Turning depression inside out

Life events, cognitive emotion regulation and treatment in adolescents

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Cover Jet van der Horst | Jetswerk
Layout Renate Siebes | Proefschrift.nu
Printed by Ridderprint, Ridderkerk
ISBN 978-90-393-6522-9

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Depressie binnenstebuiten gekeerd

Levensgebeurtenissen, cognitieve emotieregulatie
en de behandeling van adolescenten

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de
Universiteit Utrecht op gezag van de rector magnificus,
prof. dr. G.J. van der Zwaan, ingevolge het besluit van het
college voor promoties in het openbaar te verdedigen
op vrijdag 22 april 2016 des middags te 2.30 uur

door

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geboren op 30 augustus 1958
te Heerlen

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The work described in this thesis was partly supported by grant 157004005 (Project Study Adolescent Depression. An evaluation of a cognitive behavioral intervention for adolescent depression: a randomized controlled trial) from the Netherlands Organization for Health Research and Development (ZonMw).

We are grateful for the collection of data by the Mental Health Institutions and their professionals; Accare, Altrecht, Bascule, Curium, GGZ-centraal, Herlaarhof, Lentis, Orbis, Perspectief, Praktijk Appelboom, Traverse, and Triversum.

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Chapter 1

Introduction

1.1 Introduction

Internalizing disorders, including anxiety and depressive disorders, are the most common mental health problems in adolescents (Costello, Mustillo, Erkanli, Keeler, & Angold, 2003). Depression seems to be the most invalidating disorder in adolescents because of the high prevalence (Fergusson, Horwood, & Lynskey, 1993; Hankin et al., 1998; Cohen et al., 1993; Mcgee et al., 1990), the high burden of disease (Hoeymans, Gommer, & Poos, 2006), a high risk of recurrence (Curry et al., 2011), high comorbidity (Mitchell, McCauley, Burke, & Moss, 1988; Goodyer & Cooper, 1993; Herbert et al., 1996) and the increased risk of suicide (Portzky & Van Heeringen, 2009). Depression during adolescence also has long lasting effects on functioning into adulthood and therefore results in a huge problem for our society as well.

Depression in adults has been recognized for ages and was already described by Robert Burton in his book Anatomy of Melancholy in 1621 (as cited in Rey & Hazell, 2009). This is in contrast to the recognition of depression in children, which only started during the seventies of the twentieth century with the first studies on defining characteristics of childhood depression (Rey & Hazell, 2009). Since then, ample research into juvenile depression has been done, specifically regarding prevention and treatment.

1.2 Background

1.2.1 Main features of depression

Depressive disorders are characterized by persistent and pervasive feelings of unhappiness or sadness, irritability, boredom and loss of pleasure in everyday activity. Associated symptoms are lack of energy, disturbance of appetite or sleep, negative thinking, suicidal thoughts and feelings of worthlessness. These symptoms lead to impaired functioning of the individual and can affect behavior, attitude, thinking and somatic functioning. However, such depressive symptoms are easily overlooked or unidentified by others as depressed adolescents tend to withdraw from social contacts, or as these symptoms to some extent may indicate some level of physical illness as well (Thapar, Collishaw, Pine, & Thapar, 2012). The severity of depressive symptoms can vary on a continuum from subclinical symptoms to a disabling major depressive disorder.

1.2.2 Prevalence and burden of disease

International studies show prevalence rates for depressive disorders in adolescents that range between 2 to 5.6 % (Costello, Egger, & Angold, 2005; Costello, Erkanli, & Angold, 2006). At symptom level, prevalence rates increase to 14 to 25% for adolescents who have experienced one episode of a depressive disorder (Ryan, 2005). The highest incidence rates of depression are found in adolescence compared to other age groups, indicating the importance of this developmental phase for the occurrence of depression (Kessler, 2005; Thapar et al., 2012).

In the Netherlands, the year prevalence among youth between 13 and 17 years old, was found to be 2.8% (Verhulst, Van der Ende, Ferdinand, & Kasius, 1997). In 18 to 24-years-olds, year- and life time- prevalence of depression was respectively 9% and 15.3% (De Graaf, Ten Have, & Van Dorsselaer, 2010). The risk for a depression in this age category was also found to be higher than in older age categories (De Graaf et al., 2010). A cohort study on Dutch adolescents found that before the age of 15 years 5.6% (n = 86) had experienced an episode of depression (Monshouwer et al., 2012). With increasing age in adolescence, the prevalence of depression continues to grow.

Depression in adults is predicted to be the number one cause of disability by 2030 (World Health Organization, 2011). Depressive disorders in five-year-olds and above is the leading cause of disability and the second source of disease burden above physical diseases such as cancer and diabetes (Nolen-Hoeksema & Hilt, 2013) with 168 disability adjusted life years (Rijksinstituut voor Volksgezondheid en Milieu, 2013).

Furthermore, a depressive episode affects the development of emotional, cognitive, and social skills and may interfere considerably with family relationships. Being depressed puts the adolescent also at risk for exposure to negative life events, physical illness, early pregnancy, poor work, academic and psychosocial functioning (Birmaher & Brent, 2007).

1.2.3 Depressive disorders

Major Depressive Disorder (MDD) is the most common depressive diagnosis in adolescence. See Box 1.1 and 1.2 for specific descriptions of MDD and dysthymic disorder. The duration of a major depressive episode is about eight months for clinically referred youths and for adolescents in community samples, it is one to two months (Birmaher & Brent, 2007). Different labels are used to characterize stages in increase or decrease of symptoms of depression. 'Response' refers to a significant decrease in depressive symptoms and 'remission' refers to presence of only one, or no symptom of depression. 'Recurrence' means that the adolescent experienced no depressive symptoms during at least two months

Box 1.1

Major depression according to the Diagnostic Manual IV-TR (American Psychiatric Association, 2000). Core symptoms are a depressed or irritable mood or anhedonia most of the day, nearly every day during at least the past two weeks, based on self-report. Associated symptoms are:

- Fatigue or loss of energy nearly every day
- Feelings of worthlessness or excessive guilt, nearly every day
- Recurrent thoughts of death, planning suicide, suicidal ideation or attempt
- Diminished ability to think, concentrate or indecisiveness nearly every day
- Psychomotor agitation or retardation, nearly every day
- Insomnia or hypersomnia, nearly every day
- Significant weight loss or gain, or change in appetite

A major depression is diagnosed if at least 5 out of the 9 total core or associated symptoms are present.

Other signs of depression can be loss of confidence, loss of self-esteem, unexplained somatic complaints, hopelessness, helplessness, lack of reactivity, hallucinations or delusions (Rey & Hazell, 2009).

Box 1.2

Dysthymic disorder is diagnosed when a depressed mood or irritability is present for most of the day, more days than not, and for at least 1 year. The depressed or irritable mood must be persistent and may not have been absent for more than 2 months at a time. Two or more of the following associated symptoms should be also present:

- Fatigue or loss of energy nearly every day
- Feelings of worthlessness or excessive guilt, nearly every day
- Feeling hopelessness
- Diminished ability to concentrate or indecisiveness nearly every day
- Insomnia or hypersomnia, nearly every day
- Significant weight loss or gain, or change in appetite, nearly day

but then experienced a new episode (Curry, 2014). All labels indicate that depression is a dynamic psychopathological disease with different pathways.

The DSM-IV-TR (American Psychiatric Association, 2000) does not differentiate core symptoms of a depressive disorder between different age groups, besides from the duration of the presence of the symptoms. However, the manifestations of depressive symptoms can vary by age, gender and cultural background. For instance suicidal ideation occurs from puberty onwards. Younger children are more likely to show accident-prone behavior leading to life threatening accidents instead of suicidal ideation (Pfeffer, 1981).

Recently the Diagnostic Manual V (American Psychiatric Association, 2013) was introduced, but the research in this thesis was based on the Diagnostic Manual IV-TR (American Psychiatric Association, 2000).

1.2.4 Comorbidity

Comorbidity is understood as the simultaneous occurrence of separate disorders. Comorbidity was found to be present in most depressed adolescents, with two-thirds showing at least one comorbid psychiatric disorder and 10–15% showing two or more comorbidities (Ford, Goodman, & Meltzer, 2003). In clinical settings the comorbidity in depressed adolescents is large namely between 73.5% and 79% (Essau, 2008; Karlsson et al., 2006). The reason for this high rate is probably that comorbidity is related to severe impairment (Angold, Costello, & Erkanli, 1999), which leads to referral to mental health services (Rey & Hazell, 2009). Comorbidity is a predictor of poor long-term outcome (Angold et al., 1999). The most frequent psychiatric comorbid disorders in depressed adolescents are anxiety disorders, disruptive disorders (Birmaher & Brent, 2007; Essau, 2008; Karlsson et al., 2006); substance abuse (Armstrong & Costello, 2002) and somatoform disorder (Essau, 2008). Usually, depression follows after the onset of other psychiatric disorders. For instance, an anxiety disorder increases the risk to become depressed (Wittchen, Kessler, Pfister, Höfler, & Lieb, 2000). However, the presence of depression can also increase the risk of the development of other psychiatric disorders (Angold et al., 1999; Birmaher et al., 1996; Fombonne, Wostear, Cooper, Harrington, & Rutter, 2001a,b; Lewinsohn, Rohde, & Seeley, 1998, Lewinsohn, Petit, Joiner, & Seeley 2003; Rohde, Lewinsohn, & Seeley, 1991; Thapar et al., 2012).

