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REVIEW ARTICLE

Meta-Analysis: Effectiveness of SSRIs vs SSRIs in conjunction with CBT in treating depression in young adolescents

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ABSTRACT

Objective: To compare the efficacy of SSRI medication alone and SSRI+CBT combined. **Methods:** NCBI Pubmed, DARE, CSDR and NGC were searched October-November 2019. The population size, as well as the base and endpoint CGAS mean and standard deviation from the three studies included, are recorded. Statistical analysis was done in RStudio with the "meta" package. **Results:** For the SSRI only, the effect size was -1.82 with a 95% confidence interval between -2.28 and -1.37. For the SSRI and CBT combined, the effect size was -1.68 with a 95% confidence interval between -2.39 and -0.98. The effect size for both SSRI and SSRI + CBT didn't cross the null effect line, but the heterogeneity exceeds 50%. The result for the comparison of post SSRI vs. SSRI + CBT showed the effect size of -0.05 with a 95% confidence interval between -0.23 and 0.12. The size effect did cross the null effect line, but the heterogeneity was less than 50%. **Conclusion:** Both methods were shown to be effective. However, due to statistical inconsistencies, it couldn't be concluded whether the combination of SSRI and CBT is better than treatment with SSRI alone.

Keywords: Meta-analysis, SSRI, CBT, Adolescent, Depressive Disorder, Efficacy

INTRODUCTION

Depressive disorder is a common and serious mental disorder. In prepubertal children, the condition is rare, but become more common by mid-adolescence. The current estimates suggest that around 13 to 20% of adolescents will experience some form of depression before reaching 30 (Goodyer et al, 2008). When untreated, depression can lead to decreasing performance in school, interpersonal relationships, occupational adjustment, as well as increases the risk of suicide and suicidal behavior. Prescription of selective serotonin reuptake inhibitor (SSRI) medication and/or psychotherapy is recommended by the clinical guidelines for the acute management of adolescent depression (Brent et al, 2008).

Selective serotonin reuptake inhibitor is a form of antidepressant commonly used to treat depression. In several studies, SSRI seems to have an association with the risk of suicide, especially in young people. However, according to a meta-analysis performed on SSRI, the

benefits still outweigh the risks (Thapar, Collishaw, Pine & Thapar, 2012).

The best-studied psychotherapies are cognitive-behavioral therapy (CBT) and interpersonal psychotherapy (IPT). Based on two published meta-analyses on CBT, the treatment is effective but didn't show effect size higher than 0.3. Data from the largest randomized controlled trial on adolescents with moderate to severe depression suggest that CBT is effective in a milder form of depression. The IPT is also a beneficial treatment, but there aren't enough trained therapy to perform this method in most countries (Thapar, Collishaw, Pine & Thapar, 2012).

Both SSRI and CBT have been successfully treated depression in many cases. But, some evidence also shows the downside of the method. A meta-analysis was done to compare the effectivity of SSRI with a combination of SSRI and CBT. The data were extracted from studies that include both treatments and uses the children's global assessment scale (CGAS).

MATERIAL AND METHODS

Literature Study

The NCBI Pubmed database, DARE, CSDR and NGC were reviewed. The keywords that were used were: (1) 'depressive disorder'; (2) 'adolescent'; (3) 'teenager'; (4) 'selective serotonin reuptake inhibitor'; (5) 'cognitive behavioral therapy'. These keywords were then input into the search bar, framed in the following Boolean search: (1) AND [(2) OR (3)] AND (4) AND (5). Both databases were searched in between October and November of 2019.

Eligibility Criteria

The following inclusion criteria were adopted: (a) only English manuscripts, (b) trials that compared the effects of only SSRIs on patients versus SSRI in conjunction with CBT, (c) participants were aged between 11-18, (d) full-text manuscripts were available, (e) the appropriate data was available on the manuscript for the estimation (mean SD values) and using the determined scale for depression (CGAS). Excluded studies were other meta-analyses and systematic review articles.

Data Extraction

A total of 3 studies (Clarke et al., 2005; Goodyer et al., 2007, 2008) were evaluated based on the inclusion and exclusion criteria, their base and endpoint mean CGAS scores and the respective SD values. The meta-analysis was done based on the mean pre-treatment CGAS score and post-treatment CGAS score. CGAS scores were extracted from the studies to obtain the necessary data.

Statistical Analysis

All statistical analysis was done by means of the "meta" package from the RStudio software. Data input, effect size calculation, heterogeneity indicators (I^2, τ^2) and forest plot construction was all done automatically through the R package (Appendix A). Three forest plots were constructed: a forest plot of effect sizes before and after treatment with SSRI only, a forest plot of effect sizes before and after treatment with SSRI in conjunction with CBT, and a forest plot of effect sizes after treatment with SSRI versus after treatment with SSRI in conjunction with CBT (Appendix B).

