The ambiguous value of cognitive behavioral therapy to antidepressants, in children and adolescents suffering from Major Depressive Disorder: an umbrella-review

Annick de Groot

s4304519

Department of Psychology, University of Groningen

PSB3E-BT15.2022-2023.1 Bachelor Thesis (1a 22/23)

Group number: PSB3-BT_2223-1a-36

Supervisor: Dr. A.M. Roest

Secondary Supervisor: Dr. Maarten Eisma

February 2, 2022

Abstract

Depression in children and adolescents is common, across cultures all over the globe. However, this field is still understudied. Despite the major consequences. Combination therapy, mainly Fluoxetine and cognitive behavioral therapy, is recommended nowadays in children and adolescents suffering from moderate to severe depression. However, little is known about the efficacy of combination therapy and the unique added value of cognitive behavioral therapy to antidepressants. This umbrella review searched systematically for systematic reviews in PubMed and PsycINFO, and included 7 systematic reviews and 13 RCTs. According to the results, cognitive behavioral therapy seems to have a positive significant added value for Bupropion, in terms of Efficacy, and Fluoxetine, in terms of Efficacy and immediately post-intervention Remission. However, follow-up studies for Fluoxetine plus cognitive behavioral therapy on Remission favor the control condition: Fluoxetine monotherapy. So, it is still not clear whether cognitive behavioral therapy has a positive or negative added value to most of the included antidepressants. Because, the added value depends upon each pharmacological intervention, and is, therefore, still rather ambiguous. Thus, more research should be conducted on this. Further research should also be focused upon generating more RCTs in this particular field. Because, despite the urgence and need for more insights, this field is still understudied.

Keywords: major depressive disorder, combination therapy, cognitive behavioral therapy, antidepressants, children, adolescents

The ambiguous value of Cognitive Behavioral Therapy to antidepressants, in children and adolescents suffering from Major Depressive Disorder: an umbrella-review

Depression, that is, Major Depressive Disorder (MDD), in children and adolescents is common across cultures all over the globe (Evans-Lacko et al., 2018). Depression, recognized as a clinically mental disorder, may vary in severity, frequency of episodes, but is characterized by decreased feelings of happiness, pleasure and symptoms related to concentration, energy, sleep, appetite and suicide (APA, 2013; Singh & Reece, 2014). Symptoms of depression in children and adolescents are similar to symptoms of depression in adults; however, children and adolescents may be more prone to show irritability, instead of unhappy or sad feelings. Also, in general, children and adolescents do not suffer from the lack of pleasure (APA, 2013; Singh & Reece, 2014, p. 48).

Although depression is common in children and adolescents, it is a major concern as the prevalence of diagnosed depression in these groups has significantly increased over the last decade. Approximately 4.0% of children and adolescents in the United States of America (U.S.A.) suffered from diagnosed depression, in 2020, in comparison to 3.1% in 2016 (Lebrun et al., 2022). Moreover, research shows that children and adolescents, suffering from symptoms of depression, are often misdiagnosed, which might lead to mis- or untreated individuals with major consequences (Mokdad et al., 2016). A second major concern are the extensive consequences of early onset depressive symptoms in childhood and adolescence. That is, the risk of recurrence in adulthood, if left untreated, which can lead to treatment-resistance. (Cox et al., 2014). But also, depressive symptoms might be highly debilitating for children and adolescents, in terms of social development, academic functioning and family dynamics (Gore et al., 2011). A major consequence of depression in children and adolescents

is also the risk of morbidity and mortality; suicide, caused by depression, is one of the leading causes of death among children and adolescents (Thapar et al., 2012). Despite these major concerns, this area of research is enormously understudied, in comparison to, for instance, the presence of depression in adults (Tandon, 2019). For example, there is great evidence for the significant contribution of combination therapy in adults, while it remains unclear ' *whether the combination of pharmacotherapy and psychotherapy is more beneficial than pharmacotherapy alone (...) in children and adolescents*' (Xiang et al., 2022, p.2).

Current treatment interventions, for treating depression in general, can be divided into psychological and pharmacological interventions, or a combination of the two. Psychological interventions, e.g. psychotherapy, are aimed at improving skills for managing the cognitive side of depression, but also the social environment side. Cognitive behavioral therapy (CBT) is the main intervention for treating mild to moderate depression, which has been proven to be empirically validated (Singh & Reece, 2014; NICE, 2023). Pharmacological interventions are aimed at managing the neurochemical side of depression (Hetrick et al., 2021). The main pharmacological interventions can be divided into: selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs) (Singh & Reece, 2014; Hetrick et al., 2021). Up to the beginning of this century, there was a focus for pharmacological interventions in treating children and adolescents suffering from depression in any severity (Gaddow, 1991; Carrey et al. 1996; Spielmans, 2020). However, some of the recommended psychopharmaca used in children and adolescents did increase the risk of suicidal ideation and attempts (Gibbons et al., 2007; Cipriani et al., 2016). Causing the Food and Drugs Administration (FDA) of the U.S.A., in 2004, to issue a Black Box warning

