The Influence of Fluoxetine Therapy Combination of Rational Emotive Behaviour Therapy Againts the Improvement of Depression Symptoms, Cognition Function and Improvement of Brain-Derived Neurotrophic F

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Submission date: 15-Oct-2021 01:39PM (UTC+0700)
Submission ID: 1674494347
File name: 15110-Article_Text-29334-1-10-20210412.pdf (832.99K)
Word count: 4340
Character count: 23360

The Influence of Fluoxetine Therapy Combination of Rational Emotive Behaviour Therapy Againts the Improvement of Depression Symptoms, Cognition Function and Improvement of Brain-Derived Neurotrophic Factors Serum Levels in Patients with Depressive

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Abstract

Introduction: Depression is a health problem in the world that has affected more than 300 million people around the globe. This health problem is characterized by feeling sad, depressed, irritability as well as distortion of cognition such as self-criticism, feeling of guilt, feeling of worthlessness, lower self-confidence, pessimism and hopelessness where their manifestations may vary for each individual. **Method:** In this study, it compares the fluoxetine group combination of Rational Emotive Behavior Therapy (REBT) with the fluoxetine group in the treatment of reducing symptoms of depression and improving cognitive function. This research is an experimental research with pre-test and post-test control group design. The sampling technique was done by using consecutive sampling for each group. **Results:** From the results of the study it was found that the mean of Hamilton Depression Rating Scale (HDRS), the Indonesian version of the Montreal Cognitive Assessment (MoCA-Ina) and Brain-Derived Neurotrophic Factor (BDNF) serum levels in the samples given by both groups experienced statistically improvements. **Conclusion:** there is an effect on the provision of fluoxetine therapy combination of REBT compared to fluoxetine therapy alone in improving depressive symptoms, cognitive function as well as increasing BDNF serum levels.

Key words: *Depression, Cognitive function, Fluoxetine, REBT, BDNF*

Introduction

Depression is a health problem in the world that has affected more than 300 million people around the world which is characterized by feelings of sadness[1] depressed, irritability and distortion of cognition such as self-criticism, guilt, feelings of worthlessness, lower self-confidence, pessimism and hopelessness manifestations may vary for each individual ([2],[13]).

In Canada, approximately 79% of depressed patients experience functional impairments in work function, both decreasing work productivity and absenteeism. Occupational disorders often have an impact on family and psychosocial relationships in depressed patients. Cognitive dysfunction can be a major mediator of functional disorders in depression. In the study of observation for 3 years against depressed patients, complain of cognition has been reported as much as 94% during the acute depression episode, and the remaining as much as 44%, with full or partial remission of symptoms during treatment. Meta-analysis showed that cognitive deficits in executive function are still found in patients after treatment for depression, this may explain persistent psychosocial disorders in remission ([4],[6],[9]).

Cassano *et al.* conducted a double blind study comparing paroxetine treatment (20-40 mg daily) and fluoxetine (20-60 mg daily) for 1 year, and as many as 242 patients were involved. Cassano *et al.* concluded that both of these antidepressants proved to be suitable for long-term treatment of depression, and that both could improve cognition [11].

The combination of psychotherapy and pharmacotherapy is increasingly common in psychiatry as the evidence accumulates that many conditions respond better to combined treatment than to either modality alone (Gabbard and Kay 2001). Because both treatments affect the brain, in a very real sense, they are both biological treatments. However, the mechanisms of action of the two treatments may occur in very different areas of the brain. Goldapple et al. (2004), using PET, scanned 17 unmedicated patients with unipolar depression before and after a 15- to 20-session course of cognitive-behavioral therapy. They compared the findings to a separate group of 13 depressed patients who responded to paroxetine. The psychotherapy appeared to alter brain regions that medications did not touch. The psychotherapy was associated with increases in metabolic activity in the anterior cingulate and the hippocampus. By contrast, paroxetine showed increases in metabolic activity in the prefrontal cortex and decreases in the brain stem and subgenual cingulate [20].

Analysis of research conducted in the TADS (Treatment for Adolescents with Depression Study Team) study has shown that a new CBT strategy that can potentially heal (i.e., Rational Emotive Behavior Therapy (REBT)), clinical improvement is mediated by changes in perfectionism and distorted thinking. Felicia *et al*'s results show that the REBT/CBT group, pharmacotherapy (i.e., sertraline), and a combination of both are equally effective in the management of young depression ([7],[18],[20]).

