Preliminary randomized double-blind placebo-controlled trial of tryptophan combined with fluoxetine to treat major depressive disorder: antidepressant and hypnotic effects

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Objective: Because the initial phase of treatment of depression with a selective serotonin reuptake inhibitor is often complicated by a delayed onset of action of the antidepressant or severe insomnia or both, we investigated whether tryptophan, an amino acid with both antidepressant-augmenting and hypnotic effects, would benefit patients with depression at the beginning of treatment with fluoxetine. **Design:** Randomized, double-blind, placebo-controlled trial. **Patients:** Thirty individuals with major depressive disorder. **Interventions:** Treatment over 8 weeks with 20 mg of fluoxetine per day and either tryptophan (2 to 4 g per day) or placebo. **Outcome measures:** Mood was assessed using the 29-item Hamilton Depression Rating Scale (HDRS-29) and the Beck Depression Inventory (BDI). Laboratory sleep studies were done at baseline and after 4 and 8 weeks of treatment using standard procedures. **Results:** During the first week of treatment, there was a significantly greater decrease in HDRS-29 depression scores, and a similar trend in BDI scores, in the tryptophan/fluoxetine group than in the placebo/fluoxetine group. No significant differences were noted at later time points. With respect to sleep measures, there was a significant group-by-time interaction for slow-wave sleep at week 4. Further analysis revealed a significant decrease in slow-wave sleep after 4 weeks of treatment in the placebo/fluoxetine group, but not in the tryptophan/fluoxetine group. No cases of serotonin syndrome occurred, and the combination was well tolerated, although the 4 g per day dosage of tryptophan produced daytime drowsiness. **Conclusions:** Combining 20 mg of fluoxetine with 2 g of tryptophan daily at the outset of treatment for major depressive disorder appears to be a safe protocol that may have both a rapid antidepressant effect and a protective effect on slow-wave sleep. Further large-scale studies are needed to confirm these initial findings.

Objectif : Parce que l'apparition tardive de l'effet de l'antidépresseur, une insomnie grave, ou les deux, compliquent la phase initiale du traitement de la dépression au moyen d'un inhibiteur sélectif du recaptage

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de la sérotonine, nous avons cherché à déterminer si le tryptophane, acide aminé qui a des effets hypnotiques et augmente aussi l'effet de l'antidépresseur, serait bénéfique pour les patients atteints de dépression au début du traitement à la fluoxétine. **Conception :** Étude contrôlée par placebo, à double insu et randomisée. **Patients :** Trente personnes atteintes d'un trouble dépressif majeur. **Interventions :** Traitement pendant huit semaines avec 20 mg de fluoxétine par jour combinée au tryptophane (2 à 4 g par jour) ou à un placebo. **Mesures de résultats :** On a évalué l'humeur au moyen de l'échelle de dépression de Hamilton à 29 questions (Ham-D-29) et de l'inventaire de dépression de Beck (IDB). On a réalisé des études du sommeil en laboratoire au départ et après quatre et huit semaines de traitement en suivant les procédures normalisées. **Résultats :** Au cours de la première semaine de traitement, les résultats selon l'échelle de Hamilton ont diminué beaucoup plus chez les sujets qui prenaient la combinaison tryptophane/fluoxétine que chez ceux qui prenaient le placebo et la fluoxétine, et l'on a constaté une tendance semblable des résultats selon l'IDB. On n'a constaté aucune différence significative plus tard. En ce qui concerne les mesures du sommeil, on a constaté une importante interaction dans les regroupements selon le temps en ce qui concerne le sommeil à ondes lentes à quatre semaines. Une analyse plus poussée a révélé une diminution importante du sommeil à ondes lentes après quatre semaines de traitement chez les sujets qui prenaient la combinaison placebo/fluoxétine, mais non chez ceux qui prenaient la combinaison tryptophane/fluoxétine. Il n'y a eu aucun cas de syndrome de la sérotonine et la combinaison était bien tolérée, même si la dose de 4 g par jour de tryptophane a produit de la somnolence diurne. **Conclusions :** La combinaison de 20 mg de fluoxétine et de 2 g de tryptophane tous les jours au début du traitement des troubles dépressifs majeurs semble constituer un protocole sûr qui peut avoir à la fois un effet antidépresseur rapide et un effet protecteur du sommeil à ondes lentes. D'autres études à grande échelle s'imposent pour confirmer ces constatations initiales.

