

## EFFECTS OF JOINT ADMINISTRATION OF IMIPRAMINE AND AMANTADINE IN PATIENTS WITH DRUG-RESISTANT UNIPOLAR DEPRESSION

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The paper describes the effect of amantadine (AMA) supplementation on imipramine (IMI) therapy in patients (with treatment-resistant unipolar depression) who fulfilled DSM IV criteria for major depression. Twelve patients were enrolled to the study on the basis of history of their illness and therapy. Following 2 weeks of washout period, the patients were treated with IMI twice daily (100–150 mg/day) for 6 weeks, and then AMA was introduced (twice daily, 100–150 mg/day) and administered jointly with IMI for further 6 weeks. Thereafter, AMA was withdrawn, and the patients were treated with IMI alone for 2 weeks. Hamilton Depression Rating Scale (HDRS) and Beck Depression Inventory (BDI) were used to assess efficacy of antidepressant therapy. IMI changed neither HDRS nor BDI score after 3 or 6 weeks of treatment when compared with washout (before treatment). AMA supplementation significantly reduced both HDRS and BDI scores after 3- or 6-week supplementation. AMA augmentation of IMI treatment was beneficial and lasted even after AMA withdrawal. Moreover, pharmacokinetic data indicate that AMA did not influence significantly the plasma concentration of the IMI and its metabolite, desipramine, in the patients during joint treatment with AMA and IMI, what suggests the lack of pharmacokinetic interaction.

These results suggest that joint therapy with IMI and AMA may be successful in the treatment-resistant unipolar depression.

**Key words:** imipramine, amantadine, clinical and pharmacokinetic studies, therapy-resistant unipolar depression, human

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## INTRODUCTION

It is known that all of currently used antidepressant drugs (ADs) show the therapeutic efficacy in a maximum of 60–80% of patients in a major depressive episode (unipolar or bipolar) fail to demonstrate substantial clinical improvement following their first treatment with antidepressant medication (defined as at least 50% reduction in symptoms score) [e.g. 12, 27]. Therefore, to improve therapy, a combination of ADs from various pharmacological groups or a combination of an AD and a substance that can enhance its effect is used in clinical practice. Recently, much attention has been devoted to the involvement of glutamatergic system and NMDA receptors in particular, in the mechanism of action of ADs [17]. Drugs that antagonize NMDA receptors seem to provide a potential target yielding more efficacious antidepressants. Our previous study indicated that combined treatment with imipramine (IMI) and amantadine (AMA) produced more potent antidepressive activity in the forced swimming model of depression than does either of the drugs alone and that dopamine  $D_{2/3}$  and  $\alpha_1$ -adrenergic receptors may contribute to the mechanism of synergistic action of AMA and IMI in that test [25, 26]. Therefore, in our studies, we decided to treat the selected group of therapy-resistant unipolar patients with IMI, an AD used in clinical practice, together with AMA, an uncompetitive NMDA receptor antagonist, already admitted for

clinical use for the treatment of other diseases, such as Parkinson's disease [3]. AMA – by antagonizing the glutamatergic inhibitory inputs on presynaptic dopaminergic neurons – enhances the dopaminergic neurotransmission [30]. Despite the known dopamine role in the pathophysiology of major depression [e.g. 4], the role of antidepressant medications that enhance dopamine activity in brain has only recently been explored [e.g. 13, 18].

The present study was designed to investigate the effect of AMA supplementation on IMI therapy in patients with treatment-resistant unipolar depression. The plasma levels of IMI and its metabolite, desipramine, were also determined in order to check possible pharmacokinetic interactions with AMA.

## MATERIALS and METHODS

The study was approved by the hospital's institutional review board. Written informed consent was obtained from the patients after the procedures had been fully explained. Subjects, eligible for study participation met DSM IV diagnostic criteria for major depression, and have failed various 8-week trials of antidepressants at the therapeutic doses. Before study entry, all patients were interviewed by 2 psychiatrists. A complete psychiatric and medical history was taken.