A psychiatric disorder is associated with increased risk of suicide, and being depressed in particular raises the chance of suicide 11 to 27 times (Rohde, 2013). In a systematic review of 128 studies, Evans and colleagues (2005) found a lifetime prevalence rate of suicide attempts of 9.7% (N = 613,188) and of 29.9% for suicidal thoughts in adolescents worldwide. In North American adolescents and young adults (15-to 24-year-olds), suicide is the leading cause of death (Jacobson & Gould, 2013). Yearly suicide rates in Dutch youth, aged 10 to 20, raised from 2 to 3 out of 100.000 in the past 20 years (Centraal Bureau voor de Statistiek, 2014). Suicide occurs more than twice as much in Dutch boys than in girls (Van Hemert & De Kruijf, 2009). Girls reported significantly more suicide attempts, deliberate self-harm, and suicidal plans, threats and thoughts than boys (Evans, Hawton, Rodham, Psychol, & Deeks, 2005).

1.2.5 Etiology and risk factors

It is important to know what causes depression in adolescents. Adolescence is characterized by major biological, social and psychological changes. Depression is determined by complex

interactions between biological susceptibility and vulnerabilities as well as environmental influences (Birmaher & Brent, 2007; Birmaher et al., 1996; Caspi et al., 2003; Kendler, Kuhn, Vittum, Prescott, & Riley, 2005; Pilowsky, Wickramaratne, Nomura & Weissman, 2006; Pine, Cohen, Gurley, Brook, & Ma, 1998; Reinherz, Paradis, Giaconia, Stashwick, & Fitzmaurice, 2003; Weissman et al., 2005, 2006). The contribution of each separate risk factor is difficult to assess because the risk factors are strongly related and also are found to be associated with future adversities (Thapar et al., 2012). Knowledge about the etiology of depression has increased in the last decade, but explaining or predicting which individual actually becomes depressed is still difficult because of the many factors involved (Hankin, 2012). Nevertheless, the following factors are considered risk factors for depression; peer victimization through bullying, maltreatment, inherited risks, hormones and psychosocial adversity (Nolen-Hoeksema & Hilt, 2013).

Exposure to psychosocial stress and depressive symptomatology within the family are the two strongest predictive factors associated with the development of an MDD (Thapar et al., 2012). For instance different parent and family factors, ranging from parental pathology, to parental cognitive style, to family emotional climate, are associated with an increased for risk for depression in youth (Sander & McCarty, 2005). Genetic as well as environmental factors can be of influence on parent and family factors (Pilowsky, 2009). Parental depression is also associated with family discord, which is associated with depression in offspring (Rey & Birmaher, 2009; Twenge & Nolen-Hoeksema, 2002). More specifically, post partum depression in mothers is associated with the quality of early attachment, which in turn contributes to later depressive symptoms and is supposed to influence the responsiveness of the hypothalamic-pituitary-adrenal axis to stress (Pilowsky, 2009). Another individual risk factor is gender, as being female raises the incidence of depression from 1 to1 during childhood into 2 to 1 by early adulthood (Twenge & Nolen-Hoeksema, 2002). The mechanism responsible for this increase is still unclear and explanations vary from genetic, hormonal as well as social theories.

Social risk factors should also be taken into account. For instance, neighborhood characteristics can account for a substantial proportion of variance in internalizing scores in children, reflecting depressive and anxiety related symptoms (Xue, Leventhal, Brooks-Gunn, & Earls, 2005).

Also stressful life events generating psychosocial stress are recognized as very important in the etiology and maintenance of internalizing problems (Grant, Compas, Thurm, McMahon, & Gipson, 2004), specifically in depressive symptoms (Kendler, Karkowski, & Prescott, 1999). Stressful life events, in contrast to other types of stress, e.g. academic stress,

are associated with a larger increase in depressive symptoms (Charbonneau, Mezulis, & Hyde, 2009; Flynn & Rudolph, 2010; Flynn, Kecmanovic, & Alloy, 2010; Hammen, 2006; Hankin, Mermelstein, & Roesch, 2007; Rudolph, 2008). For example maltreatment, sexual abuse or death within the family or loss of a close friend (Pilowsky, 2009) are associated with an increased risk of developing mental disorders during adulthood, including depression (Collishaw et al., 2007; Comijs et al., 2007; Cuijpers et al., 2011). Three different types of stressful life events have been identified that may be specifically important; loss, health threats and relational challenges (Garnefski, Boon, & Kraaij, 2003; Lazarus, 2006). Loss refers to the loss of a loved one, including a pet. Health threats include different somatic and psychological threats for instance serious illness, psychological abuse, alcohol or drug abuse. Relational challenges refer to different difficult transitions in relations such as parental divorce, moving, changing schools, romantic break-ups, pregnancy, being bullied, conflict with parents or friends or being expelled from school. In a Dutch secondary school sample ($N = 129$), loss experiences were reported most often as the most negative event experienced in adolescents' lives (59.7%), followed by "relational stress experience" (23.3%) and "health threat experiences for self or others" (17.1%) (Garnefski et al., 2003). However, all three types of stressful life events were similarly associated with depressive symptoms in adolescents, aged 14 to 18 in a community sample (Garnefski et al., 2003).

Furthermore, depressive symptoms in themselves can generate stressful life events, which again increase the risk of developing a depressive episode (Abela, Nueslovici, & Chan, 2004; Grant et al., 2006; Waaktaar, Borge, Fundingsrud, Christie, & Torgersen, 2004).

In this thesis, stressful life events are studied in relation to internalizing symptoms and depression. An important life event concerns death within the family. It is estimated that 1% to 5% of children in the USA experience the loss of a parent before they are 15 years old. One out of five parental bereaved children develops emotional and behavior problems, including internalizing problems, for which referral to special services is justified (Dowdney, 2000). Significant disturbances in self-esteem, job and school performance and interpersonal relationships are also reported as a result of the loss of a parent (Balk & Corr, 2001). Unresolved bereavement two years after parental bereavement has been linked to psychiatric problems (Cerel, Fristad, Verducci, Weller, & Weller, 2006) including agitated depression (Carr, 2003). This finding suggests that death within the family or the aftermath is associated with psychiatric problems. However, it is well possible that some children already experienced psychiatric problems before bereavement occurred, which lead to unresolved bereavement. Furthermore, recent debate on bereavement suggests that a distinct prolonged grief disorder apart from depressive symptoms should be considered (Spuij et al., 2012).

1.3 Treatment

1.3.1 Theoretical models underlying treatment

Depression is multi-determined and thereby many different theoretical models emerged trying to explain the genesis of depression from different perspectives, namely biological, psychological or social processes. Biological models stress that genetic vulnerability is important for the development of a depression. Research on twins showed a genetic contribution to vulnerability for onset of depression during adult life (Kendler et al., 1999). Adolescent depressive symptoms were also found to be significantly influenced by genetics (Taphar & Rice, 2006). So far, research on genetic determinants has not generated clinical applicable interventions apart from medication. Therefore the focus in this thesis will mainly be on theories from psychological and social perspectives.

First, the social learning theory of Lewinsohn (Cuijpers, Muñoz, Clarke, & Lewinsohn, 2009) hypothesizes that environmental changes can increase negative experiences or decrease positive reinforcing events and this may even lead to avoiding potential positive reinforcing situations. If self-awareness increases, a downward spiral may be created and depressive symptoms can occur. The depressive symptoms may sustain and increase the depressed feelings. For instance an adolescent can have a negative social experience with one peer, which leads him to retract from most peer contacts instead of searching for positive reinforcing experiences with peers. This results in isolation of the adolescent, which in turn could enhance depressive feelings. The adolescent might very well interpret the lack of peer contact as being disliked by peers or not being worthwhile as a person, which deteriorates the depression even more (Clarke, Lewinsohn, & Hops, 1990).

Second, Beck's cognitive theory hypothesizes that negative cognitive schema's are formed after experiences in early life and that these schemes can be triggered again by life events in later life. Cognitive schemes, in particular negative cognitions increase the risk for depression in adolescents (Pilowsky, 2009). Negative automatic thoughts and cognitive distortions then maintain the depressed mood. The cognitive triad, referring to negative cognitions about the self, the world and the future, can influence the way stressful life events and outcomes are perceived and increase the risk of depression. For instance, negative cognitions, including catastrophic misinterpretations of grief reactions, were significantly associated with unresolved grief as well as severity of depression (Boelen & Spuij, 2008).

Third, based on attribution theory of Abramson (Abramson, Seligman & Teasdale, 1978), learned helplessness may be considered as a result of making internal global

attributions when failing to control the occurrence of negative events is repeatedly experienced.

Fourth, the dual process model of cognitive vulnerability to depression hypothesizes the increase of depressive symptoms by associative thought processing, if no correction occurs by reflective processing (Beevers, 2005). Life stress appears to deplete cognitive resources, which are necessary for the reflective processes that are used to correct associative processing (Beevers, 2005). This dual process of self-referent association and cognitive reflection is considered to be important for the regulation of emotions.