The initial phase of treatment for major depressive disorder is notoriously difficult, largely due to the delayed onset of action and the early side effects of antidepressants. Insomnia, either primary or medication-induced, contributes significantly to this problem. Approximately 80% of patients with depressive disorder complain of a deterioration in the quantity or quality of their sleep.[1-3] Complicating this problem is the fact that many antidepressants can cause prolonged worsening of sleep. This issue has been highlighted with the arrival of selective serotonin reuptake inhibitors (SSRIs), which induce insomnia more than tricyclic antidepressants.[4-6] Insomnia triggered or exacerbated by SSRIs can decrease quality of life and lessen compliance at the outset of treatment, contributing to suboptimal outcomes.

Previous research suggests that L-tryptophan, the amino-acid precursor of serotonin, may be a useful adjunct in the treatment of major depressive disorder. Work done in the 1960s and 1970s demonstrated that tryptophan has a robust augmenting effect when used with the older monoamine oxidase inhibitors.[7-10] In the largest study of tryptophan used with a tricyclic antidepressant, placebo was compared with amitriptyline alone, tryptophan (3 g per day) alone, and amitriptyline plus tryptophan in patients with mild to moderate depressive disorder in a 12-week, double-blind protocol.[11] Based on Hamilton Depression Scale scores, the 3 active treatments were equivalent in their effect, and all significantly better than placebo. Other work suggests that tryptophan added to clomipramine may have beneficial effects.[12,13] However, several negative studies of tryptophan augmentation of tricyclics have also been published.[14-16] Taken as a whole, this body of work suggests that tryptophan does not have a consistent augmenting effect when used with reuptake inhibitors; however, to our knowledge, no studies of tryptophan augmentation of SSRIs for major depressive disorder have yet been published.

The hypnotic effects of tryptophan have been studied over many decades. Tryptophan has been shown to increase total sleep time and the amount of slow-wave sleep, to shorten sleep latency, and to decrease the amount of time awake after sleep onset.[17-21] These effects may be mediated directly by direct central serotonergic activation[22] or indirectly by an increase in melatonin levels.[23] Other studies have not supported a hypnotic effect of tryptophan.[24-26] The discrepancy seen across studies may be due to different study populations and the fact that tryptophan absorption and metabolism may be greatly affected by time of day, route of administration, and the macronutrient content of concomitant food intake.[27,28]

The dearth of recent studies of tryptophan can be attributed to its withdrawal from use in both the US and the UK about a decade ago because eosinophilic-myalgia syndrome (EMS) developed in several individuals who received over-the-counter tryptophan that was contaminated during production at a single manufac-

turer.[29] In Canada, a prescription-only tryptophan product has been available since 1990, with no cases of EMS reported.[30] The primary safety concern in Canada has been the possible induction of a serotonin syndrome characterized by severe agitation, nausea and confusion when tryptophan is combined with other serotonergic drugs. Steiner and Fontaine[31] reported serotonin syndrome in 5 patients with obsessive–compulsive disorder receiving 50 to 100 mg of fluoxetine and 1 to 4 g of tryptophan daily. To our knowledge, there are no reports of serotonin syndrome when lower doses of fluoxetine are used with tryptophan.

Given evidence that tryptophan may have both antidepressant-augmenting effects and hypnotic properties, we examined whether tryptophan added to fluoxetine would be superior to fluoxetine alone in the treatment of major depressive disorder. Assessing the optimal dosage of tryptophan and possible side effects of this combination was also a high priority. Three major hypotheses were established *a priori*. First, based on previous research demonstrating that the addition of tryptophan can have a rapid effect on mood,[7,8,10] we hypothesized that, in the early phase of treatment, individuals receiving tryptophan plus fluoxetine would have a greater improvement in mood than those receiving placebo and fluoxetine. Second, we hypothesized that tryptophan might also provide an incremental antidepressant effect over an entire 8-week course of treatment with fluoxetine. Third, based on a large body of sleep research,[17–21] we hypothesized that tryptophan would improve various measures of sleep, including sleep onset latency, total slow-wave sleep and time awake.