concerning antidepressants in children and adolescents (Spielmans, 2020) Therefore, knowledge about validated evidence-based interventions, specifically aimed at treating children and adolescents, suffering from depression, is very important. After the Black Box warning, combination therapy has been recommended to children and adolescents suffering from moderate to severe depression (McDermott et al., 2010; Singh & Reece, 2014; NICE, 2023). Combination therapy combines psychological and pharmacological interventions, and focuses on the cognitive side, the social environment side and the neurochemical side of depression (Singh & Reece, 2014). Combination therapy may increase the efficacy, because different mechanisms are targeted and there could be a potential synergy effect (Somayaji et al., 2018). The pharmacological intervention might also remove the edge of symptoms, in order to start cognitive behavioral therapy more easily (Cuijpers et al., 2020). Mainly the combination of cognitive behavioral therapy and SSRIs, especially Fluoxetine plus cognitive behavioral therapy, is recommended to children and adolescents suffering from moderate to severe depression (Singh & Reece, 2014; NICE, 2023). However, this intervention is mainly based upon extrapolating findings within adult populations (McDermott et al., 2010; Zhou et al., 2020). It is still not clear whether this intervention really is effective in children and adolescents (Xiang et al., 2022). Also, little is known about the unique added value of cognitive behavioral therapy to pharmacological interventions in children and adolescents, suffering from depression (McDermott et al., 2010; Ma et al., 2014; Cox et al., 2014; Zhou et al., 2020).

Current literature about the interventions, to the extent it is written, is plagued by contradicting results, low confidence and heterogeneity (Spindel, 2008; Cox et al., 2014; Ghandour et al., 2018; Aman & Pearson, 2020)). This might be caused due to differences

between measurement tools, differences between short and long term consequences, differences in targeting group, i.e. children, adolescents and adults differ, but are mostly generalized (see e.g., McDermott et al., 2010; Singh & Reece, 2014; Davey et al., 2019; Zhou et al., 2020), differences in interventions and different responses of individuals to the same intervention (Xiang et al., 2021;)

Therefore, there is a need for summarizing, overviewing and the integration of current literature, so far. Systematic reviews provide a high form of evidence, because they combine results from multiple studies (Aromataris et al., 2015). Therefore, summarizing systematic reviews, on the subject will make a contribution to this particular field of research. The research question is: What is the added value of Cognitive Behavioral Therapy to antidepressants in treating children and adolescents with Major Depressive Disorder?

Methods

Search strategy and information sources

Studies were systematically searched in two databases: PsycINFO and PubMed, on October 17th, 2022. Lean Library was used as interface, by means of a University of Groningen student account, for retrieving the studies. Studies were found by means of the search strings, shown in Attachment A. The search string of PubMed was specified upon the Title/Abstract field. The search string of PsycINFO was specified upon the Abstract field.

The following filters were applied in the database search strategy. Methodology: literature review, systematic review, meta-analysis or meta-synthesis. Language: Dutch or English. Species: humans. Age: children (6-12 years) and/or adolescence (12-18 years). Publication date: 10 years. Range of publication date was set to ten years, after an initial search run, in order to prevent even more overlap of included RCTs. Because, recent reviews contain the older RCTs, but also the more recent ones.

After the search run through the databases, duplicates were excluded from the database, by means of Mendeley Reference Manager. After that, the remaining studies were screened on title and abstract and selected, by means of different eligibility criteria for inclusion and exclusion. The following inclusion criteria were applied to the total number of retrieved studies:

- Studies on the subject of Major Depressive Disorder were included;
- Studies on combination therapy of cognitive behavioral therapy and antidepressants, in comparison to pharmacological monotherapy intervention, were included;

- Studies on children and adolescents were included;
- Studies on Efficacy, Remission and Acceptability of combination therapy (cognitive behavioral therapy and antidepressants) were included;

The following exclusion criteria were applied:

- Studies primary focusing on other mood or personality disorders, or illnesses, e.g. type 1 diabetes, as subject, were excluded (referred to as Reason 1 in Figure 1);
- Studies primary focusing on treatment-resistant depression were excluded (referred to as Reason 2 in the flow chart, Figure 1);
- Studies primary focusing on prevention of depressive disorders (referred to as Reason 3 in the flow chart, Figure 1);
- Studies primary focusing on other outcomes, e.g. safety, were excluded (referred to as Reason 4 in the flow chart, Figure 1);
- Studies other than systematic review, meta-analysis or meta-synthesis, e.g. a RCT, were excluded (referred to as Reason 5 in the flow chart, Figure 1);

