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PRELIMINARY COMMUNICATION

EFFECT OF METYRAPONE SUPPLEMENTATION ON IMIPRAMINE THERAPY IN PATIENTS WITH TREATMENT-RESISTANT UNIPOLAR DEPRESSION

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Effect of metyrapone supplementation on imipramine therapy in patients with treatment-resistant unipolar depression. Z. ROGÓŻ, G. SKUZA, J. WÓJCIKOWSKI, W.A. DANIEL, A. WRÓBEL, D. DUDEK, A. ZIĘBA. Pol. J. Pharmacol., 2004, 56, 849–855.

The paper describes the effect of metyrapone supplementation on imipramine therapy in patients (with treatmen-tresistant unipolar depression) who fulfilled DSM IV criteria for major depression. Nine 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 imipramine twice daily (100 mg/day) for 6 weeks, and then metyrapone was introduced (twice daily, 500 mg/day), and administered jointly with imipramine for further 6 weeks. Hamilton Depression Rating Scale (HDRS) and Beck Depression Inventory (BDI) were used to assess efficacy of antidepressant therapy. Imipramine changed neither HDRS nor BDI score after 6 weeks of treatment when compared with baseline (before treatment). Metyrapone supplementation significantly reduced both HDRS and BDI scores after 6-week supplementation. Moreover, pharmacokinetic data indicate that metyrapone did not influence significantly the plasma concentration of imipramine and its metabolite, desipramine in the patients during joint treatment with metyrapone and imipramine, what suggests the lack of pharmacokinetic interaction.

This preliminary study is the first demonstration of the benefit of metyrapone supplementation in imipramine therapy of treatment-resistant unipolar depression and suggests that a change in the level of neurotransmitters, hormones and immunological parameters, which are disturbed in depression, may contribute to the mechanism of the action of this drug.

Key words: *imipramine, metyrapone, 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 who have experienced a major depressive episode (unipolar or bipolar). These patients fail to demonstrate substantial clinical improvement following their first treatment with antidepressant medication (defined as at least 50% reduction in symptom score) [11, 29]. Therefore, in order 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. Among agents which are expected to potentiate antidepressant efficacy, there are inhibitors of glucocorticoid synthesis. In fact, they have shown antidepressant-like properties in some animal models of depression [1, 8, 10]. Also clinical studies have demonstrated the antidepressant effect of metyrapone, aminoglutethimide and ketoconazole; however, these drugs are used mainly in drug-resistant depression [14, 16, 19, 22, 27, 34]. To date, in clinical studies, glucocorticoid synthesis inhibitors or antagonist of glucocorticoid receptors have been administered alone at relatively high doses, so their side-effects were occasionally observed [19]. Combinations of a glucocorticoid inhibitor and an antidepressant drug should help decrease their doses and, in consequence, also alleviate side effects. Among glucocorticoid synthesis inhibitors, metyrapone (which inhibits the enzyme 11-hydroxylase) has the weakest effect on gonadal hormone levels [22, 28]. We found previously that combined treatment with imipramine and metyrapone produced a more potent antidepressant-like effect than either of the drugs given alone in the forced swimming test in rats [24]. It is well known that patients with endogenous depression often display an enhanced activity of the hypothalamic-pituitary-adrenal (HPA) axis [2, 17–19, 30, 32]. Since the hyperactivity of the HPA axis may be a significant factor in the pathogenesis of depression, and since the lack of normalization of the axis activity in the course of therapy with ADs often correlates with the absence of their therapeutic effect, it seems purposeful to examine the effect of joint administration of ADs and glucocorticoid inhibitors in the treatment-resistant depression.

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

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 have been fully explained. Subjects, eligible for study participation met DSM IV diagnostic criteria for major depression, and have failed to satisfactorily respond to 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.

Patients (inpatients) were recruited on the basis of history of their illness and therapy. Nine patients were admitted, including 3 men and 6 women, aged 44–64 years. The mean duration of the illness was 9–20 years, with the number of depressive episodes averaging 3–9. 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 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).