Methods

Subjects

Subjects consisted of consecutive patients referred to the mood disorder clinics of the Clarke Division of the Centre for Addiction and Mental Health, and The Toronto Hospital, who met the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) criteria for non-psychotic major depressive disorder based on the Structured Clinical Interview for DSM-IV (SCID).[32] To ensure a relatively homogenous sample and to avoid confounding variables for sleep studies, subjects with a diagnosis of dysthymic disorder, bipolar disorder or ongoing substance abuse were excluded. Subjects were required to be free of all psychotropic medication for at least 1 month before study entry. Subjects were selected to range in age from 18 to 65 years of age and to score 16 or greater on the 29-item Hamilton Depression Rating Scale (HDRS-29);[33] this version of the HDRS includes an 8-item addendum to assess atypical symptoms of depression, such as increased eating behaviour and fatigue. The HDRS-29 was chosen because of the very high rates of atypical symptoms reported in outpatient populations with depressive disorder.[34] A cutoff score of 16 (reflecting mild to moderate depressive disorder) was used to achieve a wide range of symptom severity in our sample; previous research suggests that the antidepressant effects of tryptophan may be clearest in moderate cases of depressive disorder.[11]

Individuals who had previously taken fluoxetine or tryptophan, or who had failed more than 2 previous antidepressant trials of at least 8 weeks at adequate dosages, were excluded. Other exclusion criteria included major ongoing medical illness, sleep disorder, pregnancy or lactation and active suicidal ideation. All participants provided written informed consent, and the protocol satisfied the University of Toronto Ethics Committee requirements.

Procedure

Treatment protocol and group definition

All prospective research subjects were initially administered a diagnostic interview using the SCID and the HDRS-29. Individuals meeting the required entry criteria were given a placebo pill for 5 days under single-blind conditions. Placebo responders (i.e., those having a 33% or greater reduction on the HDRS-29) were excluded from further study. All remaining individuals entered the active treatment protocol and were randomly assigned to 1 of 2 treatment conditions: fluoxetine/placebo or fluoxetine/tryptophan. All were started on a morning dose of fluoxetine (20 mg) and continued this medication over the next 8 weeks. In addition to fluoxetine, each participant also received 2 further pills on each day, taken 20 to 40 minutes before bedtime. One group received placebo, and the other tryptophan.

To minimize side effects at the outset of treatment, subjects in the tryptophan protocol received an initial dosage of 1 g daily for 3 days (one active pill and one placebo pill), then 2 g daily to the end of week 4. At week 4, the dose of tryptophan or placebo was doubled from 2 to 4 pills per day; in the tryptophan protocol this

meant an increase to a dosage of 4 g per day. This increase was built into the protocol, as it was unknown what dosage would optimally achieve the augmentation or hypnotic effects under investigation.

Depression ratings were assessed using the HDRS-29 administered by a trained research psychiatrist and the Beck Depression Inventory (BDI),[35] which is self-rated. HDRS-29 and BDI ratings were done at baseline (day 0) and days 8,22, 28, 43 and 56; an additional BDI rating was done on day 36.

Patients were advised to avoid taking hypnotic medication throughout the protocol, and were excluded if unable to comply.

Adverse events

Adverse events were systematically recorded throughout the study and were assessed using a checklist administered by a research assistant on days 8 and 36 of the protocol. This allowed us to assess the tolerability of both the 2 g and 4 g daily dosages of tryptophan in combination with fluoxetine. The adverse-effects checklist rated the severity of each adverse effect from 0 (not present) to 3 (severe).

Sleep studies

Each study participant completed a baseline sleep study at the end of the placebo run-in, before administration of active medication. Subsequent sleep studies were done after 4 and 8 weeks of treatment. Subjects arrived at the laboratory at 9 p.m.; sleep studies commenced at 11 p.m., and lights were turned on at 7 a.m. Total time in bed was thus standardized for all study nights. Each sleep assessment consisted of a subjective report based on semi-structured interviews and polysomnography. Sleep recordings were carried out in a sleep laboratory and included an electroencephalogram from central (C3-A2 and C4-A1) leads, an electrooculogram (EOG, left and right outer canthi) and an electromyogram (EMG, submental), according to standardized procedures.[36] Electrophysiological recordings were made using Nihon Kohden (Neurofax) electroencephalograph amplifiers with on-line digitizing at a sampling rate of 100 Hz using The Datalab Windows-based software (Rembrandt, Medcare Automation, Amsterdam). Sleep records were scored in 30-second epochs using the sleep analysis software SleepView (Rembrandt, Medcare Automation).

Timing of sleep studies

For each sleep assessment, comprised of 2 consecutive overnight studies, an adaptation night in the sleep laboratory was used to eliminate well-documented first-night effects.[37] The pretreatment sleep study was done to establish a baseline before active antidepressant treatment was implemented. The second sleep study was carried out following week 4 of the protocol to demonstrate the effects of fluoxetine, with or without tryptophan, on sleep in these individuals with depressive disorder. Based on previous research, it was anticipated that patients receiving fluoxetine alone would experience sleep architectural changes and possibly an increase in intervening wakefulness during the night.[4-6] It was also hypothesized that, based on its hypnotic properties, tryptophan might reverse these expected effects of fluoxetine on sleep.

