# Cognitive-Behavioral Therapy Added to Fluoxetine in Major Depressive Disorder after 4 Weeks of Fluoxetine-Treatment: 16-Week Open Label Study

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***Background:*** *Major depressive disorder (MDD) not responding to antidepressant treatment poses challenges in planning therapy and prognostic uncertainties. Adjunctive treatment to antidepressants with cognitive-behavioral therapy (CBT) may be useful for these patients.*
***Objective:*** *Determine the efficacy of CBT augmentation in patients with MDD not responding to fluoxetine.*
***Material and Method:*** *Ten patients diagnosed with MDD, by Diagnostic and Statistical Manual of Mental Disorders Fourth edition (DSM-IV) criteria between December 2007 and July 2008 were enrolled to the present study. All patients had taken fluoxetine at least 20 mg a day and for at least 4 weeks prior to consent. Baseline Montgomery Asberg Depression Rating Scale (MADRS) ratings were all moderate to severe (22-44 point). The maximum number of sessions of CBT was 16. Patients treated with CBT for at least 8 weeks were defined as the completed treatment group. Response was defined as a reduction in MADRS score by at least 50 percent from baseline and remission was defined as a reduction in score of 10 or less.*
***Results:*** *Fluoxetine augmentation with CBT was a significantly effective treatment in patients with MDD not responding to 4 week-fluoxetine treatment alone according to MADRS, Clinical Global Impression-Severity of illness and the 9-item Patient Health Questionnaire, Thai Version ($p < 0.001$, $p = 0.002$ and 0.004 respectively). The overall response and remission rates were 100% and 70% respectively. The VAS satisfaction scores increased from baseline significantly ($p < 0.001$). Overall quality of life of all patients by WHOQOL-BREF was improved significantly ($p < 0.001$).*
***Conclusion:*** *Adding CBT to fluoxetine in patients with MDD who did not respond to 4 weeks treatment of fluoxetine had significantly more efficacy than previous fluoxetine treatment alone. With no control group, a randomized and controlled method might substantiate these promising preliminary findings.*

***Keywords:*** *Cognitive-behavioral therapy, Major depressive disorder, Fluoxetine*

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Major depressive disorder (MDD) is a common mental illness. The life-time prevalence of MDD is about 11%[1]. It is associated with significant morbidity and economic burden[2]. Depression also is a significant contributor to suicidal behavior and completed suicide[3,4]. Research efforts into effective treatment combinations for initial treatment resistance are important to influence reduction of morbidity and mortality.

Fluoxetine is a selective serotonin reuptake inhibitor (SSRI) antidepressant. It is an effective antidepressant in MDD and has fewer side effects than tricyclic antidepressants (TCAs)[5-7]. Although most patients with depression respond to fluoxetine, some do not, warranting consideration of alternative or combined treatments. Fluoxetine augmentation by other medication, especially tricyclics, may be effective for these patients. However, some patients prefer

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psychotherapy augmentation because of adverse events or other reasons. Hence, fluoxetine augmented by psychological treatment may be a positive second step.

CBT is a focused and time-limited psychotherapy, which is effective in MDD. It is a well-established and effective treatment for a number of mental illnesses such as depression, panic disorder and generalized anxiety disorder etc[8]. CBT for depression yields significant clinical improvements from 51-87%[9]. Some studies report that the response rate of CBT combined with antidepressant in adults is higher than preceding antidepressants or CBT alone[7,10]. CBT combined with fluoxetine was also more effective than fluoxetine or CBT alone in adolescents[11]. However, adjunctive CBT in patients with MDD who do not respond to antidepressants has not been studied.

The primary purpose of the present study was to determine the efficacy of CBT in treating depressed patients who do not respond to fluoxetine. The secondary purpose was to evaluate patient satisfaction and quality of life in depressed patients not responding to 4-week treatment of antidepressants.