At the beginning of the present study, the 2 weeks of a washout period was introduced, and no benzodiazepines or other psychotropic agents were allowed. Thereafter, nine patients (3 men and 6 women) were treated with imipramine (Imipramin, Polpharma, Warszawa, Poland) twice daily (100 mg/day) for 3 and 6 weeks, and then metyrapone (Novartis Pharma, Bern, Schwitzerland) was introduced (twice daily, 500 mg/day) and administered jointly with imipramine for further 3 and 6 weeks. Hamilton Depression Rating Scale (HDRS) [7] and Beck Depression Inventory (BDI) [4] were used to assess efficacy of antidepressant therapy.

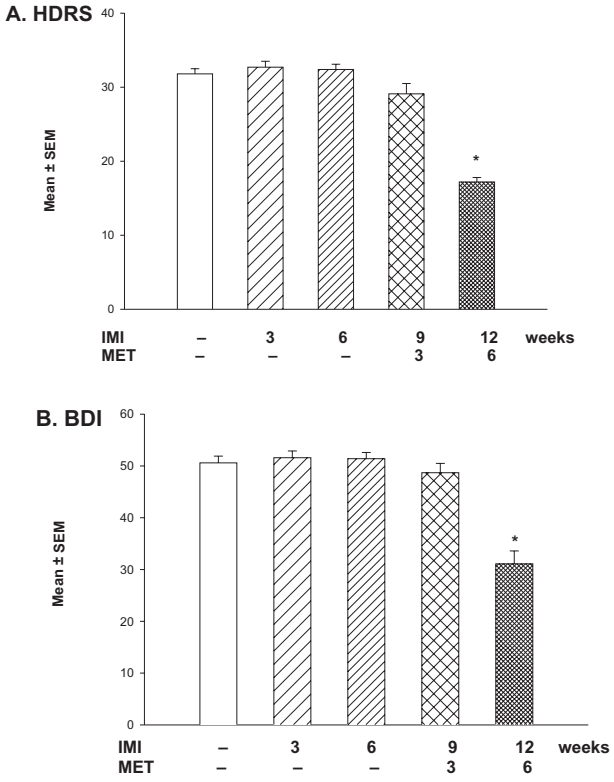

Fig. 1. The effect of metyrapone (MET) supplementation on imipramine (IMI) therapy, evaluated by (**A**) Hamilton Depression Rating Scale (HDRS) and (**B**) Beck Depression Inventory (BDI) scores in patients with treatment-resistant unipolar depression. IMI (100 mg/day, twice daily) was given for 6 weeks, and then MET (500 mg/day, twice daily) was introduced, and administered joint with IMI for further 6 weeks. Data represent the mean ± SEM of 9 patients. * $p < 0.001$ *vs.* respective value at the beginning of the treatment (baseline)

Pharmacokinetic studies were conduced only in patients who expressed their consent to be tested in this direction (6 patients). Blood samples were collected before the morning dose of imipramine and metyrapone. Plasma concentrations of imipramine and its metabolite desipramine were determined with the HPLC method based on the procedure described by Sutfin and Jusko [31]. To 1 ml of the blood plasma containing imipramine and desipramine, 300 µl 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 µm, 4.6 × 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.

The clinical and pharmacokinetic data were evaluated by a one-way analysis of variance (ANOVA), followed, when appropriate, by individual comparisons with the control using Dunnett's test.