Main Outcomes

For all three forest plots, Hedges' g as a measure of effect size was used due to the small sample sizes. The pooled effect size was weighted by the inverse variance method and

measured using both fixed and random-effects model, depending on the forest plot. For the forest plots comparing the effects of pre-and post- SSRI and pre- and post- SSRI and CBT, the random effects model was chosen. For the forest plot comparing post-SSRI and post-SSRI and CBT, the fixed effect model was chosen.

Quantitative Assessment of Heterogeneity

Heterogeneity was evaluated through the I^2 value with the criteria $p < 0.01$ for heterogeneity. The τ^2 value-- the variance between the true effects of the studies-- was also taken into consideration when evaluating the heterogeneity.

RESULTS AND DISCUSSION

Overview

Initially 2754 studies were extracted through matching keywords to the title and/or abstract of the related studies. After removing non-relevant studies, 205 studies were left for review. 173 studies were excluded after reviewing the abstract as they were not eligible for this meta-analysis. The remaining 32 studies had their full-text screened for eligibility, and through this process 27 more were excluded as they did not fulfill the inclusion criteria. From the remaining 5 studies, 2 more were excluded as they did not have the required scale for depression. The final amount chosen was three studies (n = 281 patients) after reviewing the inclusion criteria (Appendix C).

Primary Outcome

When assessing the effects of SSRI treatment, SSRIs were found to have a statistical impact on the patients, with an effect size of -1.82 and a 95% confidence interval between -2.28 and -1.37 (Appendix B, Fig. 1). The negative effect size is due to the way CGAS is measured, with a larger score indicating a better functioning level of the patient, so the lower the effect size, the better, as it indicates improvement. As this does not cross the null effect line, there is a statistical impact.

With CBT treatment, the effect size was -1.68 with a 95% confidence interval between -2.39 and -0.98 (Appendix B, Fig. 2). Again, as the effect size does not cross the null effect line, there is a significant statistical impact in this reduction.

However, when comparing post-SSRI vs post-CBT treatment, the effect size was -0.05 with a 95% confidence interval between -0.23 and 0.12 (Appendix B. Fig. 3). The effect size does cross the null effect line, implying that indeed the true value of this study may be zero, and thus, there is no visible statistical impact.

Quantitative Assessment of Heterogeneity

With heterogeneity values of over 50% for both SSRI and SSRI plus CBT only treatments, it implies that the inconsistencies between these studies are more than just due to chance, meaning that conclusions drawn from these forest plots, despite being statistically significant, may be inconclusive. With the last forest plot comparing post-SSRI and post-SSRI plus CBT, heterogeneity is below 50%, suggesting that whatever inconsistency is not statistically significant.

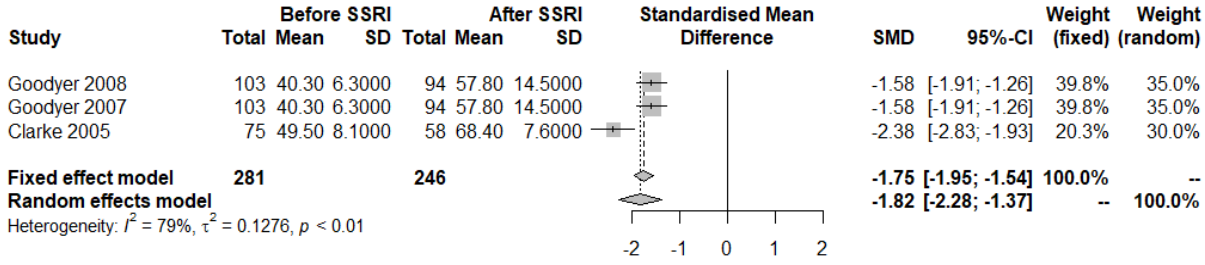

Figure 1. Forest plot of effect sizes (Hedges' g) between pre- and post-treatment with SSRI mean CGAS scores. Used to determine strength and efficacy of SSRI by comparing baseline to endpoint scores. The vertical line represents the overall drug effect. The SMD column shows the standardized mean differences, 95% CI being the 95% confidence interval. The weight shows the bearing the effect sizes had on the pooled effect size, I^2 is the measure of heterogeneity, and τ^2 being the variance in the true effect sizes of the studies. As $p < 0.01$, the null hypothesis that the effect sizes are common is rejected, and the random-effect model was considered in this forest plot.