## Material and Method

### *Participants*

Patients diagnosed with major depressive disorder (MDD) by the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth edition (DSM-IV)[12] between December 2007 and July 2008 were enrolled to the present study. Patients were recruited from Maharaj Hospital, University Hospital of the Faculty of Medicine, Chiang Mai University and Suanprung Psychiatric Hospital, Thailand. The ethical review committee for research in human subjects, Ministry of Public Health the research and the ethic committee of the Faculty of Medicine, Chiang Mai University both approved the protocol.

Inclusion criteria were male or female patients, age 18-60 years, a DSM-IV diagnosis of MDD at consent, and taking at least 20 mg/day of fluoxetine at least 4 weeks prior to consent. The Montgomery Asberg Depression Rating Scale (MADRS) inclusion criterion was moderate to severe (22-44 points). Exclusion criteria were a current or past diagnosis of psychotic disorder, bipolar disorder, substance dependence (except nicotine and caffeine), moderate to severe suicidal behavior as per the MADRS, a general medical condition preventing continuation or treatment response and having received any psychotherapy within 3 months prior to consent. Discontinuation criteria included intolerably adverse events from fluoxetine treatment, cooperation difficulties with CBT, so much improvement of symptoms such that it was not necessary to continue CBT, consent withdrawal, loss to follow-up more than 4 weeks and finally judgment of the therapist with the patient's approval that it was beneficial to discontinue CBT.

### *Intervention*

All of the therapists had CBT training with supervision. The training course included a four-day workshop by David Westbrook, a director of the Oxford Centre for Cognitive Behavioral Therapy. All of the therapists were supervised by trained therapists at least 12 sessions. The therapists developed a manual for the present study. The patients met the therapist for a CBT session every week and a session lasted one hour. The maximum number of therapy sessions was 16. Completion of CBT treatment was defined as the group of patients treated for at least eight sessions. Every session of therapy was recorded with an MP3 recorder and randomly audited for adherence to the manual. The doses of fluoxetine were fixed after study commencement.

### *Outcome measures*

The primary outcome measure for severity of depression was the MADRS. The secondary outcome measures for depression were the 9-item Patient Health Questionnaire-Thai Version (PHQ-9T) and Clinical Global Impression-Severity of illness (CGI-S). The quality of life was assessed with the 26-item WHOQOL-BREF Thai version, and satisfaction of therapy was measured by visual analog scale for satisfaction (VAS satisfaction).

### *Statistical analysis*

The effectiveness was analyzed by using the intention-to-treat, last observation carried forward principle. As there was normal distribution, the MADRS and WHOQOL-BREF were analyzed with the student paired t-test. However, PHQ-9T, CGI-S, WHOQOL-BREF and VAS for satisfaction were not distributed normally and therefore, the Wilcoxon signed rank test was used for analyzing these data. The rate of response (MADRS reduced to 50% from baseline) and remission (MADRS < 10) are presented. A p-value of less than 0.05 was considered statistically significance different from the baseline.

## Results

### *Base-line clinical and demographic data*

Ten subjects with MDD were enrolled in the present study. The demographic data and characteristics of participants are presented in Table 1. The average age of the subjects was 34.4 (± 8.6 years). Two subjects were male patients and eight were female patients. Seven subjects were married and three were single. The mean onset of MDD and treatment were at age 30.4 (± 8.1 years). The average baseline dose of fluoxetine was 26.0 ± 14.3 mg/day. The average baseline scores for the MADRS, CGI-S, VAS for satisfaction, PHQ-9T and WHOQOL-BREF are presented in Table 1.

**Table 1.** Baseline characteristics of patients with MDD (n = 10)

| Variable | Mean (SD) |
|---|---|
| Age (years) | 34.4 (8.6) |
| Sex (n) | |
| Female | 8 |
| Male | 2 |
| Marital status | |
| Single | 3 |
| Married and cohabiting | 7 |
| Age at onset of MDD (years) | 30.4 (8.1) |
| Age at treatment (years) | 30.4 (8.1) |
| Number of admission | 1.1 (1.0) |
| Dose of fluoxetine (mg) | 26.0 (14.3) |
| MADRS | 33.0 (5.2) |
| PHQ-9T | 19.8 (3.9) |
| CGI-S | 4.5 (1.0) |
| VAS for satisfaction | 4.2 (0.4) |
| WHOQOL-BREF | 67.5 (13.7) |