A final recording was carried out at the end of the study following the identical protocol, as described above.

Sleep end points

End points in terms of insomnia measures and changes in sleep with depressive disorder were latency to sleep onset (stage 2 and REM sleep), sleep efficiency (the percentage of time asleep divided by the percentage of time in bed), the number of arousals, and the relative contributions of REM sleep and non-REM sleep stages to total sleep time.[38] Subjective ratings of sleepiness were done within an hour before and 15 minutes after each sleep study using the Stanford Sleepiness Scale.[39]

Statistical analysis

Depression ratings

Hypothesis 1: To assess whether tryptophan combined with fluoxetine had a rapid antidepressant effect, depression scores were compared in the 2 study groups over the first week (days 0, 8) using a 2 (treatment group) × 2 (time) repeated-measures analysis of variance (ANOVA).

Hypothesis 2: The possibility that tryptophan might provide longer-term antidepressant effects over 4 and 8 weeks of treatment was explored using repeated-measures ANOVA based on data collected on days 0, 8, 22 and 28 for first-month effects, and days 0, 28, 43 and 56 for longer-term effects.

Where appropriate, paired *t*-tests and simple effects tests were used to compare changes from baseline across the 2 groups.

Sleep measures

Hypothesis 3: For each of the key outcome variables, a 2 (group) × 3 (time) repeated-measures ANOVA was performed. Where appropriate, paired *t*-tests and simple effects tests were used to compare changes from baseline across the 2 groups.

Based on our specific hypotheses regarding the effects of tryptophan, and on our relatively modest sample size, significance was set at $p = 0.05$.

Results

Patients

In the study period between Nov. 1, 1996, and Dec. 1, 1997, a total of 44 individuals were recruited. There were 5 responders to the initial placebo run-in; thus, 39 individuals began the active treatment phase. Of these, 30 completed the entire protocol, including 6 sleep studies and 8 weeks of treatment. Nine subjects did not complete the entire protocol, including 4 randomized to receive placebo and 5 randomized to receive tryptophan. Of the 4 dropouts in the placebo group, 1 declined active treatment after his baseline sleep study, 2 did not return regularly and dropped out before week 4, and 1 exhibited psychotic symptoms over the first weeks of active treatment. Of the 5 dropouts in the tryptophan group, 1 dropped out before receiving active treatment, 2 were lost to follow-up in the first weeks of treatment, 1 developed a surgical problem at week 4, and 1 exhibited confusion; further assessment revealed that this latter individual had experienced cognitive difficulties before the onset of the study and likely suffered from a mild organic brain syndrome that predated treatment.

Among the 30 patients who completed the study, there were 11 women and 6 men in the placebo group, and 10 women and 3 men in the tryptophan group. There were no significant differences between the 2 treatment groups in age (mean 41.8 standard deviation [SD] 12.6 years in the placebo group v. mean 45.5 SD 11.0 years in the tryptophan group), age of onset of depression (mean 29.8 SD 13.1 years in the placebo group v. mean 29.4 SD 13.3 years in the tryptophan group), or number of previous depressive episodes (mean 3.5 SD 2.1 in the placebo group v. 3.8 SD 4.4 in the tryptophan group).

Depression measures

Only the 30 individuals who had completed the entire protocol were included in the following analyses. There was no significant difference in baseline HDRS-29 depression scores between the 2 groups (mean 24.0 SD 6.1 in the fluoxetine/placebo group v. mean 27.2 SD 5.6 in the fluoxetine/tryptophan group, $t = -1.50$, $p = 0.15$); however, baseline BDI scores were significantly lower in the fluoxetine/placebo group (mean 18.3 SD 5.0 in the fluoxetine/placebo group v. mean 23.1 SD 6.9 in the fluoxetine/tryptophan group, $t = -2.14$, $p = 0.04$).

Fig. 1 indicates that both treatment groups experienced a decrease in HDRS-29 ratings over the 8 weeks of the study.

In terms of our first hypothesis, that in the early phase of treatment, individuals receiving tryptophan plus fluoxetine would have a greater improvement in mood than those receiving placebo and fluoxetine, repeated-measures ANOVA of HDRS-29 scores over the first week of treatment indicated a significant main effect of time ($F = 39.70$, $p < 0.001$), but not of group ($F = 0.20$, $p = 0.66$). Consistent with our working hypothesis, the group-by-time effect was significant ($F = 6.62$, $p = 0.016$). The mean change from baseline score (Fig. 2) for the tryptophan/fluoxetine group was mean –7.8 SD 4.8 (paired $t = -5.88$, $p < 0.001$), and for the placebo/fluoxetine group it was mean –3.3 SD 4.5 (paired $t = -2.83$, $p = 0.012$).