Based on previous studies where it compared levels of Brain-Derived Neurotrophic Factor (BDNF) fluoxetine and sertraline groups in week 6 showed significant differences. From week 6 BDNF comparison of the two groups, it showed that the fluoxetine group was superior in increasing BDNF compared to the Sertraline group. Ramanathan *et al*. claimed that fluoxetine can improve the cognitive condition of patients suffering from depression. The improvement will occur mainly in learning capacity and memory. However, this particular study was developed in the experimental animal model of Wistar rat[3],[9],[19].

Based on the facts above, the researchers were interested to find out whether REBT can increase the response of fluoxetine therapy can accelerate the improvement of clinical symptoms of depression, restore cognitive function as before the patient suffers from depression as well as increasing levels of BDNF serum as the main indicator of improvement in psychosocial function. In this case the researchers will use a research instrument namely Hamilton Depression Rating Scale (HDRS) and the Indonesian version of the Montreal Cognitive Assessment (MoCa-Ina). The HDRS is a questionnaire consisting of 21 items used to find out indications of depression and as a guide in evaluating the recovery process. Cognition function can be measured using the MoCa-Ina instrument, which includes visuospatial/executive, naming, memory, attention, language, abstraction, delayed recall and orientation [17].

Method

This research is an experimental study with the design of pre-test and post-test control group design. This study was planned to be performed on November 2019 - finish.

This research was planned to be carried out in Psychiatry Polyclinic of UNHAS Makassar Hospital, and its hospital channels. The populations in this study were all depressed patients based on the fifth edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-5) and the WHO's tenth edition of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) who underwent outpatient treatment at the Psychiatry Polyclinic of UNHAS Hospital and its channel hospital.

The sample in this study were depressed patients based on DSM-5 and ICD-10 who underwent outpatient care at the Psychiatry Polyclinic of UNHAS Hospital and its channel hospital, which met the inclusion criteria: all male and female patients diagnosed with depression based on DSM-5 and ICD-10, ages 18-35 years old, minimum education was elementary school, depressed patients who sought treatment for the first time, recurrent depressed patients who dropped out of antidepressant drugs for a minimum of 3 months and patients willing to take part in the study. Sampling techniques for each group were carried out by means of consecutive sampling, i.e. all patients who meet the research criteria until the sample required is fulfilled. The type of data in this study was primary data obtained directly from research subjects. The research instrument used in this

study consisted of HDRS and MoCA-Ina questionnaire sheets. Measurement of BDNF serum levels in the blood of study samples.

Ethical statement

This study received ethics approval from the Universitas Hasanuddin hospital ethical committee.

Data Processing Techniques

Processing was carried out after recording the medical record data needed into the questionnaire by using a computer program SPSS 23.0 and Microsoft Excel to obtain the expected statistical results.

Paired T test and unpaired T test are used when the data are normally distributed as well as Wilcoxon Test and Mann Whitney Test are used when the data are not normally distributed.

Results

Table 1. Sociodemographic Characteristics based on Frequency (N=37)

Variable	Variable Group	n	%
Sex	Male	18	45.9
	Female	19	51.3
Job	Civil Servant	2	5.4
	Employee	16	43.2
	Entrepreneur	5	13.5
	Housewife	12	32.4
	Unemployed	2	5.4
Status	Married	25	67.6
	Not Married	11	29.7
	Divorce	1	2.7
Education	Middle School	7	18.9
	High School	15	40.5
	Higher Education	15	40.5
Tribe	Bugis-Makassar	21	56.8
	Toraja	2	5.4
	Jawa	4	10.8
	Luwu	3	8.1
	Tionghoa	4	10.8
	Enrekang	1	2.7
	Mandar	2	5.4