Fifth, a more specific mechanism linked to the occurrence of depression is difficulty in regulating evoked emotions (Campbell-Sills & Barlow, 2007; Gross & Muñoz, 1995; Mennin & Farach, 2007). The concept of emotion regulation is characterized by Aldao, Nolen-Hoeksema, & Schweizer (2010) as "*… processes through which individuals modulate their emotions consciously and non-consciously (Bargh & Williams, 2007; Rottenberg & Gross, 2003) to appropriately respond to environmental demands (Campbell-Sills & Barlow, 2007; Cole, Martin, & Dennis, 2004; Gratz & Roemer, 2004; Gross, 1998; Gross & Munoz, 1995; Thompson, 1994). Individuals deploy regulatory strategies to modify the magnitude and/or type of their emotional experience or the emotion-eliciting event (Diamond & Aspinwall, 2003; Gross, 1998).*" Emotion regulation is considered to be necessary for a healthy adaptation and successful functioning in the context of difficult and stressful experiences. Maladaptive emotion regulation has repeatedly been linked to various mental disorders, including the onset of depressive symptoms (Ehring, Fischer, Schnülle, Bösterling, & Tuschen-Caffier, 2008; Joormann & D'Avanzato, 2010). Maladaptive emotion regulation is also a risk factor for the recurrence of depression in adults (Rude & McCarthy, 2003). Furthermore, findings suggest that the relationship between maladaptive emotion regulation strategies and psychopathology may be stronger when clinical severity is higher (Aldao et al., 2010). Only a few studies have researched and established the relationship between stressful life events and emotion (dys)regulation in adults (Abravanel & Sinha, 2014) and adolescents (Moriya & Takahashi, 2013).

In this thesis we will focus on specific conscious emotion regulation. Maladaptive cognitive emotion regulation such as self-blame, rumination or catastrophizing have been linked to depressive symptoms in adolescents (Martin & Dahlen, 2005; Schroevers, Kraaij, & Garnefski, 2007; Garnefski & Kraaij, 2006). Adaptive cognitive emotion regulation strategies such as positive reappraisal, positive refocusing and putting things into a broader perspective, are associated with less depressive symptoms (Garnefski et al., 2003; Kraaij et al., 2003).

1.3.2 Treatment effectiveness

Depression is a serious problem that needs to be treated in an early stage with an effective treatment to shorten the depressive episode in order to avoid further deterioration (Birmaher & Brent, 2007; Ryan, 2005). In the Netherlands, the effectiveness of psychological treatments for depression in adolescence has not been studied so far. International research showed that effectiveness of treatment of depression and sustainment of effectiveness over time is less from ideal. For instance Weisz, McCarty and Valeri (2006) performed a meta-analysis, which included studies with a large diversity of investigated interventions. They found a modest effect size of 0.34 for psychotherapy. Older meta-analyses indicated medium (0.72, Michael & Crowley, 2002) to large (1.27) effect sizes of different psychological treatments (Lewinsohn & Clarke, 1999). The degree of effectiveness of psychotherapeutic interventions in depressed adolescents varies considerably because of the sample, outcome measures and types of control condition (Curry, 2014). Depression continues to improve after the end of a short-term therapy (Curry, 2014).

Although it seems promising that a major depressive episode can diminish and disappear without treatment, the probability of recurrence is high, prevalence of 20 to 60% after 1 to 2 years after remission, and this rises to 70% after 5 years (Birmaher, Arbelaez, & Brent, 2002; Costello et al., 2002). Even after receiving treatment, 46.6% ($N = 88$) of the depressed adolescents who recovered, experienced recurrence of depression within 4 years after baseline (Curry et al., 2011).

Most intervention research has been conducted on Cognitive Behavioral Therapy (CBT) and it established rigorous evidence on its efficacy. Although, a meta-analysis showed a promising medium effect size of 0.53 for CBT, it also reflected the need for the improvement of treatment, as a large group of depressed adolescents did not recover after CBT treatment (Klein, Jacobs, & Reinecke, 2007). Furthermore, generalizability of effect sizes was questioned more than once because the study samples did not match the complex and severe cases in routine mental health care (Weisz et al., 2006).

Unfortunately, what is known about effective treatment is not used regularly in Dutch mental health care (Hermens et al., 2015). Many different non-evidence based treatments are deployed, apart from the first choice treatment recommended in multidisciplinary guidelines (CBT, Interpersonal Therapy (IPT), medication) (Hermens et al., 2015). Professionals in routine mental health care make decisions in favor of non-evidence based treatments for different reasons such as compatibility to the caseload such as comorbidity, severity of depression and inflexibility of treatment protocols (Addis & Krasnow, 2000). This

suggests that knowledge about what works for whom and why, can support professionals to plan differential treatment in order to gain maximum results in a relatively short period of time (Curry et al., 2006). Such knowledge can be retrieved from the evaluation of moderators or mediators of treatment effects.

To improve treatments, knowledge about possible moderators and mediators of treatment is desperately needed, but scarce (David-Ferdon & Kaslow, 2008; Weisz et al., 2006). A systematic review of randomized controlled studies on adolescent depression (N = 13) found that predictors and moderators were only studied in a few studies since 2000 and the outcomes provide little consistent knowledge about moderators (Nilsen, Eisemann, & Kvernmo, 2012). Webb and colleagues (2012) performed a review on potential mediators based on the theory of change within CBT for adolescent depression, namely therapeutic alliance, therapist adherence and competence, and cognitions. The conclusion was that only a few studies have focused on mechanisms of change and that the results were mixed. For instance the supposed core component of CBT, cognitive restructuring, was only investigated as a mediator in three studies and inconsistent findings were found (Webb, Auerbach, & de Rubeis, 2012). These mixed findings on moderators and mediators understate the argument made by Kraemer (2013) that moderator and mediator relationships are specific to one population, outcome, treatment and moderator and do not hold automatically for other circumstances.

1.4 Current thesis

1.4.1 Perspectives

In view of the large burden of disease for the depressed adolescents, their families and society as a whole, studies on risk factors and mechanisms for development of a depression, as well as effect studies concerning specific treatment procedures for adolescents with depression, are definitely needed. This thesis combines several research questions targeting different concepts in relation to depression, namely risk factors and development of adolescent depression and the treatment of adolescent depression. Thereby the thesis contains three different parts.

A. Focus on risk factors: life events

In the current thesis, first the role of life events, in particular family bereavement, and the onset of mental health problems in adolescents and adulthood are studied. Existing mental

health problems before the occurrence of family bereavement are taken into consideration as a moderator. Research questions are:

1. Is parental death during childhood associated with mental health problems, age of onset, incidence of mental health problems, use of mental health services during adulthood and functional limitations during adulthood?
2. Are mental health problems of family-bereaved adolescents predicted by pre-existing mental health problems, pre-loss family functioning, or multiple bereavements?

B. Focus on mechanisms: emotion regulation

Secondly, one of the mechanisms that could explain why some adolescents develop internalizing symptoms or even get depressed after experiencing stressful life events, while others do not, is emotion regulation. In particular cognitive emotion regulation is studied as a mechanism, which might mediate the strength of the association between stressful life events and depressive symptoms. The research question is:

3. Are depressive symptoms in adolescents mediated by cognitive emotion regulation strategies after stressful life events, more specifically, the loss of a loved one, health threats or relational challenges?

C. Focus on treatment: CBT versus TAU

Thirdly, taken it a step further is trying to influence depressive disorders by cognitive behavioral therapy. Behavior and cognitions should be addressed in a, for adolescents, feasible way. Generalizability to clinical practice of the previous effectiveness studies in depressed adolescents is lacking because of non-clinical samples. The effectiveness of CBT, specifically the individual D(o)epression course, versus Treatment as Usual (TAU) is tested within a randomized trial in routine clinical practice. The potential moderators are investigated. Research question is:

4. Is CBT more effective than TAU within routine care provided by professionals already working in mental health institutions?

1.4.2 Design of the studies

Four different studies are presented with different populations and designs (see Figure 1.1 and 1.2).

Figure 1.1 Model of the study 1.

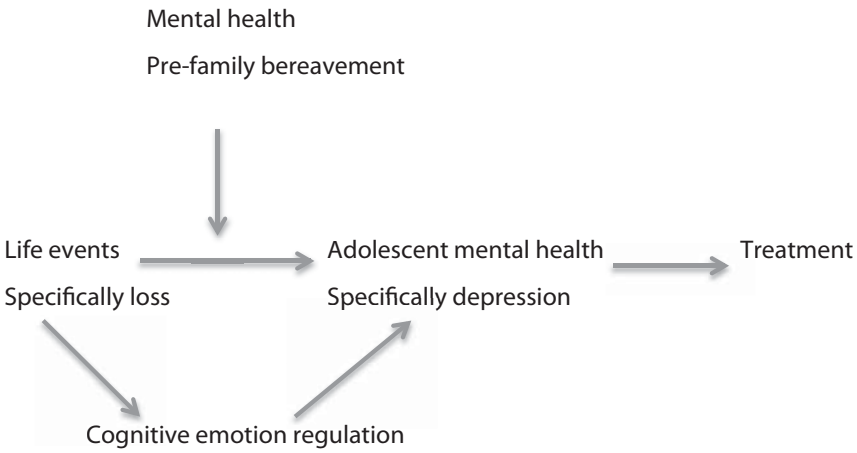

Figure 1.2 Model of the studies 2 to 5.