Repeated-measures ANOVA of BDI scores over the first week of treatment revealed a significant main effect of time ($F = 10.98$, $p = 0.003$). There was a trend for a group-by-time effect ($F = 3.61$, $p = 0.069$), while the main effect of group was nonsignificant ($F = 1.54$, $p = 0.23$). The BDI score after 1 week of active treatment was significantly lower than baseline in the tryptophan/fluoxetine group (paired difference mean –4.8 SD 6.3, paired $t = -2.65$, $p = 0.02$), but not in the placebo/fluoxetine group (paired difference mean –1.3 SD 3.4, paired $t = -1.54$, $p = 0.14$).

In terms of our second hypothesis, that tryptophan might provide an incremental antidepressant effect over an entire 8-week course of treatment with fluoxetine, repeated-measures ANOVA of HDRS-29 scores across days 0, 8, 22 and 28 indicated a significant main effect of

time ($F = 25.25$, $p < 0.001$). The group-by-time effect ($F = 2.00$, $p = 0.14$) and the main effect of group ($F = 0.05$, $p = 0.82$) were nonsignificant. Repeated-measures ANOVA of BDI scores across days 0, 8 and 28 revealed no significant differences attributable to group.

Across days 0, 28, 43 and 56, the group-by-time effect ($F = 0.41$, $p = 0.75$) and the main effect of group ($F = 0.40$, $p = 0.53$) were nonsignificant. No significant findings attributable to group were found for BDI scores over these time points. Based on the lack of differences attributable to group, no further analyses were completed on these data.

Sleep measures

In terms of our third hypothesis, that tryptophan would improve various measures of sleep including sleep onset latency, total slow-wave sleep and time awake, Table 1 summarizes the sleep measures for the 2 study groups at weeks 0, 4 and 8 of the protocol. At baseline, there were no significant differences between the 2 groups on any of the sleep measures. With active treatment, there were main effects of time for REM onset latency (ROL), Stage 2 sleep percentage, slow-wave sleep percentage (SWS%) and REM sleep percentage. Collapsing data for the 2 groups, paired t-tests revealed a highly significant increase in ROL at week 4 versus baseline (paired difference 56.8 SD 87.8, $t = 3.43$, $p = 0.002$), and at week 8 versus baseline (paired difference 67.2 SD 96.0, $t = 3.77$, $p = 0.001$). There was no significant change between weeks 4 and 8. Percentage of Stage 2 sleep increased significantly from baseline to week 4 (paired difference 7.1 SD 13.4, $t = 2.79$, $p = 0.01$), then decreased significantly between week 4 and week 8 (paired difference –4.1 SD 10.1, t = –2.17, $p = 0.04$). SWS% decreased significantly over the first 4 weeks of treatment (paired difference –5.5 SD 8.0, $t = -3.59$, $p = 0.001$), and over the full 8 weeks of treatment (paired difference –4.6 SD 7.1, $t = -3.53$, $p = 0.001$) but not