RESULTS

Characteristics of the patients participating in the study are presented in Table 1. Nine patients were admitted, including 3 men and 6 women, aged 44–64 (52.4 ± 2.3) years. The mean duration of illness was 9–20 (14.7 ± 1.1) years, with the number of depressive episodes averaging 3–9 (6.4 ± 0.7), and each of them lasted at least 1 month. Clinical and functional effect of the administration of imipramine alone or together with metyrapone (five time points), are presented in Figure 1. No differences were seen between baseline scores of male and female patients (HDRS and BDI score). Imipramine changed neither HDRS nor BDI score after 3 or 6 weeks of treatment when compared with baseline depression scale (before treatment) (Fig. 1). Metyrapone augmentation significantly reduced both HDRS and BID scores after 6-week (but not after 3-week) administration of metyrapone in combination with the imipramine therapy. The following results (mean ± SEM) were obtained. The scores on HDRS dropped from 31.8 ± 0.7 to 17.2 ± 0.6 [$F(4,40) = 52.70$, $\alpha = 0.001$] (reduction by 46%, Fig. 1A). Three female subjects tended to react more strongly [in 3 (No 3, 5 and 6) of 6 patients depression scores decreased by more than 50% from the baseline]. A weaker reaction was observed in other three female and three male patients (a decrease by 40–45.5% from the baseline depression scores) (Tab. 1). Also results of ratings according to BDI scores lowered from 50.6 ± 1.3 to 31.1 ± 2.5 points [$F(4,40) = 26.81$, $\alpha = 0.001$] (reduction by 39.5%, Fig. 1B).

No significant side-effects resulting from the above treatment were observed throughout the study.

Table 1. Characteristics of depressed patients participating in the study

Patients No	Sex	Age (years)	Duration of illness (years)	HDRS			BDI		
				baseline	IMI 6	IMI 12 MET 6	baseline	IMI 6	IMI 12 MET 6
1.	m	57	12	30	31	17	50	47	38
2.	f	45	15	31	31	18	51	54	36
3.	f	60	17	31	33	15	45	50	28
4.	f	53	12	33	36	18	54	56	39
5.	f	45	14	29	31	14	44	47	17
6.	f	53	9	36	35	16	56	53	23
7.	f	64	17	34	34	20	54	56	35
8.	m	51	20	30	31	18	50	49	28
9.	m	44	16	32	30	19	51	51	36
Mean ± SEM		52.4 ± 2.3	14.7 ± 1.1	31.8 ± 0.7	32.4 ± 0.7	17.2 ± 0.6	50.6± 1.3	51.4 ± 1.2	31.1 ± 2.5

Nine patients were recruited on the basis of history of their illness and therapy. Following the 2 weeks of washout period, the patients were treated with imipramine twice daily (100 mg/day, IMI) for 6 weeks, and then metyrapone was induced (twice daily, 500 mg/day, MET), and administered jointly with IMI for further 6 weeks. Hamilton Depression Rating Scale (HDRS) and Beck Depression Inventary (BDI) were used to assess efficacy of IMI or IMI + MET therapy; before treatment (baseline), f – females, m – male

Table 2. The concentration of imipramine (IMI) and its metabolite, desipramine (DMI), and total drug concentration (IMI + DMI) in plasma of patients treated with imipramine (twice daily, 100 mg/day) alone or in combination with metyrapone (twice daily, 500 mg/day, MET)

Plasma concentrations (ng/ml)	IMI 3 weeks	IMI 6 weeks	IMI 9 + MET 3 weeks	IMI 12 + MET 6 weeks
IMI	103.6 ± 32.9	105.2 ± 42.1	106.5 ± 21.9	113.9 ± 31.5
DMI	118.3 ± 23.3	127.8 ± 25.7	114.0 ± 22.7	130.0 ± 26.9
IMI + DMI	221.8 ± 31.5	233.0 ± 52.2	220.5 ± 42.5	243.9 ± 54.0

The plasma level of IMI and DMI was measured after 3 or 6 weeks of IMI administration and then MET was induced, and administered jointly with IMI for further 3 or 6 weeks. The whole period of IMI administration was 12 weeks, including 6 weeks of joint administration with MET. The results represent the mean ± SEM of 6 patients. The data were statistically evaluated by ANOVA followed by individual comparisons using Dunnett's test. All the results are statistically insignificant

The concentrations of imipramine and its demethylated metabolite desipramine in plasma of the patients are presented in Table 2. Drug concentrations were within the therapeutic range in a majority of the patients (imipramine + desipramine 100–300 ng/ml) at most of the studied time points of the therapy, i.e. before the addition of metyrapone to the imipramine treatment and during the combined therapy. Metyrapone did not influence the mean concentration of imipramine [$F(3,20) = 0.75$, ns] and desipramine [$F(3,20) = 0.14$, ns] or (imipramine + desipramine) [$F(3,10) = 0.18$, ns] in plasma of the patients. The differences in drug concentrations between patients after 6-week imipramine treatment and those treated for 6 weeks with a combination of imipramine + metyrapone did not reach statistical significance (Tab. 2).