Study 1. Parental Death during Childhood and Psychopathology in Adulthood.
The first study is described in detail in Chapter 2. This first study was done using data from the NEMESIS study, a longitudinal population based epidemiological study in adults aged 18to 64 years (N = 7,076). Mental disorders were assessed at multiple assessment point.

Study 2. Mental health of adolescents before and after the death of a parent or sibling
The second study (Chapter 3) contains a detailed description of a prospective longitudinal assessment of change in mental health following bereavement, which was done in a large representative sample from the 'Tracking Adolescents Individual Lives Survey' (TRAILS). This is a four-wave prospective cohort study of Dutch adolescents (N = 2,230) of whom 131 (5.9%) had experienced family bereavement at the last wave (T4). At the first wave, mean age was 11.09 years (SD = 0.56) and at the last wave it was 19 years (SD = 0.60). Mental health problems were assessed at the wave prior to the bereavement and in the wave after the bereavement and the focus was on internalizing- and externalizing problems. Family functioning was also assessed at the wave prior to the bereavement.

Study 3. Adolescent depression and negative life events, the mediating role of cognitive emotion regulation

The third study described in Chapter 4 concerns a community sample of 346 adolescents and a clinical sample of 52 depressed outpatients, who all reported stressful life event(s). The mean age was 16.94 at the moment of assessment (*SD* = 2.90). The relationship between loss, health threats and relational challenges with depressive symptoms is evaluated, as well as the mediating role of maladaptive and adaptive cognitive emotion regulation strategies.

Study 4. Effectiveness of cognitive behavioral therapy (CBT) in clinically depressed adolescents: individual CBT versus treatment as usual (TAU)

The design of this study is described in Chapter 5. In Chapter 6 the results of this study are presented. Individual CBT is investigated with a multi-site, Randomized Control Trial using block randomization. The targeted population was clinically referred depressed adolescents aged 12 to 21 years old. The inclusion reached 101 within the research period. Adolescents were randomly assigned to the experimental (*N* = 44, CBT) or control condition (*N* = 44, TAU). Four assessments (pre, post, follow up at 6 and 12 months) and two mediator assessments during treatment were conducted. Primary outcome measure is depression diagnosis based on a semi-structured interview. Secondary outcome measures include depressive symptoms, severity and improvement of the depression, global functioning, quality of life, suicide risk, comorbidity, alcohol and drug use, parental depression and psychopathology, parenting and conflicts.

1.4.3 General discussion

In Chapter 7, summaries of the findings of the different studies conducted within this thesis are presented. The findings of the different studies will also be integrated and discussed.

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Part A

Focus on risk factors: life events

Mary, now aged 35, lost her mother to cancer when she was 12 years old. Somehow she managed to keep up with life. Now she is a mother herself of a three-year-old daughter. Her daughter will never know her grandmother. If she thinks of the loss of her mother she becomes sad at times and the feelings of longing for her mother and grieve still seem to change. By now she knows that she is able to endure and overcome the sadness. Somehow it made her stronger and helped to focus on important things in life. She knows that the feelings of gratefulness for having known her mother will prevail.

Chapter 2

Parental death during childhood and psychopathology in adulthood

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Psychiatry Research, *198* (2012), 516–520.
doi:10.1016/j.psychres.2011.10.024

Abstract

We examined the association between parental death during childhood and lifetime and twelve-month psychopathology, age of onset, incidence of mental health problems, use of mental health services during adulthood and functional limitations during adulthood.

We conducted a longitudinal, population based epidemiological study in adults aged 18–64 years (N = 7,076). Mental disorders were assessed with a standardized diagnostic interview (CIDI). Few indications were found that there was a significant increase in mental disorders in adulthood among people who had lost a parent before the age of 16 (n = 541). Parental death was not associated with mental disorders (12 months; lifetime), age of onset, incidence of mental disorders, functional limitations or use of mental health services. The majority of children overcome the loss of a parent during childhood without experiencing increased mental health problems, reduced functional limitations or a greater need for mental health services during adulthood.

Introduction

It is estimated that 1 to 5% of children in the USA experience the loss of a parent before they are 15 years old. In itself a tragic, disrupting and irreversible event which leaves the child with an ongoing bereavement process as he or she develops into adulthood. Most longitudinal research on the bereavement process is limited to a duration of 2 years after the death of a parent (Balk & Corr, 2001). During these two years, the effects of bereavement are severe, and unresolved bereavement during this period has been linked to psychiatric problems (Cerel et al., 2006), agitated depression, chronic illness and enduring and intense clinical reactions such as guilt (Carr, 2006). Significant disturbance in self-esteem, job and school performance and interpersonal relationships are also reported as a result of the loss of a parent (Balk & Corr, 2001). Parental bereavement may also influence physical health in later life by stress related illness (Agid et al., 1999; Krause, 1998).

Research on the effect of parental death during childhood on adult psychopathology is inconclusive (Luecken, 2008). Some population based studies do find that parental death during childhood is significantly associated with adult psychopathology (Reinheirz et al., 1999; Kendler et al., 2002; Morgan et al., 2007), while others do not (Sareen et al., 2005). A population based study in Norway found that parental death by suicide during childhood or adolescence is associated with long-term risk for suicide and hospitalization for specific psychiatric disorders (Wilcox et al., 2011).

Retrospective studies of adults with mental health problems establish a link between the death of a parent during childhood and psychopathology during adulthood especially in depression (Appleby et al., 1999; Kendler et al., 2002). Most of these retrospective studies, however, are limited to samples of clinical patients, and are not representative for the general population (Dowdney, 2000). Furthermore, there is little consensus about the specific type of pathology affected (Jacobs and Bovasso, 2009). Most studies in this area, however, do not use representative, prospective population based data and rigorous diagnostic criteria to establish the presence of mental disorders. Therefore, in the current study, we use data of a representative sample (N = 7,076) of the general population to examine the association between parental death during childhood and adult psychopathology, both cross-sectionally and prospectively. We will also examine whether age of onset for the various mental disorders is different for parentally bereaved and non-bereaved. Furthermore, we will examine whether parental death during childhood is associated with the use of mental health services and with functional limitations.

Method

Procedure

The Netherlands Mental Health Survey and Incidence Study (NEMESIS) was based on a multistage, stratified, random sampling procedure (Bijl et al., 1998a, 1998b). In brief, a sample of 90 municipalities was drawn, using urbanisation as stratification criterion; the sample resulted in an adequate distribution of the respondents over the 12 Dutch provinces. Then a sample of private households was drawn from the postal registers. The selected households were first sent a letter of introduction followed by a telephone contact. In each household, the member with the most recent birthday was selected, on condition that (s) he was between 18 and 64 years and sufficiently fluent in Dutch to be interviewed. To establish contact, the interviewers made a minimum of 10 phone calls or visits to a given address at different times of the day and week.

In the initial data collection phase, 7,076 respondents were interviewed in person (year of interview: 1996; response rate 69.7%). All participants in the first interview (T0) were approached for the follow-up wave, one year (T1) after T0. Of the 7,076 persons who had taken part at T0, 5,618 could be re-interviewed at T1 (response: 79.4%). After adjustment for demographic variables (see below), a 12-month mental disorder at T0 only slightly increased the probability of loss to follow-up between T0 and T1 (*OR* = 1.20; 95% CI 1.04–1.38). To correct for the combined effect of initial nonresponse and dropout, post-stratification weights were calculated.

Measurements

Mental disorders were assessed according to DSM-III-R criteria. The instrument used was the Composite International Diagnostic Interview (CIDI; World Health Organization, 1997), Dutch 1.1 version (Ter Smitten et al., 1998). The CIDI is a structured interview developed by the World Health Organization (WHO; Robins et al., 1988) which can be administered by trained lay interviewers. It is known to have a high interrater and test-retest reliability (Wittchen, 1994). In the current study, we use the lifetime and 12-month diagnoses of the most common mood disorders, anxiety disorders and substance-use disorders. The specific disorders are described in Table 2.1. Schizophrenia and eating disorders were not included in this study because the numbers of subjects were small ($n < 26$ for both disorders). The CIDI was administered to all respondents at all two measurements T0 and T1.