Figure 1 *PRISMA Flow Chart*

Then, the remaining studies were retrieved, if possible, and screened full text based on published results. With regard to retrieval, studies which were not able to be retrieved using the University of Groningen account or were not available on Research Gate, were excluded. With regard to results, studies that published results for multiple disorders, population groups or interventions, were excluded if the results for the inclusion criteria were not published separately. Also, reference lists of eligible studies were consulted for potential additional studies on the subject to check if these were not retrieved by means of the initial search strategy.

Participants and Subjects

The search strategy generated an initial total of 1.071 results, both PubMed and PsycINFO combined. After applying the inclusion and exclusion criteria and screening of the studies only seven studies could be included in the umbrella review.

The seven included studies are described in Table 1. Noteworthy, from the total of 29 RCTs covered in the included systematic reviews, there were 16 duplicates. So, only 13 unique RCTs are included, to prevent biased results. For an overview of all included RCTs, consult Attachment B.

Study	Type	Relevant RCTs/ Total	Relevant participants/Total	Type of depression	Diagnostic criteria	Age participants	Combination	Control	Baseline severity scale
Xiang et al. (2022)	SR and MA	6/14	920/1.325	MDD, DD, DDNOS	DSM-IV	11-18 years	SSRI plus CBT Fluoxetine plus CBT Sertraline plus CBT Bupropion plus CBT	SSRI Fluoxetine Sertraline Bupropion	CDRS-S HAMD CDI BDI RADS
Zhou et	SR	4/71	808/9.51	MDD,	DSM-	11-18	Sertraline plus	Fluoxeti	CDRS-

al. (2020)	and NMA		0	DD, DDNOS	IV	years	CBT Fluoxetine plus CBT	ne Sertraline	R RADS CDI
Goodyer (2019)	PR	3/14	647/75.417	MDD	DSM or self-report or family history	11-17 years	Fluoxetine plus CBT SSRI (plus care) plus CBT	Fluoxetine SSRI (plus care)	CDRS-R
Forman-Hoffman (2016)	SR	3/5	663/2.884	MDD	USPSTF-criteria	12-18 years	Fluoxetine plus CBT	Fluoxetine	CDRS-R
Singh & Reece (2014)	MA	3/49	786/4.707	MDD	Not mentioned	8-18 years	Fluoxetine plus CBT	Fluoxetine	Not mentioned
Ma et al. (2014)	MA	6/21	974/4.969	MDD	Not mentioned	12-17 years	Fluoxetine plus CBT	Fluoxetine	Not mentioned
Cox et al. (2014)	MA	4/11	736/1.307	MDD, DD, DDNOS	DSM-IV plus CDRS-R (45 or more) or K-	12-18 years	SSRI (plus care) plus CBT Bupropion plus CBT Sertraline plus	SSRI (plus care) Bupropion Sertrali	CDRS-S CES-D BDI RADS

	SADS	CBT	ne
		Fluoxetine	Fluoxeti
		plus CBT	ne

RCT – randomized controlled trial, SR – systematic review, MA – meta-analysis, NMA – network meta-analysis, PR – practicioner review, MDD – major depressive disorder, DD – dysthymia, DDNOS – depressive disorder not otherwise specified, DSM – diagnostic and statistical manual of mental disorders, USPSTF – United Stated preventive services taskforce, CDRS-R – children depression rating scale revised, K-SADS – Kiddie schedule for affective disorders and schizophrenia, SSRI – selective serotonin reuptake inhibitor, CBT – cognitive behavioral therapy, HAMD – Hammilton rating scale for depression, CDI - children's depression inventory, BDI - Beck depression inventory, RADS - Reynolds adolescents depression scale

Table 1 *Characteristics of the included studies*

Data selection

This umbrella review summarizes and integrates outcomes from different systematic reviews, meta-analyses and meta-syntheses. The outcomes are focused upon Efficacy, Remission and Acceptability. The definitions and operationalizations of the outcomes are based upon the definitions and operationalizations given in the included studies, which are shown in Attachment C. Efficacy is continuous data defined as the response of a patient (so, the overall change in depressive symptom score), and operationalized as standard mean difference (SMD) of the concerned score and scale, with a 95% confidence interval (CI). The

SMD is a standard effect size; therefore, it is possible to compare these effect sizes, despite the fact that included studies used different severity scales. Remission is dichotomous data defined as whether a patient scores below the threshold on depressive symptom score (absolute score depends on baseline severity scale used), and operationalized as odd ratio (OR) of being in remission versus not being in remission, with a 95% CI. Acceptability is dichotomous data defined as all-cause discontinuation of the participant in the treatment or control group, and operationalized as OR, of continuation versus discontinuation, with a 95% CI