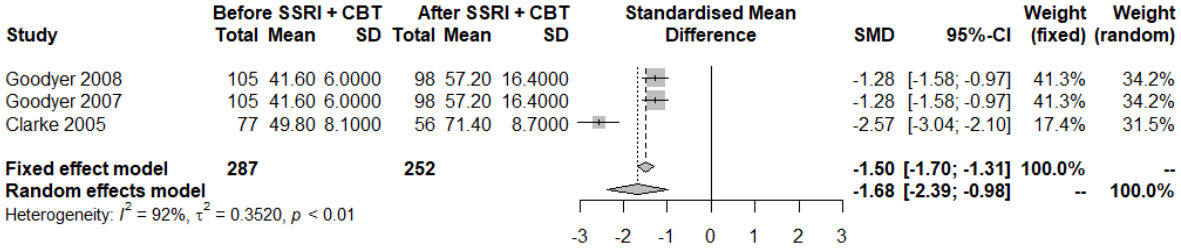

Figure 2. Forest plot of effect sizes (Hedges' g) between pre- and post-treatment with CBT mean CGAS scores. Used to determine strength and efficacy of CBT by comparing baseline to endpoint scores. The vertical line represents the overall drug effect. The SMD column shows the standardized mean differences, 95% CI being the 95% confidence interval. The weight shows the bearing the effect sizes had on the pooled effect size, I^2 is the measure of heterogeneity, and τ^2 being the variance in the true effect sizes of the studies. As $p < 0.01$, the null hypothesis that the effect sizes are common is rejected, and the random-effect model was considered in this forest plot.

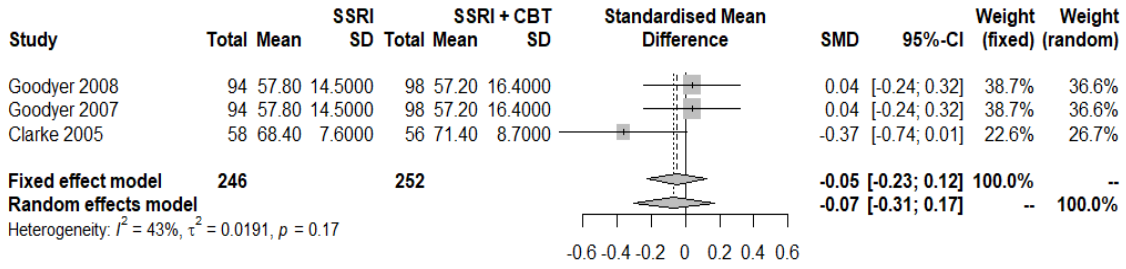

Figure 3. Forest plot of effect sizes (Hedges' g) between post-treatment with SSRI and post-treatment with CBT mean CGAS scores. Used to determine strength and efficacy of CBT versus SSRI by comparing endpoint scores. The vertical line represents the overall drug effect. The SMD column shows the standardized mean differences, 95% CI being the 95% confidence interval. The weight shows the bearing the effect sizes had on the pooled effect size, I^2 is the measure of heterogeneity, and τ^2 being the variance in the true effect sizes of the studies. As $p > 0.01$, the null hypothesis that the effect sizes are common is accepted, and the fixed-effect model was considered in this forest plot.

Table 1. Before and after SSRI treatment mean CGAS effects, and number of participants in the study.

		Before SSRI			After SSRI		
Author	**Year**	**Mean**	**SD**	**n**	**Mean**	**SD**	**n**
Goodyer et al.	2008	40.3	6.3	103	57.8	14.5	94
Goodyer et al.	2007	40.3	6.3	103	57.8	14.5	94
Clarke et al.	2005	49.5	8.1	75	68.4	7.6	58

Table 2. Before and after CBT treatment mean CGAS effects, and number of participants in the study.

		Before CBT			After CBT		
Author	**Year**	**Mean**	**SD**	**n**	**Mean**	**SD**	**n**
Goodyer et al.	2008	41.6	6	105	57.2	16.4	98
Goodyer et al.	2007	41.6	6	105	57.2	16.4	98
Clarke et al.	2005	49.8	8.1	77	71.4	8.7	56

Table 3. Before and after CBT treatment mean CGAS effects, and number of participants in the study.

		After SSRI			After SSRI + CBT		
Author	**Year**	**Mean**	**SD**	**n**	**Mean**	**SD**	**n**
Goodyer et al.	2008	57.8	14.5	94	57.2	16.4	98
Goodyer et al.	2007	57.8	14.5	94	57.2	16.4	98
Clarke et al.	2005	68.4	7.6	58	71.4	8.7	56

Limitations

This meta-analysis only included three studies, which is the bare minimum for a meta-analysis. In addition, the sample size is ver y small, and may not be representative for the whole population of children and adolescents suffering from major depressive disorder. Some people in the study also dropped out, which may lead to inconsistencies as these studies do not mention using LOCF (Last Observation Carried Forward), which ensures that data from patients that drop out can be used; hence, the meta-analysis was conducted with the assumption that all papers are using LOCF. Furthermore, selection bias was not reviewed in this meta-analysis, as the authors may have been more biased to papers that do show improvement with patients treated both with SSRI and CBT in conjunction in comparison to just SSRIs.

CONCLUSION

While SSRIs and both SSRI and CBT in conjunction proved efficacious in treating adolescents with major depressive disorder, whether or not one treatment plan is better than the other cannot be said due to statistical inconsistencies during the meta-analysis. Further meta-analyses need to be performed with more studies and a larger sample size in order to be able to draw a conclusive interpretation of the data and the true effect

that these treatments have on children and adolescents with major depressive disorder.

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