Table 2.1 The risk of lifetime mood, anxiety and substance use disorders in adults who have lost at least one of their parents by death during childhood, in Odds Ratios (*OR*)

	PD[a] versus NP Unadjusted for demographics			PD versus NP Adjusted for demographics[b]			PD versus NP Adjusted for demographics and adversity[c]		
	OR	95% CI	*p*	*OR*	95% CI	*p*	*OR*	95% CI	*p*
Any mood disorder	1.21	0.98–1.50	.08	1.19	0.96–1.48	.12	1.00	0.78–1.28	.98
MDD	1.23	0.98–1.55	.74	1.22	0.96–1.54	.10	1.05	0.81–1.36	.70
Dysthymia	1.22	0.87–1.70	.25	1.10	0.78–1.55	.58	0.85	0.58–1.25	.42
Bipolar disorder	0.77	0.38–1.57	.47	0.84	0.41–1.72	.63	0.69	0.32–1.51	.36
Any anxiety disorder	1.04	0.83–1.30	.74	1.01	0.80–1.26	.96	0.83	0.65–1.06	.13
Simple phobia	0.84	0.62–1.15	.27	0.82	0.60–1.13	.22	0.71	0.51–0.99	.046*
Social phobia	1.15	0.84–1.57	.39	1.13	0.82–1.54	.46	0.92	0.65–1.31	.65
Agoraphobia	0.98	0.60–1.60	.94	0.92	0.56–1.51	.75	0.80	0.47–1.35	.40
Panic disorder	1.09	0.70–1.70	.70	1.06	0.68–1.66	.81	0.90	0.55–1.46	.60
Generalized anxiety	0.73	0.37–0.43	.36	0.67	0.34–1.32	.24	0.51	0.24–1.10	.09
Substance use disorder	0.73	0.57–0.93	.011*	0.85	0.66–1.11	.24	0.83	0.63–1.10	.18
Alcohol abuse	0.61	0.44–0.84	.002**	0.71	0.51–1.00	.047*	0.69	0.49–0.98	.038*
Alcohol dependence	1.11	0.77–1.61	.57	1.30	0.89–1.91	.17	1.35	0.91–2.00	.14
Drug abuse	0.38	0.13–1.12	.08	0.48	0.16–1.43	.19	0.48	0.16–1.47	.20
Drug dependence	0.55	0.23–1.29	.17	0.66	0.28–1.55	.34	0.62	0.26–1.49	.28
Any disorder	1.05	0.88–1.26	.57	1.10	0.92–1.30	.27	0.97	0.80–1.19	.80

* $p < .05$; ** $p < .01$

[a] Parental death (PD) before the age of 16 years; (NP = no parental death before age of 16 years).

[b] These analyses were adjusted for demographic variables (gender, age, employment status, single versus married, educational level and urbanized versus rural).

[c] Adjusted for divorce, physical abuse, psychological abuse, sexual abuse, neglect and parental psychological problems.

In the current study we examined lifetime and 12 month prevalences of mental disorders, as well as the age of onset.

Parental death was assessed by asking the respondents if they had lost a parent by death before the age of 16 years. A total of 541 respondents (7.4%) reported the death of a parent before the age of 16.

Demographic variables included: gender, age, employment status, single versus married or cohabitating, education (lower versus higher) and urbanized versus rural.

Adversities other than parental death was defined broadly and included: divorce, physical abuse, psychological abuse, sexual abuse before age of 16 years, neglect and parental psychological problems. It was assessed by asking the respondents if they had experienced one of these adversities.

Functional limitations were measured with the Medical Outcomes Study Form-36 (MOS-SF-36; Stewart et al., 1988) with the scales; mental health, role limitations- emotional, physical functioning, role limitations-physical measure, social functioning, vitality, pain and general health perceptions (physical and mental health components). The Cronbach's alpha of all the scales were all above .77. The scores on each of the 8 scales were transformed to a 1 to 100 scale, with higher scores meaning better functioning.

Use of mental health care services was assessed by asking the respondents how many times they were treated for psychiatric illness, alcohol or drugs use in primary care, daycare, clinical care or alternative treatments.

Results

Lifetime prevalence and twelve-month prevalence of psychiatric disorders in adults who experienced parental death before the age of 16 years in comparison to adults who did not

We first examined in the baseline data (at T0) to establish whether there was an association between parental death during childhood and adult psychopathology. We conducted a series of logistic regression analyses, with each of the lifetime prevalence rates of mood, anxiety and substance-related disorders as the dependent variable, and parental death (yes/no) as predictor. First, we examined these associations in bivariate analyses, and then we conducted all analyses once more but adjusted for demographic variables (gender, age, employment status, single versus married, educational level and urbanized versus rural) and again adjusted for childhood adversities (divorce, physical abuse, psychological abuse,

sexual abuse before age of 16 years, neglect and parental psychological problems) (Table 2.1). We repeated these analyses once more for twelve-month prevalence of psychiatric disorders. The adults who lost a parent during childhood did not show a significantly higher life-time prevalence or twelve-month prevalence of mental disorders including anxiety disorder, major depressive disorder, dysthymia, bipolar disorder or any disorder. The lifetime prevalence of alcohol abuse (*OR* = 0.71, 95% CI 0.51–1.00, *p* = .05) remained significantly lower than in the general population after adjusting for demographics and even after adjusting for other childhood adversities (*OR* = 0.69, 95% CI 0.49–0.98, *p* = .038). Twelve-month prevalence rate of alcohol abuse (*OR* = 0.42, 95% CI 0.23–0.77, *p* = .005) was significant lower but after adjusting for demographics it was no longer significant.

To test interactions between gender and parental death, we conducted a series of logistic regression analyses, with each of the mental disorders as the dependent variable and gender, parental death and the interaction term as predictors. None of the interaction terms was found to be significantly associated with a mental disorder, indicating no differential effects of parental death on psychopathology in adulthood between men and women.

Age of onset of psychiatric disorders in adults who experienced parental death before the age of 16 years in comparison to adults who did not

We also examined whether there was an association between parental death and age of onset of mental disorders. We conducted a series of linear regression analyses with age of onset of each of the major categories of mental disorder (mood, anxiety, substance-use, any) as the dependent variable. In none of these analyses was parental death a significant predictor of age of onset.

We repeated these analyses while adjusting for demographic variables. Only the dependent variable *any substance dependence* had a significantly lower association (β = -.08, *p* = .035) with parental death before the age of 16 years than in the general population.

First ever incidence of a mental disorder within one year and the relationship with the experience of parental death during childhood

It is hypothesised that adults who lost a parent before the age of 16 years have an increased risk of developing a mental disorder for the first time in their lives between T0 and T1. A logistic regression was conducted. The predictor was parental death before the age of 16 years and the dependent variable being the incidence of a mental disorder. Incidence of simple phobia (*OR* = 1.80; 95% CI 1.04–3.12; *p* = .04) and panic disorder (*OR* = 2.54; 95%

CI 1.14–5.65; $p = .02$) were significantly associated with parental death before the age of 16 years (Table 2.2). Adjusted for demographic variables (gender, age, employment status, single versus married, educational level and urbanized versus rural), only panic disorder was predicted by death of a parent before the age of 16 (*OR* = 2.52; 95% CI 1.12–5.67; $p = .03$).

Table 2.2 First ever incidence of a mood, anxiety and substance use disorder in adults who have lost at least one of their parents by death during childhood: Odds Ratios (*OR*)

	PD[a] versus NP Unadjusted for demographics			PD versus NP Adjusted for demographics[b]		
	OR	95% CI	*p*	*OR*	95% CI	*p*
Any mood disorder	0.97	0.45–2.08	.94	0.05	0.55–2.04	.88
MDD	1.03	0.54–2.04	.92	0.98	0.45–2.12	.96
Dysthymia	0.42	0.04–4.60	.48	0.37	0.03–1.02	.41
Bipolar disorder	0.70	0.09–5.69	.74	0.74	0.09–6.08	.78
Any anxiety disorder	1.31	0.73–2.35	.37	1.24	0.69–2.25	.47
Simple phobia	1.80	1.04–3.12	.04*	1.73	0.99–3.03	.05
Social phobia	0.41	0.09–1.95	.26	0.38	0.08–1.81	.22
Agoraphobia	0.49	0.11–2.25	.36	0.44	1.00–2.03	.29
Panic disorder	2.54	1.14–5.65	.02*	2.52	1.12–5.67	.03*
Generalized anxiety	0.70	0.18–2.71	.61	0.65	0.17–2.54	.54
Substance use disorder	0.72	0.29–1.83	.50	0.93	0.37–2.35	.88
Alcohol abuse	0.70	0.32–1.54	.37	0.85	0.38–1.90	.70
Alcohol dependence	0.41	0.04–3.88	.44	0.41	0.04–3.95	.44
Drug dependence[c]	0.51	0.04–6.43	.60	0.65	0.05–8.46	.75
Any disorder	1.03	0.73–1.44	.88	1.03	0.73–1.44	.88

* $p < .05$

[a] Parental death (PD) before the age of 16 years; (NP = no parental death before age of 16 years).

[b] These analyses were adjusted for demographic variables (gender, age, employment status, single versus married, educational level and urbanized versus rural).

[c] Data for drug abuse could not be calculated because the number of subjects was too small.

Functional limitations in relation to the experience of parental death during childhood

In order to establish whether there was a correlation between functional limitations and parental death during childhood a series of multiple regression analyses were conducted. The predictor was parental death before the age of 16 and the dependent variables were the 8 scales of the MOS-SF (Stewart et al., 1988), while we controlled for demographics (gender, age, employment status, single versus married, educational level and urbanized

versus rural). There was no indication that parental death before the age of 16 years was related to a lower outcome on any of the scales of the MOS-SF (Table 2.3).

Table 2.3 Functional limitations in adults who lost at least one of their parents by death during childhood compared to those who did not[a]

	Parental death (*N* = 541)		No parental death (*N* = 7,076)	
	M	*SD*	*M*	*SD*
General health perceptions	73.30	17.24	74.56	17.95
Physical functioning	90.57	17.92	92.21	15.47
Pain	83.70	22.74	85.44	21.55
Mental health	81.83	15.34	81.85	14.98
Role limitations - physical	85.72	30.11	85.82	29.82
Role limitations - emotional	92.31	23.43	92.13	23.41
Social functioning	89.45	18.10	89.71	17.91
Vitality	72.16	18.16	71.37	18.30

[a] Multiple regression analyses did not indicate any significant difference between parental bereavement individuals and others (adjusted for demographic variables: gender, age, employment status, single versus married, educational level and urbanized versus rural).