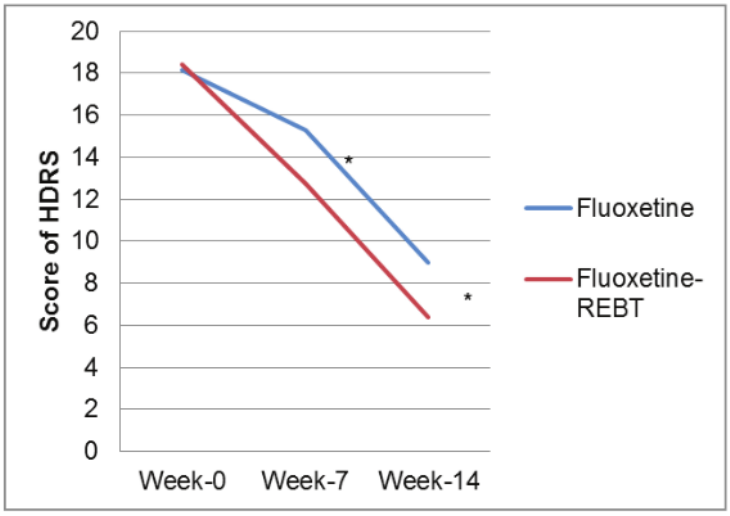

Figure 1. Average Comparison of HDRS Scores for Fluoxetine and Fluoxetine-REBT

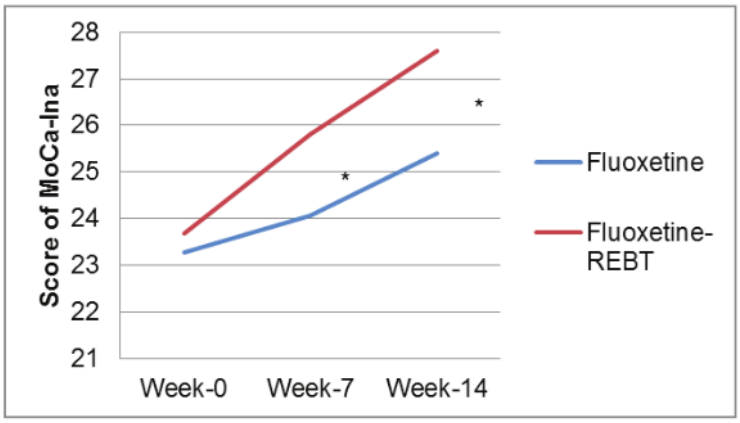

Figure 2. Average comparison of MoCa-Ina scores of the fluoxetine group and fluoxetine-REBT

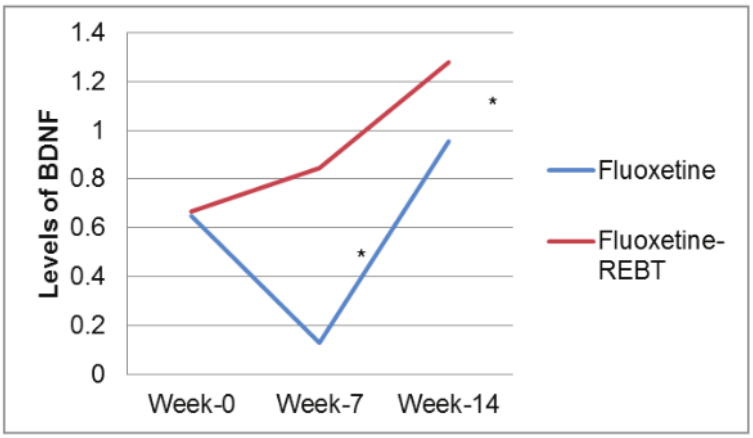

Figure 3. Average comparison of BDNF levels in the fluoxetine group and fluoxetine-REBT

Table 2. Comparison of BDNFS levels (ng/ ml)

Observation	Group		P
	Mean (+SD) Fluoxetine (N=15)	Mean (+SD) Fluoxetine – REBT (N=15)	
Week-0	0.651+0.009	0.668+0.006	0.563
Week-7	0.130+0.221	0.845+1.101	0.000
Week-14	0.954+0.171	1.276+0.326	0.000

Mean + SD

* *Significant p<0.05*; Analysis of multivariate (Mann-Whitney U with t-test)

Table 3. Difference in HDRS score

Observation	Group		P
	Mean (+SD) Fluoxetine (N=15)	Mean (+SD) Fluoxetine – REBT (N=15)	
Difference week 0 – 7	2.86+0.639	5.67+0.617	0.000
Difference week 7 – 14	6.27+1.668	6.33+2.663	0.935
Difference week 0 – 14	9.13+1.506	12.00+2.449	0.001