Data were presented as number and mean (standard deviation)
Abbreviations: MADRS: Montgomery Asberg Depression Rating Scale; PHQ-9T: 9-item Patient Health Questionnaire, Thai Version; CGI-S: Clinical Global Impression - Severity; VAS for satisfaction: visual analog scale for satisfaction; WHOQOL-BREF; WHO quality of life-BREF

### *Treatment*

There were 10 patients. Seven patients completed the treatment. The other three patients had early response to treatments. Two patients remitted from depression as early as week 4. The average number of CBT session attended was 8.4 (± 3.5). The range of numbers of CBT sessions was 4 to 12 sessions.

### *Efficacy*

Analyses revealed a significant improvement within patients in the MADRS, PHQ-9T and CGI-S scores from baseline to the last sessions in the intention-to- treat sample. The MADRS score was reduced significantly from baseline as early as week 4 ($p < 0.001$). The PHQ-9T scores were reduced from baseline significantly in weeks 8, 12, and 16 ($p = 0.04$, 0.01 and 0.004, respectively). The CGI-S scores were significantly reduced from baseline at weeks 4, 8, 12 and 16 ($p = 0.004$, 0.002, 0.002 and 0.002, respectively) (Table 2 and Fig. 1).

All patients responded to adjunctive CBT with fluoxetine treatment-the overall rate of response was 100 percent. The response rates at weeks 4 and 8 were 40 and 70% respectively (Fig. 2). The overall rate of remission was 70%. The rates of remission at weeks 4 and 8 were 20 and 40% respectively. All patients were satisfied with CBT treatment. The VAS satisfaction scores were reduced from baseline significantly at week 4, 8, 12, and 16 ($p < 0.001$). Overall quality of life of all patients was improved significantly. The

**Table 2.** Mean differences from baseline (week 0) of measurements of MDD in 10 patients in the intention to treat sample

| Measurement | Week 4 | Week 8 | Week 12 | Week 16 |
|---|---|---|---|---|
| MADRS (SD) | 16.70 (8.92)[a] | 21.10 (9.23)[a] | 24.60 (6.19)[a] | 24.60 (6.19)[a] |
| PHQ-9T[b] | 10.9 (7.05) | 13.2 (6.53) | 14.4 (5.52) | 14.4 (5.52) |
| CGI-S[c] | 2.1 (1.73) | 2.7 (1.50) | 3.3 (1.16) | 3.3 (1.16) |
| VAS for satisfaction[d] | -0.5 (0.53)[d] | -0.7 (0.48)[d] | -0.8 (0.42)[d] | -0.8 (0.42)[d] |
| WHOQOL-BREF[e] | -24.2 (22.90) | -31.30 (20.13) | -36.5 (18.99) | -36.5 (18.99) |

[a] $p < 0.001$ for comparison with base-line score by paired t-test
[b] Analyses by Wilcoxon signed ranks test, p-value at week 4,8,12 and 16 = 0.04, 0.01, 0.004 and 0.004 respectively
[c] Analysis by Wilcoxon signed ranks test, p-value at week 4,8,12 and 16 = 0.004, 0.002, 0.002 and 0.002 respectively
[d] $p < 0.001$ for comparison with base-line score by Wilcoxon signed rank test
[e] Analyses by paired t-test, p-value at week 4,8 = 0.009, 0.001 respectively and $p < 0.001$ at week 12 and 16