Table 1. Characteristics of depressed patients participating in the study

Subject	Sex	Age [years]	Duration of illness [years]	Number of episodes	Duration of episode [months]
1	F	47	21	12	2–12
2	F	52	28	12	4–11
3	M	50	30	8	6–12
4	F	42	14	8	2–10
5	M	51	16	11	4–12
6	F	42	4	4	6–12
7	F	35	20	14	3–13
8	M	46	11	5	3–15
9	F	46	4	3	5–12
10	F	37	5	6	2–6
11	F	48	20	12	3–9
12	F	33	14	10	1–6
Mean $\pm$ SEM		44.1 $\pm$ 1.8	15.6 $\pm$ 2.5	8.8 $\pm$ 1.0	

## Subjects

Patients (inpatients) were recruited on the basis of history of their illness and therapy. The mean duration of illness was  $15.6 \pm 2.5$  years with a number of depressive episodes averaging  $8.8 \pm 1.0$ . The duration of the last episode of depression was 2–15 ( $9.3 \pm 1.2$ ) months. Over these years, the therapy of the patients consisted of treatment with various tricyclic antidepressants, followed by one or more selective serotonin reuptake inhibitors or one of the so-called antidepressants of new generation (e.g. venlafaxine). None of these therapies was effective. Antidepressant therapy has also been augmented by the addition of lithium or/and carbamazepine, and this treatment was never successful. Over the long-lasting period of their illness, the patients have been also treated with benzodiazepines, neuroleptics and mood stabilizers (full documentation of the treatment prior to the present study can be accessed).

## Study design

At the beginning of the present study, the 2 weeks of washout period was introduced, and no benzodiazepines or other psychotropic agents were allowed. Thereafter, twelve patients (3 men and 9 women, aged 33–52 years) were treated with IMI (Imipramin, Polfa Stargard Szczeciński, Poland) twice daily (100–150 mg/day) for 6 weeks, and then AMA (Amantix, Merz Pharmaceuticals, Frankfurth am Main, Germany) was introduced (twice daily, 100–150 mg/day) and administered jointly with IMI for further 6 weeks. Following this period of joint administration of these two drugs, AMA was withdrawn, and the patients were treated with IMI only, for additional 2 weeks. All patients were offered continuation of the drug at study completion.

## Clinician ratings

Patient self-report instruments and clinician ratings were applied to assess clinical status, overall functioning, and quality of life at six time points (i.e. at the beginning of the study, after 3 and 6 weeks of IMI administration, and next 3 and 6 weeks of joint administration of IMI together with AMA, and at the end of the study, i.e. after 2 last weeks of IMI administration alone). Hamilton Depression Rating Scale (HDRS) (21-item) [8] and

Beck Depression Inventory (BDI) [1] were used to assess efficacy of antidepressant therapy.

## Drug assay in plasma of the patients

Pharmacokinetic studies were conducted only in patients who expressed their consent to be tested in this direction (9 patients). Blood samples were collected before the morning dose of IMI and AMA. Plasma concentrations of IMI and its metabolite desipramine were determined with the HPLC method based on the procedure described by Suftin and Jusko [29]. To 1 ml of the blood plasma containing IMI and desipramine, 300  $\mu$ l of 25% ammonium hydroxide were added, and the drugs were extracted with 2 ml of hexane containing 1.5% of isoamyl alcohol (v/v). Recovery of the parent compound and its metabolite after extraction amounted to about 96%. The residue obtained after evaporation of the plasma extracts was dissolved in a mobile phase (described below) and injected into the LaChrom HPLC system (Merck-Hitachi), equipped with an L-7480 fluorescence detector. The analytical column Econosphere C18 (5  $\mu$ m, 4.6  $\times$  250 mm) was purchased from Alltech (Carnforth, England) and was maintained at an ambient temperature. The mobile phase consisted of methanol and acetonitrile (1:1, v/v) containing 1 ml/l of triethylamine. The flow rate was 1 ml/min. Fluorescence of the samples was measured at an excitation wavelength of 240 nm and a 370 nm emission wavelength. All plasma samples were assayed in duplicate.