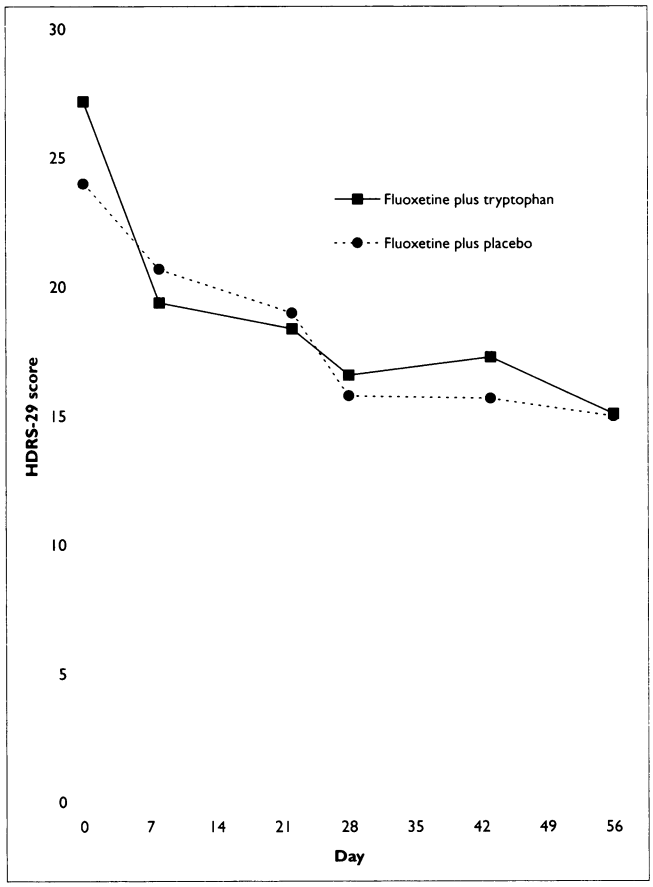

Fig. 1: Raw scores on the 29-item Hamilton Rating Depression Scale (HRDS) over 8 weeks for patients receiving fluoxetine plus tryptophan ($n = 13$) or fluoxetine plus placebo ($n = 17$).

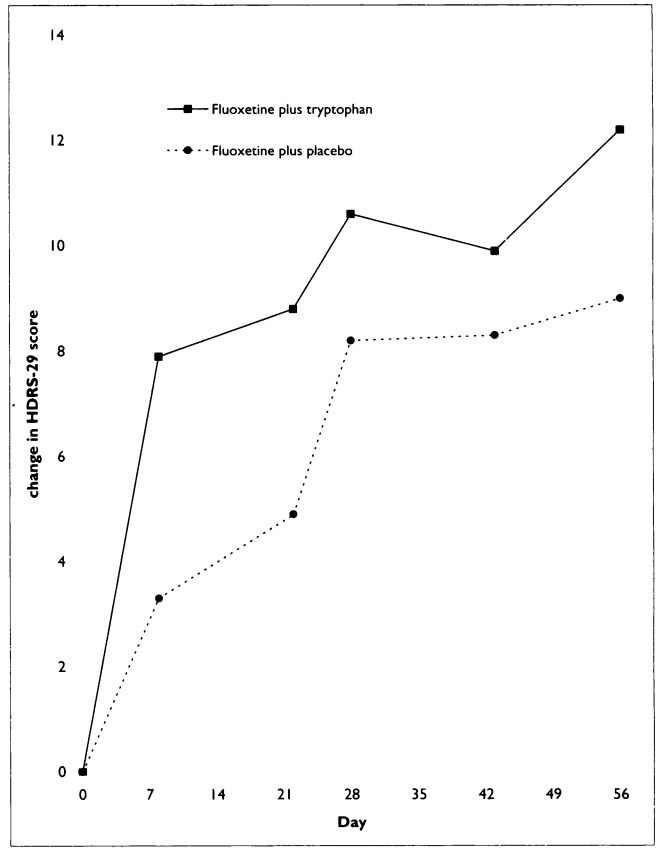

Fig. 2: Change in score from baseline scores on the HDRS for patients receiving fluoxetine plus tryptophan ($n = 13$) or fluoxetine plus placebo ($n = 17$). *Significant difference between the fluoxetine plus tryptophan group and the fluoxetine plus placebo group ($F = 6.62$, $p = 0.016$).

between weeks 4 and 8. REM sleep percentage decreased over the first 4 weeks of treatment (paired difference –5.0 SD 8.1, $t = -3.24$, $p = 0.003$), but was not different at week 8 versus either baseline or week 4.

No main effects of group were found. There was a significant group-by-time effect for SWS%. Paired *t*-tests indicated a significant decrease in SWS% at week 4 in the placebo group (paired difference –7.3 SD 8.6, $t = -3.52$, $p = 0.003$) but not in the tryptophan group (paired difference –2.5 SD 6.3, $t = -1.32$, $p = 0.22$). A simple effects test on these difference scores using baseline SWS% as a covariate indicated a trend for a greater decline in SWS% in the placebo group than in the tryptophan group at week 4 ($F = 3.45$, $p = 0.075$). At week 8, there was a significant decrease in the SWS% from baseline in the placebo group (paired difference –4.6 SD 8.0, $t = -2.37$, $p = 0.03$) and in the tryptophan group (paired difference –4.7 SD 5.9, $t = -2.77$, $p = .018$). After the decline in SWS% in the placebo group at week 4, there was a significant increase between weeks 4 and 8 (paired difference 2.8 SD 4.2, $t = 2.72$, $p = 0.015$), whereas a more gradual decrease from pretreatment through weeks 4 and 8 was evident with tryptophan.

No significant differences attributable to group were found on subjective sleep ratings using the Stanford Sleepiness Scale.

Adverse events

The most serious treatment complication encountered in this study was the development of psychosis in an individual receiving fluoxetine and placebo, which may or may not have been due to the treatment. Otherwise, there were no cases of serious toxicity reported in either treatment group. We cannot rule out the possibility that the few early dropouts who were lost to follow-up may have experienced side effects that were not reported to us. Notwithstanding, we found the combination of tryptophan and fluoxetine to be very well tolerated overall.

