mirtazapine's tolerability and its apparent advantages over the SSRIs, there was a suggestion by the expert panel that patients who are intolerant to SSRIs, TCAs, or venlafaxine stand to benefit from mirtazapine.

Many of the clinicians showed a great deal of interest in mirtazapine's lack of effect on or even improvement of sexual function, as they are seeing substantial numbers of patients who are taking SSRIs or venlafaxine complaining of sexual dysfunction. Dr. Thase added that while nausea is responsible for attrition in the first few weeks of treatment with an SSRI, sexual dysfunction was responsible for attrition later on. Venlafaxine appears to be a less suitable alternative as many intolerant patients experienced side effects similar to those of the SSRIs. Professor Montgomery suggested that venlafaxine could have more side effects than the SSRIs. By contrast,

Figure 3. Endpoint Change in HAM-D Items Initial, Middle, and Delayed Insomnia After 6 Weeks of Treatment With Mirtazapine (5–35 mg/day), Amitriptyline (40–280 mg/day), or Placebo*

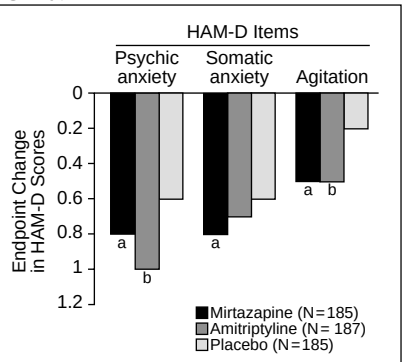


*Intent-to-treat group, last-observation-carried-forward (LOCF) analysis.
Data on file, NV Organon, Oss, The Netherlands.
[a]p ≤ .05 mirtazapine vs placebo.
[b]p ≤ .05 amitriptyline vs placebo.

Table 5. Anxiety Symptoms Commonly Seen in Depressed Patients

Generalized anxiety symptoms
Somatic symptoms (eg, gastrointestinal symptoms, headache)
Agitation
Anorexia/weight loss
Panic attacks
Obsessive-compulsive symptoms

Figure 4. Endpoint Change in HAM-D Items Psychic Anxiety, Somatic Anxiety, and Agitation After 6 Weeks of Treatment With Mirtazapine (5–35 mg/day), Amitriptyline (40–280 mg/day), or Placebo*



*Intent-to-treat group, LOCF analysis.
Data on file, NV Organon, Oss, The Netherlands.
[a]p ≤ .05, mirtazapine vs placebo.
[b]p ≤ .05, amitriptyline vs placebo.

mirtazapine seems to be devoid of these effects.[30] Recently published data also show that, in patients suffering from intolerable nausea during SSRI treatment, addition of mirtazapine results in almost immediate resolution of this adverse event.[31]

The weight gain observed in some patients treated with mirtazapine could be a potential drawback for those presenting with overeating. However, Dr. Nierenberg said that it could be a clinical benefit for the many patients who present with weight loss as a symptom of depression. Dr. Winokur agreed, adding that this may be particularly relevant in the elderly population. He said: "I've recently started consulting at nursing homes, and I am seeing a number of patients every week complaining of weight loss. Although it is impossible to say what the exact reason is, it makes sense to use an antidepressant that is not associated with an anorectic effect or weight loss in these patients."

Dr. Winokur also made a similar argument with respect to the sedation seen with low doses of mirtazapine, which, taken together with its improvements in slow wave sleep, makes it an optimal option for patients who present with symptoms such as insomnia (Figure 3), agitation, anxiety, or comorbid anxiety disorders (Table 5 and Figure 4). This prompted a suggestion from Dr. Nierenberg that mirtazapine should perhaps be regarded as a particularly beneficial antidepressant for patients with melancholia.

Improvement in slow wave sleep produced by mirtazapine was also seen as a major advantage. Existing hypnotics are seen as having many important drawbacks, and, while sleep continuity and latency were important factors, a drug like mirtazapine that could influence sleep architecture was particularly interesting.

Mirtazapine's low potential for interactions with other drugs can be advantageous in treating depression in patients with coexisting somatic disorders, where polypharmacy is common, and, in particular, in the elderly population with depression.

Lastly, Professor Kasper reported some preliminary results from two pilot studies he was conducting looking at the use of mirtazapine in recurrent brief depression and seasonal affective disorder.[32] He said: "We have had little success in treating patients with recurrent brief depression previously, but in an open-label study with mirtazapine involving 12 patients, we have found a good reduction in the frequency of depressive periods, their length, and suicidal thoughts." Initial results from the seasonal affective disorder trial involving 10 patients taking a dose of 30 mg of mirtazapine were also promising.[33]

The value of combination therapy as a strategy in the treatment of depression was debated by the panel. Professor Benkert was of the opinion that it is a strategy most popular among general practitioners rather than psychiatrists. Dr. Davidson suggested that it is often a sign of clinical despair rather than a logical strategy for treatment.

One of the most popular combination therapies was acknowledged to be the concomitant use of benzodiazepines to alleviate the acute agitation, anxiety, and suicidality that may occur alongside antidepressant treatment. The expert panel was of opinion that there are some legitimate reasons for trying combination therapy: for a more rapid onset of action, higher efficacy, and treatment-refractory patients.

Dr. Davidson said the combination of pindolol with SSRI seems relatively promising in terms of increasing the onset of action of these antidepressants, although he acknowledged

that not all the data were positive and further investigations were probably required.[34–37] He made similar comments about the use of lithium in terms of onset of action.

Reference was made to results of the study by Nelson and colleagues[38] combining fluoxetine and desipramine, and it was agreed that the logic behind this strategy was basically to turn a selective drug into a dual action drug resulting in increased efficacy.

In terms of the management of treatment-refractory or only partially responsive patients, augmentation with lithium and T_3 were both regarded as relevant strategies. Combination of antidepressant drugs was regarded as more hazardous, particularly because of the danger of serotonin syndrome, which could be fatal. The group agreed it was more preferable to switch antidepressants rather than combine.

Conclusions

- An understanding of the pharmacology of antidepressants can be relevant in discussing treatment options for different groups of depressed patients.
- A dual mechanism of action, enhancement of both noradrenergic and serotonergic neurotransmission, is likely to be advantageous in the treatment of more severe forms of depression and in patients presenting with prominent symptoms of anxiety, agitation, and/or sleep disturbances.
- The receptor affinities of the different classes of antidepressants can be clearly related to their side effect profile and tolerability.
- Mirtazapine's unique pharmacologic profile appears to be related to advantages over other classes of antidepressants in terms of its efficacy and tolerability.
- The fact that mirtazapine has a low potential for interactions suggests that it can be combined with other drugs in patients for whom polypharmacy is unavoidable.

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