## Statistical analysis

The clinical and pharmacokinetic data were evaluated by one-way analysis of variance (ANOVA), followed by Dunnett's test.

## RESULTS

Characteristics of the patients participating in the study are presented in Table 1. Twelve patients were admitted, including 3 men and 9 women, aged 33–52 ( $44.1 \pm 1.8$ ) years. The mean duration of illness was  $15.6 \pm 2.5$  years, with the number of depressive episodes averaging  $8.8 \pm 1.0$ , each lasting at least 1 month (Tab. 1). The duration of the last episode of depression was 2–15 ( $9.3 \pm 1.2$ ) months (Tab. 2). Over those months (in the last episode of depression), the therapy of the patients consisted of treatment with tricyclic antidepressants, followed

Table 2. Treatment with antidepressants during the last episode of depression (before therapy with imipramine and amantadine) in twelve patients participating in the study

Patients No.	Duration of the last episode (months)	Antidepressants used during the last episode of depression (months = m)
1.	9	Clomipramine 150 mg (3 m), clomipramine 150 mg + lithium 750 mg (3 m), citalopram 40 mg (3 m)
2.	11	Amitriptyline 200 mg (2 m), clomipramine 150 mg (2 m), clomipramine 150 mg + lithium 750 mg (2 m), venlafaxine 225 mg (3 m), fluoxetine 60 mg (2 m)
3.	10	Clomipramine 200 mg (3 m), desipramine 200 mg (2 m), sertraline 200 mg (4 m)
4.	9	Venlafaxine 225 mg (4 m), fluoxetine 60 mg (3 m), amitriptyline 150 mg (2 m)
5.	12	Clomipramine 150 mg (2 m), clomipramine 200 mg + lithium 750 mg (4 m), paroxetine 40 mg (2 m), venlafaxine 225 mg (2 m), venlafaxine 225 mg + lithium 750 mg (2 m)
6.	12	Clomipramine 200 mg (3 m), amitriptyline 200 mg (2 m), amitriptyline 200 mg + lithium 750 mg (2 m), fluoxetine 60 mg (3 m), desipramine 150 mg (2 m)
7.	13	Amitriptyline 150 mg + carbamazepine 400 mg (2 m), desipramine 200 mg (3 m), fluoxetine 60 mg (3 m), sertraline 200 mg (3 m), venlafaxine 225 mg (2 m)
8.	15	Sertraline 200 mg (3 m), clomipramine 200 mg (2 m), clomipramine 200 mg + carbamazepine 400 mg (3 m), fluvoxamine 200 mg (4 m), fluoxetine 60 mg (3 m)
9.	12	Clomipramine 150 mg (5 m), amitriptyline 200 mg (4 m), sertraline 200 mg (3 m)
10.	3	Clomipramine 150 mg (1 1/2 m), venlafaxine 225 mg (1 1/2 m)
11.	4	Clomipramine 200 mg + lithium 750 mg (2 m), venlafaxine 225 mg (2 m)
12.	2	Citalopram 40 mg (1 m), clomipramine 200 mg + carbamazepine 600 mg (1 m)

None of these therapies was effective

by one or more selective serotonin reuptake inhibitors or one of the so-called antidepressants of new generation (e.g. venlafaxine). None of these therapies was effective. Antidepressant therapy has also been augmented by the addition of lithium or/and carbamazepine, and this treatment was never successful either (Tab. 2).