Table 2 summarizes the frequency of adverse events in the 2 study groups at day 8 and day 36. The first 10

Table 1: Sleep measures for the patients with major depressive disorder in a randomized double-blind placebo-controlled trial of tryptophan combined with fluoxetine

	Group; week; mean (and standard deviation)							
	Fluoxetine plus placebo			Fluoxetine plus tryptophan				
Variable	0	4	8	0	4	8	Time effect, *F*	
Sleep onset latency, min	(84)	(17)	(26)	(12)	(23)	(22)	$F = 0.96$ df = 2,25 Not significant (NS)	$F = 0.47$ df = 2,25 NS
REM onset latency, min	(30)	(77)	(90)	(44)	(80)	(86)	$F = 7.28$ df = 2,25 $p = 0.003$	F = 0.65 df = 2,25 NS
	(18)	(8)	(9)	(11)	(14)	(14)	F = 0.60 df = 2,25 NS	$F = 0.73$ df = 2,25 NS
Awakenings index, number of	(3.6)	(4.0)	(6.1)	(3.8)	(1.9)	(3.1)	$F = 1.10$ df = 2,23 NS	$F = 0.75$ df = 2,23 NS
Wake, %	(7.5)	(7.2)	(7.8)			(11.6)	$F = 2.62$ df = 2,25 $p = 0.09$	$F = 0.05$ df = 2,25 NS
Stage 1 sleep, %	(3.4)	(3.5)	(3.8)	(5.8)	(2.1)	(1.7)	$F = 0.24$ df = 2,25 NS	$F = 2.98$ df = 2,25 $p = 0.07$
Stage 2 sleep, %						(7.1)	$F = 4.45$ df = 2,25 $p = 0.02$	$F = 0.23$ df = 2,25 NS
Stage 3 and 4 (slow-wave) sleep, %		(9.1)	(8.9)	(7.3)	(7.8)	(5.6)	$F = 5.77$ df = 2,25 $p = 0.009$	$F = 3.85$ df = 2,25 $p = 0.035$
REM, %	(8.1)	(7.7)	(6.6)	(4.3)	(5.1)	(8.1)	$F = 5.56$ df = 2,25 $p = 0.01$	$F = 0.35$ df = 2,25 NS

subjects in the protocol (3 in the tryptophan group and 7 in the placebo group) were not administered the side-effects checklist on day 8 due to an administrative error. This error was corrected mid-study, and 6 of these 10 subjects (2 in the tryptophan group and 4 in the placebo group) were administered the side-effects checklist on day 36. Thus, a total of 20 subjects (10 in the tryptophan group and 10 in the placebo group) were administered the questionnaire on both day 8 and day 36, with 6 more completing the checklist on day 36 only.

For data collected on each of days 8 and 36 of the protocol, the frequency of each side effect was compared across the 2 treatment groups using the χ^2 test. There were no statistically significant differences across the 2 groups for any of the side effect items on either day. Considering only the 20 subjects who were administered the side-effects checklist on both days, 4 patients in the tryptophan group and none in the placebo group reported new onset of daytime drowsiness at day 36, following the increase in daily dosage from 2 to 4 g. Similarly, 3 subjects in the tryptophan group and none in the placebo group reported new onset of tiredness/fatigue at day 36. Five individuals in the tryptophan group and 4 in the placebo group reported new onset of middle/late insomnia at day 36.

Discussion

The primary goal of this preliminary study was to determine whether combining tryptophan with fluoxetine at the very outset of treatment of major depressive disorder would have mood-enhancing or sleep-promoting effects. We found that, in the first week of treatment, tryptophan addition produced a significantly greater decrease in depression scores than did placebo addition to fluoxetine. No additional antidepressant benefit of tryptophan was noted over the full course of treatment. Tryptophan addition also appeared to lessen the impact of fluoxetine-induced decrements in slow-wave sleep. No serious toxicity was found with the fluoxetine/tryptophan combination. Taken as a whole, these results provide preliminary evidence that combining tryptophan (particularly a 2 g daily dosage) with 20 mg daily of fluoxetine may be a useful strategy in the early phase of treatment of major depressive disorder.