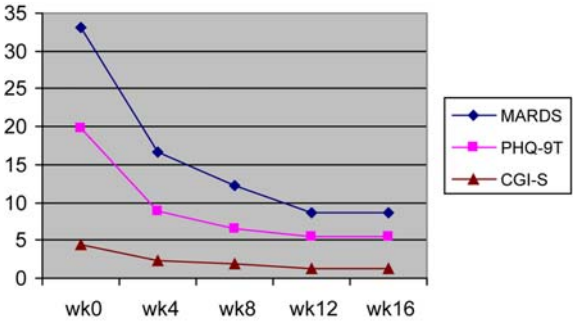


**Fig. 1** Mean score on MADRS, PHQ-9T, CGI-S and WHOQOL-BREF for Major depressive disorder during 16 week study

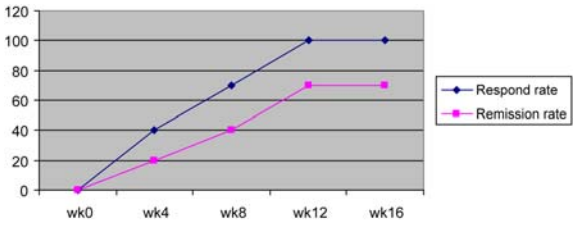


**Fig. 2** Percentage of response and remission rates of fluoxetine augmented by CBT, in 10 patients with MDD not responding to fluoxetine

WHOQOL-BREF was reduced significantly from baseline at weeks 4, 8 ($p = 0.009$ and 0.001), 12 and 16 ($p < 0.001$).

## Discussion

The authors found that the adjunctive CBT with fluoxetine yielded significant advantages in patients with MDD who did not respond to 4 weeks treatment of fluoxetine. All patients had a significant improvement in week 4 according to the MADRS and CGI-S and in week 8 according to the PHQ-9T. All patients responded to adjunctive CBT with fluoxetine by week 12 and 70% of the patients were in remission by week 12. These results were similar to a previous study for the use of both CBT and medication to treat patients with depression[11,13]. In addition, some studies report that CBT combined with fluoxetine in the treatment of depression in adolescents has greater efficacy than placebo and CBT alone[11,14].

After adjunctive CBT with fluoxetine, all patients were more satisfied with treatment than before the adjunctive treatment. The VAS satisfaction scores for CBT were significantly improved from baseline by week 4. These results are similar to previous studies for cognitive-behavioral therapy to prevent relapse from major depression in pediatric cases[15]. Similar to satisfaction, all patients had improvement in quality of life after adjunct CBT with fluoxetine. The WHOQOL-BREF was improved significantly from baseline by week 4.

The limitation of the present study was the lack of a control group (such as CBT or fluoxetine alone). A randomized controlled study would be useful to substantiate the present findings. The next limitation was the short duration of fluoxetine treatment. The 4-week fluoxetine treatment may be an inadequate period for drug response. The last limitation was a small sample size of the present study.

In summary, the adjunctive CBT with fluoxetine in patients with MDD who had not responded to treatment with fluoxetine, showed significantly more efficacy than with preceding fluoxetine treatment alone.

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# การรักษาโรคซึมเศร้าแบบเปิดสลากด้วยการบำบัดความคิด และพฤติกรรมเป็นเวลา 16 สัปดาห์ เสริมให้แก่ผู้ป่วยที่รักษาด้วยยาต้านเศร้าฟูออกซีทีน 4 สัปดาห์

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**ภูมิหลัง**: ปัจจุบันยังมีผู้ป่วยโรคซึมเศร้าอย่างรุนแรง (major depressive disorder) จำนวนหนึ่งไม่ตอบสนองต่อการรักษาด้วยยาต้านเศร้าซึ่งเป็นอุปสรรคต่อการวางแผนรักษา และการพยากรณ์โรค ดังนั้นการเสริมการรักษาด้วยการบำบัดความคิด และพฤติกรรม (cognitive-behavioral therapy) ร่วมกับยาต้านซึมเศร้าน่าจะทำให้ผู้ป่วยโรคซึมเศร้าอย่างรุนแรงตอบสนองการรักษาได้ดีขึ้น

**วัตถุประสงค์**: ในการศึกษานี้เพื่อศึกษาประสิทธิภาพของการเสริมการรักษาด้วยการบำบัดความคิด และพฤติกรรมร่วมกับยาต้านซึมเศร้าในผู้ป่วยที่ดื้อต่อการรักษาด้วยยาต้านเศร้าฟูออกซีทีน