### Clinician ratings

Clinical and functional effects of the administration of IMI alone or together with AMA (six time points), are presented in Table 3. No differences were seen between baseline scores of male and female patients (HDRS and BDI scores). IMI changed neither HDRS nor BDI score after 3 or 6 weeks of treatment when compared with baseline depression rating scale (before treatment) (Tab. 3). AMA augmentation of IMI treatment significantly reduced both HDRS (by 20.2%) and BDI (by 20.9%) scores after 3-week administration. Combined treatment with IMI and AMA for 6 weeks produced stronger reduction of HDRS scores (by 47.8) and BDI (49.5%) than co-administration of those drugs for 3 weeks. A decrease by more than 50% from the baseline HDRS scores was noted in

four patients. AMA augmentation of IMI treatment was beneficial and lasted even after AMA withdrawal (a decrease by more than 50% from the baseline HDRS scores was noted in ten patients). The following results (mean  $\pm$  SEM) were obtained (at the beginning and at the end of the present study, respectively): scores on HDRS dropped from  $32.2 \pm 1.2$  to  $12.6 \pm 1.3$  [ $F(5.66) = 50.19$ ,  $\alpha = 0.001$ ] (reduction by 60.9%, Tab. 3A), while ratings according to BDI lowered from  $48.3 \pm 2.3$  to  $18.3 \pm 1.5$  points [ $F(5.66) = 52.35$ ,  $\alpha = 0.001$ ] (reduction by 62.3%, Tab. 3B).

The most common side-effects resulting from the IMI treatment was dry mouth and blood pressure drop (by 5–10 mm) and those effects were not changed by addition of AMA to IMI therapy.

### Pharmacokinetic measurements

The concentrations of IMI and its demethylated metabolite desipramine in plasma of the patients are presented in Table 4. Drug concentrations were within the therapeutic range in a majority of the patients (IMI + desipramine 100–300 ng/ml) at most of the studied time points of the therapy, i.e. before the addition of AMA to the IMI treatment, during

**Table 3.** The effect of imipramine (100–150 mg/day, twice daily, IMI) and amantadine (100–150 mg/day, twice daily, AMA) administration in patients with drug-resistant unipolar depression. Hamilton Depression Rating Scale (A) and Beck Depression Inventory (B) were used to assess efficacy of antidepressant therapy

**A. Hamilton Depression Rating Scale (HDRS)**

Patients No.	Washout (baseline)	IMI 3 weeks	IMI 6 weeks	IMI 9 + AMA 3 weeks	IMI 12 + AMA 6 weeks	IMI 14 weeks
1.	33	30	28	23	18	16
2.	31	30	31	29	14	9
3.	33	36	32	20	7	4
4.	30	27	30	22	17	7
5.	31	30	28	26	14	11
6.	36	35	30	27	18	14
7.	41	35	33	31	24	17
8.	29	26	30	24	16	13
9.	26	27	29	24	15	10
10.	30	31	29	22	16	17
11.	37	39	40	35	23	16
12.	29	31	32	25	19	17
Mean ± SEM	32.2 ± 1.2	31.4 ± 1.2	31.0 ± 0.9	25.7 ± 1.2*	16.8 ± 1.3*	12.6 ± 1.3*
%	100.0	97.5	96.3	79.8	52.2	39.1

**B. Beck Depression Inventory (BDI)**

Patients No.	Washout (baseline)	IMI 3 weeks	IMI 6 weeks	IMI 9 + AMA 3 weeks	IMI 12 + AMA 6 weeks	IMI 14 weeks
1.	49	46	39	30	24	22
2.	54	51	57	50	26	17
3.	44	47	43	36	25	12
4.	56	54	55	41	20	8
5.	50	53	51	40	28	19
6.	53	47	42	38	28	20
7.	54	53	47	39	27	24
8.	45	40	46	37	27	20
9.	61	62	57	47	22	16
10.	42	44	38	31	23	26
11.	35	40	43	41	28	20
12.	36	40	46	28	15	15
Mean ± SEM	48.3 ± 2.3	48.1 ± 2.0	47.0 ± 1.9	38.2 ± 1.9*	24.4 ± 1.1*	18.2 ± 1.5*
%	100.0	99.6	97.3	79.1	50.5	37.7