Previous research has indicated that tryptophan can have robust augmenting effects if added to monoamine oxidase inhibitors[7-10] or clomipramine,[12,13] but only modest effects when added to other tricyclic antidepressants.[14-16] Taken together with the current results, this would suggest that tryptophan may have unique synergistic effects when used with other serotonergic drugs. This may be due to its ability to directly enhance levels of serotonin at presynaptic terminals by providing substrate for neurotransmitter synthesis; most antidepressants work via reuptake blockade or inhibition of neurotransmitter breakdown. The fact that the antidepressant-augmenting effects of tryptophan occurred in

Table 2: Side effects reported on day 8 and day 36 in patients receiving fluoxetine plus tryptophan (2 or 4 mg) or fluoxetine plus placebo

	Day of protocol; treatment group; number (and %) of patients			
	Day 8		Day 36	
	Tryptophan (2 mg) plus fluoxetine $n = 10$	Placebo plus fluoxetine $n = 10$	Tryptophan (4 mg) plus fluoxetine $n = 12$	Placebo plus fluoxetine $n = 14$
Daytime drowsiness	2 (20)	3 (30)	4 (33)	4 (29)
Tiredness/fatigue	5 (50)	2 (20)	8 (67)	6 (43)
Early insomnia	1 (10)	1 (10)	3 (25)	1 (7)
Middle/late insomnia	4 (40)	3 (30)	7 (58)	6 (43)
Headache	2 (20)	1 (10)	1 (8)	3 (21)
Difficulty concentrating	3 (30)	3 (30)	6 (50)	5 (36)
Dizziness	0	1 (10)	0	2 (14)
Nausea	2 (20)	1 (10)	2 (17)	1 (7)
Sexual dysfunction	3 (30)	2 (20)	4 (33)	3 (21)
Increased anxiety	2 (20)	1 (10)	3 (25)	4 (29)
Confusion	1 (10)	1 (10)	2 (17)	3 (21)
Akathisia	0	0	0	0
Tremor	0	0	0	2 (14)

the first week, while standard antidepressants usually take 2 to 4 weeks to work, may reflect these different mechanisms of action.[40]

As predicted, tryptophan addition to fluoxetine had a measurable effect on slow-wave sleep; however, there was no significant effect on sleep latency or night-time awakenings. In a previous study in a normal population, tryptophan promoted slow-wave sleep at a 10 g daily dosage but not at 5 g or less per day.[18] Animal studies have shown that serotonin applied to particular brain areas induces slow waves on elecroencephalography,[41] which may explain our clinical findings.

While we acknowledge the need for close monitoring of side effects when combining serotonergic agents, the current results suggest that, at the outset of treatment for major depressive disorder, 2 g of tryptophan combined with 20 mg of fluoxetine daily is well tolerated. This contrasts with the findings of Steiner and Fontaine,[31] who added 1 to 4 g daily of tryptophan to much higher dosages of fluoxetine (50 to 100 mg daily) in patients with obsessive–compulsive disorder. In addition to using a lower dose of fluoxetine, the gradual introduction of tryptophan, starting at a low initial dose, is strongly recommended. The use of prescription-only tryptophan, manufactured under the highest standards, is clearly of utmost importance. In our study, all 13 patients receiving tryptophan had an increase in dosage to 4 g daily after week 4; however, there was no apparent benefit from this increase. In fact, it may have produced daytime drowsiness in several individuals. More work is necessary to determine whether continuation of the 2 g daily dosage would be beneficial beyond 4 weeks.

The initial weeks of antidepressant treatment are often hampered by ongoing suffering and an increased likelihood of noncompliance. Insomnia, whether primary or drug-induced, contributes significantly to this problem. Tryptophan, given its safety and tolerability when used as described above, its rapid onset of action and its sleep-protective effects, may provide a significant advantage over other agents used in combination with SSRIs. Another important consideration is that there is no need for drug-level monitoring with tryptophan, as there is for lithium, thyroid hormone and tricyclic antidepressants when added to SSRIs.

Trytophan was administered as a single evening dose in the current study to optimize its hypnotic effects. Previous work has demonstrated that, after a 3 g dose of tryptophan, plasma levels return to baseline after about 8 hours.[42] This suggests that tryptophan levels were raised during the night, but only minimally during the day, in the current protocol. More work is needed to determine whether daytime administration of tryptophan might have a more robust antidepressant effect. The overall sample size was limited by the intensive nature and cost of the sleep studies in particular. As often happens with small samples, there were modest differences in baseline depression scores between the 2 groups, which may limit the interpretation of the results.

Notwithstanding, the current data offer preliminary support for both an early antidepressant effect and a slow-wave sleep protective effect when tryptophan is added to fluoxetine at the outset of treatment for major depressive disorder. Further studies with larger samples are needed to confirm these initial results.

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