Use of mental health care services and parental bereavement

Although parental death before the age of 16 does not lead to significantly more mental health problems during adulthood it could still account for significantly more use of mental health care services. A series of logistic regressions was conducted, with parental death being the predictor and lifetime use of mental health care services as dependent variable. No indication was found that parental death before the age of 16 is related to use of mental health care services (*OR* = 0.95; 95% CI 0.74–1.23; *p* = .1). This was also true after adjusting for demographics (*OR* = 0.94; 95% CI 0.72–1.21; *p* = .1). We conducted the analyses once more for different kinds of care being primary care, daycare, clinical care or alternative treatments. Once more no indication was found that parental death before the age of 16 is related to use of specific mental health care services.

Discussion

We found few indications that there is a significant increase in mental disorders, in specific first incidence of panic disorders, in adulthood after the death of a parent during childhood. This finding is in line with significant higher overall anxiety levels in 6 to 17 years old, two

years after parental bereavement, compared to non bereaved (Worden & Silverman, 1996). Specific anxieties concerning separation and death of the surviving parent are common after parental bereavement (Silverman & Worden, 1992; Sanchez et al., 1994). Also fear of abandonment, children's beliefs that they cannot count on their caregiver to take care of them in the future (Schoenfelder et al., 2011), has a longitudinal pathway to higher levels of anxiety in romantic relations even after six years, in adolescence and young adulthood and mediates higher self reported levels of depression (Schoenfelder et al., 2011). It can be hypothesized that panic disorders in adulthood are related to the fear of abandonment after the death of a parent before the age of 16 years.

We found only a small decrease in the lifetime prevalence of substance abuse and alcohol abuse for parentally bereaved compared to no parental bereavement. Parental death before the age of 16 was not associated with a younger age of onset of mental health problems or with the incidence of mental health problems. We found no indication that functional limitation was lower or that the use of mental health services was higher during adulthood after the death of a parent before the age of 16. All these findings indicate that the majority of children can overcome the loss of a parent during childhood without an increase in mental health problems, loss of functional limitations or increased need for mental health services.

Overall, mental health problems and specifically major depression experienced during adolescence are associated with long lasting effects on functioning in adulthood (Lewinsohn et al., 1999). It seems promising that we found no indication for a difference in age of onset between the parentally bereaved and non parentally bereaved.

The indication that lifetime prevalence of substance abuse and alcohol abuse may be even somewhat lower for parentally bereaved before the age of 16 can be labelled as a positive outcome although this was not a very strong association. On the other hand higher rates of alcohol and substance abuse after 21 months following a parent's death through suicide in comparison to other kinds of bereavement was found in other studies (Brent et al., 2009), indicating that the cause of death may play a crucial role in adapting to the bereavement. Possibly, the lifetime prevalence of substance and alcohol abuse may be even lower for non-suicidal parental bereavement. In this study we could not account for the cause of death.

This study has several strengths and limitations. The strengths include the relatively large, representative community sample, and the use of well-validated diagnostic instruments to assess the presence of mental disorders. It was also possible to adjust for demographics which may account for the results, in contrast to other studies which failed to control for variables that affect psychopathology (Jacobs & Bovasso, 2009).

Limitations and directions for future research

First, only some significant findings were found given the multiple analyses it is possible that the findings are the result of a type I error. The findings should be treated with caution.

Second, as the Dutch culture is highly influenced by the Christian tradition the generalization to other non-western countries is limited. The fact that also in China, with a very different culture, parental death before age of 18 years is not associated with earlier age of onset of any mental health disorder (Lee et al., 2011), however, may point at a more universal association.

Third, the age of onset of mental health problems is based on retrospective recall. Because the adversity took place before the age of 16 and the ages varied between 18 and 64 years it is entirely possible that this retrospective recall is not accurate. The assessment of psychopathology can also be influenced by social desirability although the diagnostic instruments which were used have good psychometric properties. Nonetheless, all the findings are coherent and point in the same direction.

Fourth, it was not possible to account for the cause of death which has been associated with the outcome of parental bereavement in terms of mental health (Melhem et al., 2008; Brent et al., 2009). It is unclear in what way the different causes of death predict the outcome of parental bereavement. For example, death by suicide is related to mental health problems in the deceased parent prior to the suicide, specifically major depression (Melhem et al., 2008). Mental health problems in the parent are in themselves a predictor for mental health problems in the child (Rutter & Quinton, 1984).

Fifth, in this study we could not account for the gender of the deceased parent. It has been suggested that in particular the death of the father is a predictor for mental health problems (Kessler et al., 1997; Jacobs & Bovasso, 2009).

Sixth, lifetime prevalence rates also contain the psychiatric disorders which may have started before the parental bereavement, meaning that the lifetime prevalence rate since parental bereavement would even be lower. This suggests that alcohol abuse among parentally bereaved would even be lower. In this study it was not possible to account for that.

Seventh, although the use of mental health care services is not significant higher for parentally bereaved this conclusion is limited because only the amount of treatments was measured and not the duration or costs.

Eight, the finding, that first incidence of panic disorder is significantly increased during adulthood in parentally bereaved before age of 16 years, can be of importance to conducting treatment of this mental health problem. It has been suggested that the

information about the association between parental bereavement and mental health problems in the long term and functional limitations is clinically relevant as part of the psycho-education for the parent as well as the child (Luecken, 2008). The fact that mental health problems are not inevitable could be very reassuring for parents but also for adults who lost a parent before the age of 16 years. Likewise, the finding that the functional limitations of the parentally bereaved is not impaired in comparison to the non-bereaved is relevant for the surviving parent and the adults who experienced this adversity.

Acknowledgements of authors' contributions

Yvonne Stikkelbroek designed the study, conducted the statistical analyses, drafted the initial manuscript, revised the manuscript and approved the final manuscript as submitted. *Peter Prinzie* revised the manuscript and approved the final manuscript as submitted. *Ron de Graaf* coordinated the data collection, revised the manuscript and approved the final manuscript as submitted. *Margreet ten Have* performed data collection, revised the manuscript and approved the final manuscript as submitted. *Pim Cuijpers* designed the study, revised the manuscript and approved the final manuscript as submitted.

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Mary, 17 years old, lost her mother to cancer when she was 12 years old. During the illness of her mother her life was very difficult. The family was supported a lot by acquaintances, for instance the neighbours took turns to serve dinner and to make sure that they ate healthy to keep on going. The loss of her mother felt like it was too much to bear, being alternately sad or very angry. She focused on conquering each day at a time. Small things became very important such as make her father laugh. She longed to be as normal as possible and could not bear the questions of peers and others about the loss of her mother. Her father and family worried because she was doing all right but did not want to discuss her feelings about the loss of her mother. They forced her to speak to a bereavement counselor, but she resisted.

She still misses her mother a lot and has conversations with her in her head. It helps her to reflect on her feelings and actions. She feels so different from her peers who are annoyed with their parents and act irresponsible at times. She sometimes worries about her father and is afraid that something might happen to him.

Chapter 3

Mental health of adolescents before and after the death of a parent or sibling

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European Child & Adolescent Psychiatry, *25* (2016), 49–59.
doi:10.1007/s00787-015-0695-3

Abstract

The death of a parent or sibling (family bereavement) is associated with mental health problems in approximately 25% of the affected children. However, it is still unknown whether mental health problems of family-bereaved adolescents are predicted by pre-existing mental health problems, pre-loss family functioning, or multiple bereavements. In this study, a prospective longitudinal assessment of change in mental health following bereavement was done in a large representative sample from the 'Tracking Adolescents Individual Lives Survey' (TRAILS). This is a four-wave prospective cohort study of Dutch adolescents (N = 2,230) of whom 131 (5.9%) had experienced family bereavement at the last wave (T4).

Family-bereaved adolescents reported more internalizing problems, within two years after family bereavement, compared to the non-bereaved peers, while taking into account the level of internalizing problems before the bereavement. A clinically relevant finding was that 22% new cases were found in family-bereaved, in comparison to 5.5% new cases in non-bereaved. Low SES predicted more internalizing problems in family-bereaved but not in non-bereaved adolescents. Family functioning, reported by the adolescent, did not predict mental health problems within two years. Multiple family bereavements predicted fewer externalizing problems. In conclusion, internalizing problems increase in adolescents after family bereavement in comparison to non-bereaved and these can be predicted by pre-loss factors. Awareness among professionals regarding the risks for aggravation of mental health problems after family loss is needed.