\*  $p < 0.001$  (ANOVA followed by Dunnett's test) vs. respective value at the beginning of the treatment (baseline)

the combined therapy, and after withdrawal of AMA. The relative concentrations of desipramine (compared to IMI) varied among patients, indicating interindividual differences in the activity of imipramine N-demethylase, i.e. in the activity of

cytochromes P-450 3A4 and 1A2 (CYP3A4 and CYP1A2). AMA did not influence the mean antidepressant concentration (IMI + desipramine) in plasma of the patients. The differences in drug concentrations between patients after 6-week IMI

**Table 4.** The concentrations of imipramine (IMI) and its metabolite desipramine (DMI), and total drug concentration (IMI + DMI) in plasma of patients treated with IMI (twice daily, 100–150 mg/day) alone or in combination with amantadine (twice daily, 100–150 mg/day, AMA)

Doses of IMI/AMA [mg/day]	Plasma concentrations [ng/ml]	IMI 3 weeks	IMI 6 weeks	IMI 9 + AMA 3 weeks	IMI 12 + AMA 6 weeks	IMI 14 weeks
150/150 (n = 3)	IMI	205.1 ± 65.8	188.5 ± 63.9	137.6 ± 34.3	236.4 ± 98.5	235.1 ± 85.9
	DMI	158.6 ± 38.5	192.0 ± 83.9	225.9 ± 82.8	224.5 ± 89.8	256.0 ± 85.0
	IMI + DMI	363.7 ± 44.6	380.5 ± 70.7	363.5 ± 77.3	460.9 ± 94.9	491.1 ± 111.8
100/100 (n = 6)	IMI	63.3 ± 15.7	66.0 ± 15.7	67.2 ± 16.9	86.0 ± 40.4	93.4 ± 20.5
	DMI	120.5 ± 37.0	119.9 ± 21.4	109.3 ± 28.2	97.9 ± 27.5	116.9 ± 38.8
	IMI + DMI	185.8 ± 44.2	186.0 ± 20.8	176.5 ± 25.9	183.9 ± 44.8	210.4 ± 40.3

The plasma level of IMI and DMI was measured after 3 or 6 weeks of IMI administration and then AMA was introduced, and administered jointly with IMI for further 3 or 6 weeks. The whole period of IMI administration was 14 weeks, including 6 weeks of joint administration with AMA. The results represent the mean ± SEM of 3 or 6 patients. The data were statistically evaluated by ANOVA followed by individual comparisons using Dunnett's test. All the results are statistically insignificant.

treatment and those treated for 6 weeks with a combination of IMI + AMA did not reach statistical significance (Tab. 4).

## DISCUSSION

The present result demonstrate a benefit of supplementation of the IMI therapy with AMA in twelve studied patients with unipolar depression. Clinical remission, defined as a cut-off point of 7 points or less on the HDRS was observed in two patients and a response, defined as a decrease by more than 50% from the baseline HDRS score [7, 19, 21] was noted in the next eight patients, but partial response defined as the drop by less than 50% but by more than 25% [16] was observed in the other two patients. Since no significant side-effects resulting from the above treatment were observed throughout the study, it seems that AMA is effective and safe augmenting agent in the management of treatment-resistant depression.

The obtained pharmacokinetic data indicate that AMA did not influence significantly the plasma concentration of IMI and its metabolite, desipramine in the patients during joint treatment with AMA and IMI. Therefore, the observed improvement in the clinical state of the treatment-resistant patients may be ascribed to a pharmacodynamic interaction.