Results

The combined results of the seven included studies are shown in Table 2, Table 3 and Table 4. The tables contain the published effect sizes, with a 95% Confidence Interval, of Efficacy, Remission and Acceptability for different interventions (combination therapies) with control groups (pharmacological monotherapies). Furthermore, data from post-intervention, six months follow-up and twelve months follow-up is merged with regard to the published effect sizes. Consult Attachment D, Attachment E and Attachment F for the full detailed data regarding Table 2, Table 3 and Table 4.

With regard to Efficacy, there are two significant results namely: Bupropion plus CBT, controlled for Bupropion, with a SMD (95% CI) = -0.57 (-1.11 to -0.03); and Fluoxetine plus CBT, controlled for Fluoxetine with a SMD (95% CI) = -1.22 (-1.57 to -0.87). These results favor the combination therapy over the control group and are each based upon 1 RCT. The other SMDs favor the control group over the combination therapy and these results are based upon 2 RCTs.

Intervention	**Control**	**Effect Sizes SMD (95% CI)**	**Number of RCTs/Total number of participants**
SSRI (plus care) plus CBT	SSRI (plus care)	0.08 (-0.28 to 0.43) 0.19 (-0.09 to 0.47)	2/360
Fluoxetine plus CBT	Fluoxetine	**-1.22 (-1.57 to -0.87)**	1/327
Sertraline plus CBT	Sertraline	0.34 (-0.35 to 1.03) 0.38 (-0.25 to 1.01)	2/161

Bupropion plus CBT	Bupropion	**-0.57 (-1.11 to -0.03)**	1/72

SMD – standard mean difference, CI – confidence interval, RCT - randomized controlled trial, SSRI – selective serotonin reuptake inhibitor, CBT – cognitive behavioral therapy

Tabel 2 *Efficacy (total of Post-Intervention-Six months follow-up-12-months follow up)*

With regard to Remission, there is one significant result, namely: Fluoxetine plus CBT controlled for Fluoxetine with an OR (95% CI) = 3.04 (1.44 to 6.42). This significant result favors the intervention over the control group and is immediately post-intervention. The other results for Fluoxetine plus CBT are follow-up studies. These follow-up studies favor the control group, and were conducted 3, 4 and 5 years after the original study. Furthermore, the majority of the results favor the control group over the combination therapy, although these are not significant.

Intervention	**Control**	**Effect Sizes OR (95% CI)**	**Number of RCTs/Total number of participants**
SSRI (plus care) plus CBT	SSRI (plus care)	1.10 (0.58 to 2.11)	1/152
Fluoxetine plus CBT	Fluoxetine	0.62 (0.35, 1.10) 0.75 (0.40, 1.41) 0.85 [0.44, 1.65] **3.04 (1.44 to 6.42)**	4/439*
Sertraline plus CBT	Sertraline	0.62 (0.10 to 3.76) 0.65 (0.18 to 2.29)	2/161

OR – odds ratio, CI – confidence interval, RCT – randomized controlled trial, SSRI – selective serotonin reuptake inhibitor, CBT – cognitive behavioral therapy

**Consists of follow-up studies on the original RCT, so total number of participants remains 439, instead of cumulation*

Tabel 3 *Remission (total Post-Intervention-Six months follow-up-12-months follow up)*

With regard to Acceptability, there are no significant results. The interval of Sertraline plus CBT controlled for Sertraline (0.58 to 68.24) is remarkably high, in comparison to the other results. The majority of the results favor the control group over the combination therapy, although these results are not significant.

Intervention	**Control**	**Effect Sizes OR (95% CI)**	**Number of RCTs/Total number of participants**
SSRI (plus care) plus CBT	SSRI (plus care)	1.14 (0.51 to 2.54) 1.89 (0.67 to 5.32)	2/360
Fluoxetine plus CBT	Fluoxetine	0.63 (0.26 to 1.51) 1.21 (0.58, 2.55) 1.21 (0.58, 2.55)	3/439
Sertraline plus CBT	Sertraline	0.93 (0.16 to 5.50) 6.30 (0.58 to 68.42)	2/161
Bupropion plus CBT	Bupropion	0.77 (0.16 to 3.73)	1/72

OR – odds ratio, CI – confidence interval, RCT – randomized controlled trial, SSRI –

selective serotonin reuptake inhibitor, CBT – cognitive behavioral therapy

**Consists of follow-up studies on the original RCT, so total number of participants remains 439, instead of cumulation*