Mean + SD

* *Significant p<0.05*; Analysis of multivariate (Mann-Whitney U with t-test)

Table 4. Difference in MoCa-Ina scores

Observation	Group		P
	Mean (±SD) Fluoxetine (N=15)	Mean (±SD) Fluoxetine – REBT (N=15)	
Difference week 0 – 7	0.80±0.414	2.13±1.060	0.000
Difference week 7 – 14	1.33±0.723	1.80±0.861	0.204
Difference week 0 – 14	2.13±0.743	3.93±0.883	0.000

Mean + SD

* *Significant p<0.05*; Analysis of multivariate (Mann-Whitney U with t-test)

Table 5. Difference in BDNF Serum Levels (ng/ ml)

Observation	Group		P
	Mean (+SD) Fluoxetine (N=15)	Mean (+SD) Fluoxetine – REBT (N=15)	
Difference week 0 – 7	0.065+0.216	0.778+0.099	0.000
Difference week 7 – 14	0.824+0.223	0.431+0.343	0.001
Difference week 0 – 14	0.889+0.163	1.209+0.324	0.000

Mean + SD

* *Significant p<0.05*; Analysis of multivariate (Mann-Whitney U with t-test)

Discussion

2. 3. *Participants*

This study is an experimental study using a pre-test and post-test control group design, which compares the fluoxetine group with fluoxetine-REBT. This research was conducted at the Psychiatry Polyclinic Hospital of South Sulawesi Province, Ibnu Sina Hospital, Makassar Public Hospital with a sample of 43 people. After taking the identity and data of research subjects, HDRS checks were performed. After fulfilling the criteria for the value of HDRS that has been determined the sample was divided into the fluoxetine group and the fluoxetine-REBT group, then MoCa-Ina examination and blood sampling were performed to check BDNF levels. During the follow-up sample, 7 people dropped out.

From the analysis conducted on the demographic characteristic variables in the study subjects (N = 37) the mean age was 31.07 ± 3.25 years, with the majority of female (51.3%), employee as occupation (43.2%), marital status (67.6%), high school and college education (40.5%). A study reported that depression is more common at a young age. The average age was between 20-40 years. This study shows a greater susceptibility of depression to women than men according to the literature [18]. Age and education are also important contributors to heterogeneity. At the level of individual education, patients with low levels of education and older patients exhibit severe cognitive deficits in depressive disorders ([1],[3],[17]).

Statistical Analysis

From the research it was found that the mean HDRS score in the samples given the therapy were both statistically significant on depressive symptoms. Samples who received fluoxetine-REBT therapy seen from statistical data at week 7 (mean 12.73 ± 1.580) a significant decrease in HDRS scores p <0.05 (0.000) and week-14 (mean 12.73 ± 1.580) significant decrease in HDRS score p <0.05 (0.001). The control group seen from the statistical data at week-7 (mean 15.27 ± 1.792) a significant decrease in HDRS scores p <0.05 (0.000) and week-14 (mean 9.00 ± 3.286) had a significant decrease in HDRS scores p <0.05 (0.001). The mean MoCa-Ina score for the sample given by the therapy was both statistically significant for cognitive function. Samples who received fluoxetine-REBT therapy were seen from the statistical data at week-7 (mean 25.80 ± 1.146) a significant increase in MoCa-Ina score p <0.05 (0.001) and week-14 (mean 27.60 ±1.595) a significant increase in MoCa-Ina score p <0.05 (0.001). The control group seen from the statistical data at week-7 (mean 24.07 ± 1.100) a significant decrease in HDRS scores p <0.05 (0.001) and week-14 (mean 25.40 ± 1.595) a decrease of MoCa-Ina scores significantly p <0.05 (0.001). The mean BDNF levels in the sample given the therapy were both statistically significant in depressive disorders and cognitive function. Samples who received fluoxetine-

REBT therapy seen from statistical data at week-7 (mean 0.845 ± 1.101) a significant increases in BDNF levels p <0.05 (0.000) and week-14 (mean 1.277 ± 0.326) an increase of BDNF levels significantly p <0.05 (0.000). The control group seen from the statistical data at week-7 (mean 0.130 ± 0.221) a significant increase in DNF levels p <0.05 (0.000) and week-14 (mean 0.954 ± 0.171) a significant decrease in BDNF levels p = 0.05 (0.000).