**วัสดุและวิธีการ**: กระทำการศึกษาในผู้ป่วยโรคซึมเศร้าอย่างรุนแรงตามเกณฑ์การวินิจฉัยความผิดปกติทางจิตเวช ฉบับปรับปรุงครั้งที่สี่ โดยทำการศึกษาในช่วงเดือนธันวาคม พ.ศ. 2550 ถึง เดือนกรกฎาคม พ.ศ. 2551 ผู้ป่วยทั้งหมดต้องได้รับยาต้านเศร้าฟูออกซีทีนอย่างน้อย 20 มิลลิกรัมต่อวัน และรับประทานติดต่อกันอย่างน้อย 4 สัปดาห์ก่อนยินยอมเข้าร่วมโครงการศึกษา โดยระดับของภาวะซึมเศร้าของผู้ป่วยก่อนเข้าร่วมโครงการศึกษาตามแบบประเมิน Montgomery Asberg Depression Rating Scale (MADRS) ต้องมีคะแนนอยู่ในช่วง 22-44 ซึ่งจัดว่ามีภาวะซึมเศร้ารุนแรงระดับปานกลางถึงระดับรุนแรงมาก ผู้ป่วยจะได้รับการรักษาเสริมด้วยการบำบัดความคิด และพฤติกรรมไม่เกิน 16 ครั้ง อย่างไรก็ตามถ้าผู้ป่วยได้รับการรักษา 8 ครั้ง ขึ้นไปถือว่าได้รับการรักษาครบสมบูรณ์ ถ้าผู้ป่วยมีระดับคะแนนของภาวะซึมเศร้าตามแบบประเมิน MADRS ลดลงอย่างน้อยร้อยละ 50 แสดงว่าตอบสนอง ต่อการรักษา และมีคะแนน 10 คะแนน หรือ ต่ำกว่าแสดงว่าหายจากภาวะซึมเศร้า

**ผลการศึกษา**: จำนวนผู้ป่วยเข้าร่วมโครงการมีทั้งหมด 10 ราย พบว่าการบำบัดความคิด และพฤติกรรมเสริมมีประสิทธิภาพดีในผู้ป่วย MDD ที่ไม่ตอบสนองต่อการรักษาด้วยยาต้านเศร้าฟูออกซีทีนภายใน 4 สัปดาห์เพียงอย่างเดียว หลังจากผู้ป่วยได้รับการบำบัดความคิด และพฤติกรรมเสริมพบว่าคะแนนของ MADRS, Clinical Global Impression-Severity of illness และ 9-item Patient Health Questionnaire ฉบับภาษาไทยลดลงอย่างมีนัยสำคัญทางคลินิก ($p < 0.001$, $p = 0.002$ และ $p = 0.004$ ตามลำดับ) ผู้ป่วยมีอัตราการตอบสนองต่อการรักษาสูงถึงร้อยละ 100 และมีอัตราการหายถึงร้อยละ 70 นอกจากนี้ยังพบว่าคะแนนความพึงพอใจต่อการรักษาเพิ่มขึ้นอย่างมีนัยสำคัญทางคลินิก ($p < 0.001$) และคะแนนคุณภาพชีวิตโดยรวมจากแบบประเมิน WHOQOL-BREF เพิ่มขึ้นอย่างมีนัยสำคัญทางคลินิก ($p < 0.001$) ด้วยเหมือนกัน

**สรุป**: การเสริมการบำบัดความคิด และพฤติกรรมให้แก่ผู้ป่วยโรคซึมเศร้าที่ดื้อต่อการรักษาด้วยยาต้านเศร้าฟูออกซีทีนหลังจากที่ผู้ป่วยรักษาด้วยยาเป็นเวลา 4 สัปดาห์ แล้วพบว่าเพิ่มประสิทธิภาพในการรักษา โดยทำให้ผู้ป่วยมีอาการดีขึ้น และบางรายหายจากภาวะซึมเศร้า การศึกษานี้มีข้อจำกัด เพราะเป็นการศึกษาเบื้องต้น และไม่มีกลุ่มควบคุม ดังนั้นการศึกษาอนาคตที่มีกลุ่มควบคุมเปรียบเทียบน่าจะช่วยยืนยันผลการศึกษาดังกล่าว