DISCUSSION

The present results demonstrate a benefit of supplementation of the imipramine therapy with metyrapone in nine studied patients with unipolar depression. A response, defined as a decrease by more than 50% from the baseline HDRS scores [6, 20, 23] was observed in three female patients, but partial response defined as the drop by less than 50% but by more than 25% [15] was noted in the other six patients (three females, three males). Since no significant side effects resulting from the

above treatment were observed throughout the study, it seems that metyrapone is effective and safe augmenting agents in the management of treatment-resistant depression.

The obtained pharmacokinetic data indicate that metyrapone did not influence significantly the plasma concentration of imipramine and its metabolite, desipramine, in the patients during joint treatment with metyrapone and imipramine. The relative concentrations of desipramine (compared to imipramine) varied among patients, indicating inter-individual differences in the activity of imipramine N-demethylase, i.e. in the activity of cytochromes P-450 3A4 and 1A2 (CYP3A4 and CYP1A2). Therefore, the observed improvement in the clinical state of the treatment-resistant patients may be ascribed to a pharmacodynamic interaction.

It may be suggested that metyrapone (a glucocorticoid synthesis inhibitor) may demonstrate antidepressant properties through a combination of several different mechanisms. They include the blockade of the synthesis and the subsequent reduced release of corticosterone (in rats) or cortisol (in humans) into the bloodstream. It was found that metyrapone suppressed plasma corticosterone concentration in stressed animals, but did not change the basal level of that steroid [26]. This fact seems to be of great importance, since in the light of the corticosteroid receptor hypothesis of depression, attenuation of elevated, but not basal, glucocorticoid levels is beneficial to the treatment of depression.

Glucocorticoids act *via* two distinct receptors: the high-affinity mineralocorticoid receptor (MR), and the low-affinity glucocorticoid receptor (GR). MRs are primarily involved in the regulation of basal glucocorticoid level and function, while GRs which are activated by high concentrations of steroids are more important to restoring homeostasis after stress [21]. The blockade of GR produced an antidepressant effect in experimental and clinical studies; however, due to the lack of a specific GR antagonist and because of the adverse effects of mifepristone, this treatment strategy has not been studied in detail so far [14, 19]. On the other hand, the MR antagonist spironolactone impairs the response to ADs [9]. Therefore, only the inhibitory effect of metyrapone on the stress-induced corticosterone concentration seems to be sufficient for treatment of depression. In comparison with other glucocorticoid synthesis inhibitors, such as aminoglutethimide and ketoconazole, metyrapone acts more selectively on glucocorticoid synthesis and weakly affects gonadal steroid secretion [14, 22]. However, by inhibiting 11β-hydroxylase, metyrapone causes an increase in the concentration of corticosteroids 11-deoxy precursors inducing the positive modulator of $GABA_A$ receptor – tetrahydrodeoxycorticosterone [22]. Hence, the antidepressant effect of metyrapone may be connected not only with the reduction of plasma corticosterone concentration, but also with the action of bioactive corticosterone precursors on GABAergic transmission [13].

Moreover, our previous study indicated that joint administration of metyrapone and imipramine induced more potent antidepressive activity in the forced swimming model of depression than either of the drugs alone, and that dopamine $D_{2/3}$ and $5\text{-}HT_{1A}$ receptors may contribute to the mechanism of synergistic action of metyrapone and imipramine in that test. [24].