From the research it was found that the therapeutic effect based on HDRS scores on the samples given the therapy were both statistically significant on depressive symptoms. Samples who received fluoxetine-REBT therapy seen from statistical data at week 0-7 (mean 5.67 ± 0.617) a significant decrease in HDRS scores p <0.05 (0.000). Weeks 7-14 (mean 6.33 ± 2.663) had a decrease in score but not significant p <0.05 (0.935). Weeks 0-14 (mean 12.00 ± 2.449) a significant decrease in HDRS scores p <0.05 (0.001). The control group seen from the statistical data at week 0-7 (mean 2.86 ± 0.639) a significant decrease in HDRS scores p <0.05 (0.000). Weeks 7-14 (mean 6.27 ± 1.668) a decrease HDRS scores but not significant p <0.05 (0.935). Weeks 0-14 (mean 9.13 ± 1.506) a significant decrease in HDRS scores p <0.05 (0.001). The therapeutic effect based on the MoCa-Ina score in the sample given by the therapy was both significant in cognitive function. Samples receiving fluoxetine-REBT therapy seen from statistical data at week 0-7 (mean 2.13 ± 1.060) a significant increase in MoCa-Ina score p <0.05 (0.000). Weeks 7-14 (mean 1.80 ± 0.861) a decrease in score but not significant p <0.05 (0.204). Weeks 0-14 (mean 3.93 ± 0.883) a significant increase in MoCa-Ina score p <0.05 (0.000). The control group seen from the statistical data at week 0-7 (mean 0.80 ± 0.414) experienced a significant increase in MoCa-Ina score p <0.05 (0,000). Weeks 7-14 (mean 1.33 ± 0.723) an increase in MoCa-Ina score but it was not significant p <0.05 (0.204). Weeks 0-14 (mean 2.13 ± 0.743) experienced a significant increase in MoCa-Ina score p <0.05 (0.000). The therapeutic effect was based on BDNF levels in the samples given both therapies were statistically significant in depressive symptoms and cognitive function. Samples who received fluoxetine-REBT therapy seen from statistical data at week 0-7 (mean 0.778 ± 0.099) a significant increase in BDNF levels p <0.05 (0.000). Weeks 7-14 (mean 0.431 ± 0.343) a significant increase in BDNF levels p <0.05 (0.001). Weeks 0-14 (mean 1.209 ± 0.324) a significant increase in BDNF levels p <0.05 (0.000). The control group seen from statistical data at week 0-7 (mean 0.065 ± 0.216) a significant increase in BDNF levels p <0.05 (0.000). Weeks 7-14 (mean 0.824 ± 0.223) a significant increase in BDNF levels <0.05 (0.001). Weeks 0-14 (mean 0.889 ± 0.163) a significant increase in BDNF levels p <0.05 (0.000).

Discussion

In general, the results of the current research showed that fluoxetine group and combination of REBT both respectively was effective in the treatment of depression. However, there seems to be difference significantly, where the group of fluoxetine-REBT is better in treating the symptoms of depression, cognitive functions increase the levels of BDNF serum.

HDRS scale consists of 21 questionnaire items, each item range from 0 to 4 or 0 to 2, the researcher used the 14-20 point limit and we did not classify specifically according to mild, moderate and severe symptoms of depression. The seven core depressive symptom items consisted of: mood, guilt, suicidal thoughts, work and activities, psychomotor retardation, somatic symptoms, sexual symptoms [17],[18].

The clinical response rate after 14 weeks of therapy showed there was an improvement in HDRS scores, the fluoxetine-REBT group responded better than fluoxetine therapy. The level of decline in HDRS scores after 7 weeks of therapy was around 50% of the initial HDRS score, According to [17] that from 6 weeks of antidepressant treatment clinical trials there is a reduction in scores of 50% or more on the standard depression scale. However, depressed patients who responded with a 50% decrease in HDRS scores may still show significant symptoms, especially in mood items, feelings of guilt and somatic symptoms. Some depressive symptoms are mediators of cognitive dysfunction, including psychomotor retardation, lack of motivation, fatigue, insomnia, and mood. With the combination of REBT therapy it is expected to accelerate the improvement of symptoms remaining from antidepressant treatment because REBT can help patients to cope with emotional, behavioral and irrational thoughts through a good coping mechanism in dealing with every problem that the patients face. The formation of a good coping mechanism can help patients

manage stress, so as to reduce cortisol levels in the blood. Cortisol levels in the blood that return to normal conditions can reshape neuroplasticity in the anterior region of the anterior cingulate and hippocampus ([14],[18]).