Introduction

The death of a parent or sibling during adolescence is a tragic, irreversible loss, which leads to elevated levels of psychological distress (Dowdney, 2005; Fristad, Jedel, Weller, & Weller, 1993; Harrison & Harrington, 2001; Kalter et al., 2002; Siegel, Karus, & Raveis, 1996; Silverman & Worden, 1992). The prevalence of the loss of a parent or sibling varies between 1 and 5% in previous studies (Centraal Bureau voor de Statistieken, 2013; Harrison & Harrington, 2001). The majority of bereaved adolescents exhibit acute grief reactions, sleep problems, anger, irritability, behavioural problems (Silverman & Worden, 1992) and lower self-esteem (Mack, 2001). These grief reactions can give rise to serious concerns in parent(s) and teachers about the psychological adjustment of the adolescents, although the reactions can still be normal since 75 to 80% of the children do not develop mental health problems after the death of a parent (Cerel, Fristad, Verducci, Weller, & Weller, 2006; Dowdney, 2000; Dowdney, 2005; Luecken & Roubinov, 2012; Worden, 1999) or sibling (Dowdney, 2005; Worden, 1999). Psychological adjustment after parental bereavement is most commonly characterized by depressive symptoms (Dowdney, 2000). Parentally bereaved adolescents are at risk for developing internalizing disorders (Mack, 2001), including major depressive episodes (Gray, Weller, Fristad, & Weller, 2011). Furthermore, children who lose a parent or a sibling are at risk for the same mental health problems (Harrison & Harrington, 2001; Worden, 1999).

Adolescents who overcome bereavement without developing serious mental health problems may have certain protective factors in common (Oltjenbruns, 2001). However, there is a lack of systematic attention to protective and risk factors and moderation of psychological adjustment after family bereavement (Dowdney, 2000). For professionals working within schools, hospitals and mental health care institutions, knowledge about protective and risk factors present before family bereavement may contribute to identifying children who are at risk for developing (more) mental health problems after bereavement. Early detection may prevent further aggravation of mental health problems or prevent unnecessary psychological treatment and psychiatric stigmatization.

Luecken proposed a comprehensive model of pathways linking early parental death to mental and physical health problems including risk factors (Luecken & Roubinov, 2012). Risk factors for developing mental health problems can be divided in risk factors pre and post bereavement. Post bereavement risk factors have already been identified, namely poorer quality of parenting, worse quality of the parent-child relationship, caregiver mental health problems, subsequent negative life events, low social economic status (SES) and low self-

system beliefs, including self-esteem, self-efficacy and social relatedness (Dowdney, 2000; Luecken & Roubinov, 2012). However, risk factors may already be present before the loss occurs and may influence psychological adjustment after the loss. According to Dowdney, mental health problems of the adolescent before bereavement may constitute an important risk factor (Dowdney, 2000) because stress caused by the loss can aggravate pre-existing mental health problems. For instance, a depressive disorder is associated with a higher vulnerability to stress (Braet, Vlierberghe, Vandevivere, Theuwis, & Bosmans, 2013). Retrospective studies found that a history of depression (Gray et al., 2011; Melhem, Walker, Moritz, & Brent, 2008), sexual abuse (Melhem et al., 2008) and any psychiatric disorder (Weller & Weller, 1991) were correlated with depression after parental loss. Furthermore, the presence of mental health problems before bereavement can be associated with the death of a family member. An extensive review of parental cancer showed that a significant number of children developed psychosocial problems during the illness of their parent (Krattenmacher et al., 2012).

In adolescents, gender is a risk factor for increased depressive symptoms in non-bereaved, with girls suffering twice as much as boys (Hyde, Mezulis, & Abramson, 2008; Lewinsohn, Rohde, & Seeley, 1998; Thapar, Collishaw, Pine, & Thapar, 2012). Research on gender as a risk factor for depressive problems in family-bereaved adolescents is so far inconclusive (Gray et al., 2011).

Family bereavement can cause financial hardship (e.g. decrease or loss of income), which may lead to negative life events (e.g. moving house, changing schools and loss of friends) and parenting difficulties (Dowdney, 2000). Low socio economic status is in itself associated with more negative life events (Cerel et al., 2006; Evans & English, 2002) and parenting difficulties (McLoyd, 1998) and is therefore associated with greater vulnerability to the effects of family bereavement.

Theoretical and clinical accounts suggest that family functioning, including family organization, cohesion, communication and role differentiation, pre and post bereavement is important for the effect of parental bereavement on mental health problems (Sutcliffe, Tufnell, & Cornish, 1998). Family functioning and parenting can be affected by family bereavement in a negative way, for example as a result of parental mental health problems, or in a positive way, when cohesion increases after the loss (Dowdney, 2000; Gilmer et al., 2012; Sutcliffe et al., 1998).

Experiencing the death of a parent or sibling renders a child more vulnerable to developing mental health problems in the event of future losses (Oltjenbruns, 2001). Experiencing a second family bereavement might have an even greater impact on mental health problems than a first bereavement.

The above-mentioned studies have several limitations. First, most studies in this area do not use a large and representative sample, or a comparison group (Balk & Corr, 2001). Second, research on pre-bereavement family functioning is limited to retrospective accounts of the parents or child about family functioning before bereavement took place, these accounts may be affected by their loss (Dowdney, 2000). Third, to our knowledge only one previous study focused on pre-bereavement measurements and prospective analyses of the development of mental health problems. In the current longitudinal study using a large sample (N = 2,230), the mental health of the adolescents that experienced the death of a parent (n = 55) or sibling (n = 15) was analysed prospectively.

The present study evaluates the nature and severity of changes in child mental health after bereavement in comparison with a non-bereaved peer population in a large representative sample, hereby taking into account pre-bereavement internalizing and externalizing problems and other potentially confounding variables. First, it is hypothesized that mental health problems, in particular internalizing problems, are more severe in adolescents approximately 2 years after they experienced death within their family compared to non-bereaved adolescents. Differences in outcomes of family- versus sibling-bereavement will be analysed in an exploratory way. Second, it is hypothesized that more internalizing or externalizing problems before family bereavement are associated with more internalizing or externalizing problems after bereavement compared to the non-bereaved within the same period. Third, by the time adolescents reach the age of 19, those who experienced family bereavement are expected to exhibit more mental health problems (mainly internalizing problems), than their non-bereaved peers. Secondary analyses concern the following predictors in explaining internalizing or externalizing problems after bereavement: internalizing/externalizing problems before bereavement, low family functioning before bereavement, and multiple bereavement.

Materials and method

Sample and study design

Subjects were 2,230 Dutch participants of a prospective cohort study, the 'Tracking Adolescents Individual Lives Survey' (TRAILS). This study was conducted to track the development of mental health from preadolescence into adulthood. The sampling procedure and methods are described in detail in Huisman et al. (Huisman et al., 2008). Characteristics of the subjects can be found in Table 3.1. The study has been approved by

Table 3.1 Characteristics of the sample at the four measurements

Total sample	T1	T2	T3	T4	
n	2,230	2,149	1,816[c]	1,881[d]	
Mean age (*SD*)	11.09 (0.56)	13.56 (0.53)	16.27 (0.73)	19.1 (0.60)	
% girls	50.8	51.0	52.3	52.3	
Response rate (%)	76.0[a]	96.4[b]	81.4[b]	84.3[b]	
Family bereavement					Total
Deceased persons[e]	70	38	24	23	155
n[f]	52	33	23	23	131
Mean age (*SD*)	11.14 (0.53)	13.64 (0.54)	16.51 (0.80)	19.24 (0.65)	
% girls	51.7	33.3	69.6	56.5	49.6
Mean SES (*SD*)[g]	-0.01 (0.21)				

[a] Of the 2,935 eligible children asked to participate at T1.
[b] Of the 2,230 included children at T1.
[c] Non-responders at T3 include 2 deceased, 7 who were physically or psychologically unable to participate, 4 who were detained or moved abroad, and 31 untraceable or unreachable participants. Other non-responders refused participation or did not return any information (*n* = 372).
[d] Non-responders at T4 include 5 deceased, 3 who were physically or psychologically unable to participate, and 1 detained participant, 16 untraceable and 43 unreachable participants, and 9 participants who moved abroad. Other non-responders refused participation or did not return any information (*n* = 272).
[e] Occurrence of Family bereavements.
[f] Persons who experienced their last family bereavement in this wave.
[g] Of the family-bereaved between T1 and T4.

the Dutch Central Committee on Research Involving Human Subjects. This research was conducted in the northern part of the Netherlands, in an area which supports a variety of economic activities, including (light) industry, services, educational facilities, and agriculture. The participants were recruited from suburban (80%) and rural (20%) areas. In total four data collection waves have been completed and these are used in the present study: T1 (2001–2002), T2 (2003–2004), and T3 (2005–2007) and T4 (2008–2010). At all four assessment waves written informed consent was obtained from the adolescents themselves, and for those younger than 18 years, parental consent was also obtained. At T1, parents (mothers, 95.6%) or guardians were visited at their home by well-trained interviewers and they were asked to fill out self-report questionnaires. The children filled out the questionnaires at school, in the classroom, under the supervision of one or more test assistants (T1, T2, T3). At T4 a web-based questionnaire was used.

At T4, 131 (5.9%) adolescents had suffered the loss of at least one parent or sibling during their life, and 24 (18%) of these had lost more than one parent or sibling (see Table 3.1). In total, 155 family members died before T4. The last bereavement of a parent (*n* = 87; 66%) or sibling (*n* = 44; 34%), occurred in 6% (*n* = 8) within the past 2 months, in 10%

(n = 10) between 2 and 12 months previously and in 78% (n = 102) more than 12 months previously, with 6% (n = 8) unknown. A total of 79 adolescents experienced the death of a parent or sibling between T1 and T4. Some family-bereaved did not participate at all in one of the assessments (pre or post bereavement) and these were regarded as dropouts (n = 9). The reasons for dropout are unknown. The remaining 70 adolescents were included in the analyses.