On the other hand, ADs are known to affect not only the levels of neurotransmitters and hormones, but also some immunological parameters which are disturbed in depression [3, 5, 12]. Our (unpublished) data indicate that metyrapone decreases corticosterone level, but has no effect on proliferation of splenocytes. Combined treatment with metyrapone and imipramine inhibits the stress-induced proliferative activity of splenocytes (beneficial change in the immunological system), but decreases corticosterone level to a similar extent as metyrapone alone. The lack of correlation between corticosterone level and the proliferative activity of splenocytes suggests that the synergistic action of metyrapone and imipramine is probably connected with changes in the neurotransmitter level and/or their receptors. Of possible mediators, $GABA_A$ receptors may be involved, since both tricyclic ADs and metyrapone are known to increase the level of tetrahydroallopregnanolone and tetrahydroallodeoxycorticosterone, respectively, i.e. neuroactive steroids, $GABA_A$ agonists, and, on the other hand, $GABA_A$ agonists potently decrease T cell proliferation [22, 25, 33].

This preliminary study is the first demonstration of the benefit of metyrapone supplementation to antidepressant therapy of treatment-resistant unipolar depression and suggests that the affect on the level of neurotransmitters, hormones and immunological parameters (which are disturbed in depres-

sion) may contribute to the mechanism of the action of this drug. The small sample of patients limits the generalizability of our finding, therefore, we suggest to further investigate the use of metyrapone as an augmenting agent in the treatment-resistant depression and/or depression associated with high cortisol level in larger, double-blind studies.