AMA appears to act through several pharmacological mechanisms, none of which has been identified as the one chief mode of action, and it has been suggested that AMA might work as antidepressant

not through one, but through several mechanisms thought to be related to antidepressant activity [9]. For example, one cannot exclude that antagonistic action of AMA at the level of NMDA receptors might provide an additional mechanism of antidepressant activity [2, 28]. Indeed, the mechanism of action of AMA at clinically effective doses involves NMDA system. However, by antagonizing the glutamatergic inhibitory inputs on presynaptic dopaminergic neurons, AMA enhances the dopaminergic neurotransmission [30].

In the light of our previous animal studies, indicating the role of dopamine D<sub>2</sub>/D<sub>3</sub> receptors in the mechanism of action not only of ADs drugs but also of AMA [14, 23–25], we postulate that it is the brain dopaminergic system which may underlie the beneficial therapeutic effects of joint IMI and AMA administration in the drug-resistant patients.

The critical role of dopamine in brain reward systems, the association of major depression with Parkinson's disease and the enhancement of dopaminergic activity by several antidepressant treatments suggest that deficiency of dopaminergic function might be associated with major depression. Different approaches have been used to address the issue in human studies. Neuroendocrine studies of dopamine function have not yielded substantial support for an alteration of this function in depression, however, it must be stressed that it is the tuberoinfundibular dopamine system that is investigated in the neuroendocrine strategy, which does not necessarily reflect changes in the meso(cortico)limbic dopamine system, the most

probably more relevant to depression. From SPECT studies – although conflicting results have also been reported – it may be concluded that striatal dopamine release is decreased in the studied subgroup of patients [6]. Recently, the studies with post-mortem brain tissue revealed that the binding of [<sup>125</sup>I]RTI 55 to dopamine transporter was significantly lower in the basal ganglia and central amygdaloid nuclei, whereas the binding of [<sup>125</sup>I]epidepride to D<sub>2</sub>/D<sub>3</sub> receptors was significantly higher in the basal, central and lateral amygdaloid nuclei in major depression compared with control subjects [11]. The above-cited data are consistent with the hypothesis that major depression might be associated with a deficiency of central dopaminergic transmission. Therefore, in our previous study, we have additionally measured the binding of [<sup>3</sup>H]7-OH-DPAT in the peripheral blood lymphocytes and observed that it was significantly increased upon the joint administration of IMI with AMA in patients with drug-resistant unipolar depression [5]. We are perfectly aware that the peripheral cells represent a limited model of brain neuronal function. However, correlations between the status of receptors in the brain and in peripheral blood mononuclear cells have been previously demonstrated for dopamine receptors in Parkinson's disease and schizophrenia [10, 15, 20]. Recently, a decrease in the mRNA encoding dopamine D<sub>4</sub> receptors has been shown in blood lymphocytes of untreated depressed patients, and the D<sub>4</sub> mRNA expression returned to control levels after paroxetine treatment, when patients achieved a significant clinical improvement [22]. The results of our previous study suggest that the binding of [<sup>3</sup>H]7-OH-DPAT to the peripheral blood lymphocytes might be of diagnostic value in checking the clinical improvement of the patients with unipolar depression, however, the data need to be confirmed in a larger number of patients [5].

Nevertheless, the chief finding obtained in the present study justifies the conclusion that joint therapy with IMI and AMA may be successful in the treatment-resistant unipolar depression, although – undoubtedly – conducting future controlled trials with AMA is necessary. AMA augmentation of IMI treatment was beneficial and lasted even after AMA withdrawal. Similar long-lasting effects were also described by Berman et al. [2] who studied the antidepressant effects of single infusion of ketamine. Presumably, the relatively short modula-

tion of glutamatergic neurotransmission triggers the neuroadaptive changes which allow conventional ADs to be effective in otherwise therapy-resistant patients.

Limitations of the study include the small sample size, heterogeneity of the duration of the illness and the variety of ADs used to treat the patients before. On the other hand, the benefits derived from the joint administration of IMI and AMA were significant indeed. So was the fact that clinical improvement was sustained even after AMA withdrawal.

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