Regarding the function of cognition, we use the MoCa-Ina instrument, which includes visuospatial/ executive, naming, memory, attention, language, abstraction, delayed recall and orientation. MoCa-Ina was chosen because its sensitivity is better for assessing cognitive function than other instruments. According to the literature, we used cut-off points 26 to illustrate between clinical and non-clinical symptom scores ([3],[18]).

The results of this study showed that cognitive impairment appeared early in the disease. The clinical response rate after 14 weeks of therapy showed there was an improvement in MoCa-Ina score, the incorporation of fluoxetine with REBT response rates was better than single therapy. The results confirm that this combination is more effective than the drug alone in reducing symptoms of cognitive impairment. We also found that cognitive impairment, especially executive functioning, memory, attention and delayed recall were most often affected by depressive disorders which became the major factor in the workforce performance decline ([4],[18],[19]).

After 7 weeks of fluoxetine-REBT combination therapy, BDNF levels significantly increased compared to the control group. This increase in BDNF is consistent with the literature, where SSRI antidepressants regulate cAMP Response Element-Binding protein (CREB), transcription factors that depend on Cyclic adenosine monophosphate (cAMP), and BDNF in the course of time associated with therapeutic measures (10 to 20 days). CREB transcription factors are involved in the induction of BDNF gene expression in neurons. This effect on the cAMP pathway provides a link between monoamine antidepressants and neurotropin action [18]. Some research on depression also shows an increase in BDNF levels after undergoing psychotherapy for 4 weeks [11]. BDNF is mostly found in the hippocampus and cortex, the hippocampus is a center of learning and memory. The hippocampus is also connected to the cortex region, and is very important for the integration of cognitive and emotional processes. According to previous studies in the Psychiatry Section (research in the process of publication) showed the Fluoxetine group was superior in increasing BDNF serum levels compared to the Sertralin group. The study also assessed BDNF serum levels in normal people to determine the standard of whether depressed patients have BDNF serum levels below the BDNF serum levels in normal people ([11],[18]).

Based on pharmacotherapy, the administration of fluoxetine in the first week to the fourth week did not have a significant therapeutic effect, thus it did not experience a change on the BDNF serum levels because fluoxetine only works in the prefrontal cortex. Improvement of depressive symptoms, cognitive function and increased BDNF serum levels can be achieved earlier by adding REBT therapy, where REBT works in areas of the brain that are different from fluoxetine, namely in the anterior cingulate cortex and hippocampus. This explains why fluoxetine administration in the first week to the 7th week actually experienced a decrease on the BDNF serum levels. Although in the end after 14 weeks, both the fluoxetine-REBT group and the fluoxetine group will reach normal BDNF serum levels. As a clinician, it is very important to provide appropriate therapy through pharmacotherapy combined with REBT in order to accelerate the improvement of depressive symptoms through improvement in BDNF serum levels that do not respond to fluoxetine therapy in the first week. Thus the clinician helps patients not to fall into a severe major depressive disorder and prevents suicide ideas, which according to research that suicide attempts can occur early in the beginning of therapy for severe major depressive disorders ([15],[18]).

This research is not without limitations. First, the sample size is not large enough to determine the correlation between improvement in depressive symptoms and improvement in function with an increase in BDNF serum levels. Second, the researcher did not set standards and minimum intelligence scores on the participants [15].

Conclusion

The conclusions in this study found there is an effect on the provision of fluoxetine therapy combination of REBT compared to fluoxetine therapy alone in improving depressive symptoms, cognitive function as well as increasing BDNF serum levels.

Acknowledgment: The author wish to thank dr. Erlyn Limoa Ph.D, Sp.KJ, Prof. dr. Nur Aeni M.A. Fattah, Sp.KJ(K) A&R and all study participants for comments that greatly improved the manuscript. The BDNF measurements were financed by the author.

Ethical Clearance: No ethical approval is needed.

Source of Funding: Self

Conflict of Interest: Nil

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