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REFERENCES

1. Baez M, Volosin M: Corticosterone influences forced swim-induced immobility. Pharmacol Biochem Behav, 1994, 49, 729–736.
2. Barden N, Reul JM, Holsboer F: Do antidepressants stabilize mood through actions on the hypothalamo-pituitary-adrenocortical system? Trends Neurosci, 1995, 18, 6–11.
3. Bauer ME, Perks P, Lightman SL, Shanks N: Restraint stress is associated with changes in glucocorticoid immunoregulation. Physiol Behav, 2001, 73, 525–532.
4. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J: An inventory for measuring depression. Arch Gen Psychiatry, 1961, 4, 561–571.
5. Connor TJ, Leonard BE: Depression, stress and immunological activation: the role of cytokines in depressive disorders. Life Sci, 1998, 62, 583–606.
6. Frank E, Prien RF, Jarrett RB: Conceptualization and rationale for consensus definitions of terms in major depressive disorder. Arch Gen Psychiatry, 1991, 48, 851–855.
7. Hamilton M: A rating scale for depression. J Neurol Neurosurg Psychiatry, 1960, 23, 56–61.
8. Healy DG, Harkin A, Cryan JF, Kelly JP, Leonard BE: Metyrapone displays antidepressant-like properties in preclinical paradigms. Psychopharmacology, 1999, 145, 203–208.
9. Holsboer F: The corticosteroid receptor hypothesis of depression. Neuropsychopharmacology, 2000, 23, 477–501.
10. Khisti RT, Chopde CT, Jain SP: Antidepressant-like effect of the neurosteroid 3α-hydro-5α-pregnan-20--one in mice forced swim test. Pharmacol Biochem Behav, 2000, 67, 137–143.
11. Kornstein SG, Schneider RK: Clinical features of treatment-resistant depression. J Clin Psychiatry, 2001, 62, Suppl 16, 18–25.
12. Maes M, Scharpe S, Meltzer HY, Bosmans E, Suy E, Calabrese J, Coyns P: Relationships between interleukin-6 activity, acute phase proteins, and function of the hypothalamic-pituitary-adrenal axis in severe depression. Psychiatry Res, 1993, 49, 11–27.
13. Majewska MD: Neurosteroids: endogenous bimodal modulators of the $GABA_A$ receptor. Mechanism of action and physiological significance. Prog Neurobiol, 1992, 38, 379–395.
14. Murphy BEP: Antiglucocorticoid therapies in major depression: a review. Psychoneuroendocrinology, 1997, 22, Suppl 1, S125–S132.
15. Nierenberg AA, Molroy R: Declaration of treatment failures. Mod Probl Pharmacopsychiatry, 1997, 25, 17–33.
16. O'Dwyer A-M, Lightman SL, Marks MKN, Checkley SA: Treatment of major depression with metyrapone and hydrocortisone. J Affect Disord, 1995, 33, 123–128.
17. Pearson-Murphy BE: Steroids and depression. J Steroid Biochem Mol Biol, 1991, 38, 557–559.
18. Pearson-Murphy BE: Treatment of major depression with steroid suppressive drugs. J Steroid Biochem Mol Biol, 1991, 39, 239–244.
19. Pirce LH, Malison RT, McDougle CJ, Pelton GH: Antiglucocorticoids as treatment for depression: rationale for use and therapeutic potential. CNS Drugs, 1996, 5, 311–320.
20. Prien RF, Carpenter LL, Kupfer DJ: The definition and operational criteria for treatment outcome of major depressive disorder. Arch Gen Psychiatry, 1991, 48, 796–800.
21. Ratka A, Sutanto W, Bloemers M, De Kloet ER: On the role of brain mineralocorticoid (type I) and glucocorticoid (type II) receptors in neuroendocrine regulation. Neuroendocrinology, 1989, 50, 117–123.
22. Raven PW, O'Dwyer AM, Taylor NF, Checkley SA: The relationship between the effect of metyrapone treatment on depressed mood and urinary steroid profiles. Psychoneuroendocrinology, 1996, 21, 277–286.
23. Riso LP, Thase ME, Howland RH: A prospective test of criteria for response, remission, relapse, recovery, and recurrence in depressed patients treated with cognitive behavioural therapy. J Affect Dissord, 1997, 43, 131–142.
24. Rogóż Z, Skuza G, Wójcikowski J, Daniel WA: Effect of combined treatment with imipramine and metyrapone in the forced swimming test in rats. Behavioral and pharmacokinetic studies. Pol J Pharmacol, 2003, 55, 993–999.
25. Romeo E, Strohle A, Spalletta G, di Michele F, Hermann B, Holsboer F, Pasini A et al.: Effects of antidepressant treatment on neuroactive steroids in major depression. Am J Psychiatry, 1008, 155, 910–913.
26. Roozendaal B, Bohus B, McGaugh JL: Dose-dependent suppression of adrenocortical activity with metyrapone: effects on emotion and memory. Psychoneuroendocrinology, 1996, 21, 681–693.
27. Rupprecht R, Strohle A, Hermann B, di Michele F, Spalletta G, Pasini F, Holsboer F et al.: Neuroactive steroid concentrations following metyrapone administration in depressed patients and healthy volunteers. Biol Psychiatry, 1998, 44, 912–914.
28. Sonino N: Inhibition of adrenal steroid biosynthesis by metyrapone. In: Hormone Antagonists. Ed. Agarwal MK, Walter de Gruyter, Berlin, 1982, 421–429.

29. Sourey D, Amsterdam J, de Montiggny C, Lecrubier Y, Mongomery S, Lipp O, Racagni G et al.: Treatment-resistant depression: methodological overview and operational criteria. Eur Neuropsychopharmacol, 1999, 185, 1–10.
30. Stokes PE: The potential of expressive cortisol induced by HPA hyperfunction in the pathogenesis of depression. Eur Neuropsychopharmacol, 1995, 5, 77–82.
31. Sutfin TA, Jusko WJ.: High-performance liquid chromatographic assay for imipramine, desipramine, and their 2-hydroxylateral metabolites. J Pharm Sci, 1979, 68, 703–705.
32. Thakore J: HPA axis overactivity and the pathogenesis of depression. Ir J Psychol Med, 1996, 13, 3–5.
33. Tian J, Chau C, Hales TG, Kaufman DL: GABA(A) receptors mediate inhibition of T cell responses. Neuroimmunology, 1999, 96, 21–28.
34. Wolkowitz OM, Reus VI, Chan T, Manfredi F, Raum W, Johnson R, Canick J: Antiglucocorticoid treatment of depression: double-blind ketoconazole. Biol Psychiatry, 1999, 45, 1070–1074.

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