Instruments

Demographic variables. Gender, age, and SES (Vollebergh et al., 2005) of the parents were assessed during an interview with a questionnaire at T1 with one of the parents. SES was based on a scale containing educational level (father/mother), occupation (father/mother), and family income. The internal consistency was good (α = .84) (Vollebergh et al., 2005).

Death within the family. Family bereavement was assessed by asking the adolescents if they had lost a parent or sibling by death, including stepparents, stepbrothers, stepsisters, half-brothers and half-sisters, yes or no.

Multiple bereavement within the family. This was assessed by summing the scores on death within the family in the waves prior to the last bereavement. The bereavements prior to the last family-bereavement occurred in wave T1, T2, T3 or T4.

Mental health problems. Internalizing and externalizing mental health problems were assessed with the Youth Self Report (YSR) (Achenbach, 1991) at T1 to T3 and the Adult Self-Report (ASR) (Achenbach & Rescorla, 2003) at T4. Both questionnaires contain a similar list of emotional and behavioural problems which are rated on a scale of 0 = not true, 1 = somewhat or sometimes true or 2 = very or often true, in the past 6 months. A higher score indicates more symptoms of psychopathology. Scale scores were converted into standardized scores for the YSR internalizing (31 items, M = 11.27, α = .87) and externalizing dimensions (32 items, M = 8.51, α = .85) and the ASR internalizing (39 items, M = 9.83, α = .93) and externalizing dimensions (35 items, M = 8.01, α = .89). The pre (loss) score, before bereavement, was obtained by selecting internalizing and externalizing subscale scores of the YSR at the beginning of the period in which the (last) bereavement took place. As post (loss) score, the YSR score on internalizing or externalizing problems at the end of the period in which bereavement took place was used. In the case of multiple bereavements, the last bereavement nearest to T4 was selected as the target event.

Family functioning was assessed at the wave prior to the bereavement with a modified version of the General Scale of the McMaster Family Assessment Device (FAD) (Epstein,

Baldwin, & Bishop, 1983) (12 items, α = .85). Parents could rate how they agreed with statements concerning the functioning of their family on a 4-point scale 1 = totally disagree, 2 = disagree, 3 = agree, 4 = totally agree. A low score on the scale indicates a healthy family climate and a high score represents a dysfunctional family climate (12-items, α = .85). Only the pre (loss) score was used.

Statistical analyses

The incomplete cases per scale (YSR, ASR, FAD) were imputed to maximize the number of complete cases with corrected item mean imputation (CIM) (Raaijmakers, 1999) in which person information as well as scale information was used. Scales larger than five items were not imputed if fifty percent or more of the answers were missing and the scale score was not computed. If subjects did not participate in the wave before or after the bereavement they were not included (n = 9). Consequently, the data of 70 adolescents who experienced the death of a parent (79%, n = 55) or a sibling (21%, n = 15) during wave 2, 3 or 4 were included in the analyses and treated as one group with pre and post assessments at T1, T2, T3 or T4 (see Table 3.1, Figure 3.1, 3.2). None of the bereaved adolescents lost both, a parent and a sibling. We wanted to compare the family-bereaved with the non-bereaved. Since not all three time periods (between four assessments) could be selected due to inter-correlation of those assessments only one time period was selected per non-bereaved individual. This resulted in one time period with two assessments that matched the bereaved group of which only one time period was chosen in which family bereavement took place. Therefore the non-bereaved adolescents (non-bereaved, n = 2,099) were randomly assigned to three groups (A, B and C) by SPSS 21 (IBM Corp, 2012). The assessments of Group A at T1 were included as pre score and at T2 as post score. The assessments of group B at T2 were included as pre score and at T3 as post score. The assessments of group C at T3 were included as pre score at T4 as post score. The aforementioned assessments of Group A, B and C together formed the non-bereaved group with pre and post scores of the wave. These scores are referred to as pre (loss) score and post (loss) score.

Paired sample t-tests were conducted to test changes in internalizing and externalizing problems between pre and post bereavement specified for parental bereavement, sibling bereavement, family bereavement and for the non-bereaved.

An independent sample t-test was conducted to test differences between bereaved and non-bereaved and within-group changes on internalizing and externalizing problems after computing the difference score: post (loss) score minus pretest score. Effect sizes and

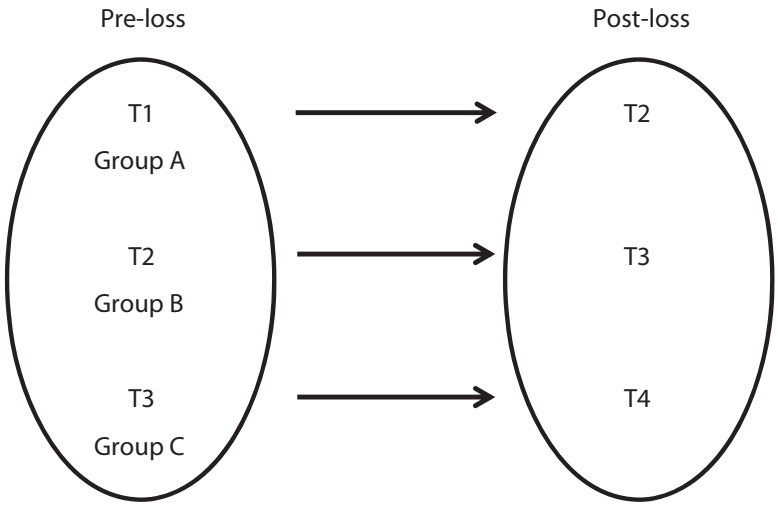

Figure 3.1 Assessments used of family-bereaved participants.

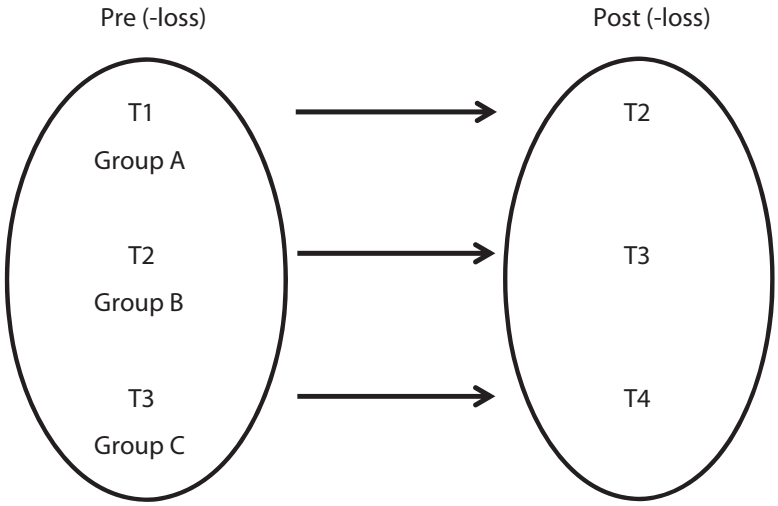

Figure 3.2 Assessments used of non-bereaved participants.

pooled Cohen's *d* were calculated. To establish clinically significant changes in internalizing and in externalizing problems before and after the loss of a family member, the cut-off score for clinical cases, according to the Dutch standard of the YSR and ASR, in internalizing and externalizing problems was used. The change in number of clinical cases pre (loss) and post (loss) was analysed in both the bereaved and non-bereaved sample. An increase in clinical cases was calculated by the number of clinical cases post loss that were not

clinical at pre loss, divided by the number of nonclinical cases at pre loss. A chi-square test was conducted. Changes in family functioning from pre to post loss were also tested with paired sample *t*-tests for the bereaved and non-bereaved.

Hierarchical multiple regression analysis was employed to determine if internalizing and externalizing problems at T4 could be predicted by family bereavement (yes/no) after controlling for gender and SES.

Hierarchical multiple regression analysis were conducted for the family-bereaved between T1 and T4, to determine if functioning (internalizing or externalizing problems, family functioning, number of family bereavements (life time)) prior to bereavement predict internalizing or externalizing problems after bereavement while controlling for gender and SES. This hierarchical multiple regression analysis was repeated once more for the non-bereaved group (without the variable amount of bereavement). Because of the small size of the family-bereaved group, we opted to conduct two separate hierarchical multiple regression analysis for the family-bereaved and the non-bereaved. In the family-bereaved group the number of family bereavements (life time) was added as the last step.

Results

Post (loss) mental health and type of bereavement

An independent *t*-test was conducted to test the difference in increase of internalizing problems between the family-bereaved and non-bereaved subsample. Internalizing problems in family-bereaved ($M = 0.08$, $SD = 0.27$) increased significantly in comparison to non-bereaved ($M = -0.04$, $SD = 0.22$) from pre to post (loss) score over the same period $t(1168) = -3.97$, $p < .001$, showing a medium effect (*Cohen's d pooled* 0.37; 95% CI = 0.13–0.62).

As a more rigorous measure, the clinical cut-off scores for the subscale internalizing problems were used to assess new clinical cases at post (loss) in order to establish clinically relevant changes. The increase in clinical cases was 22% versus 5.5%, which is four times higher in family-bereaved than in non-bereaved over the same period. The difference in increase in clinical cases was tested with a chi-square test and was found to be significant $\chi^2(1) = 16.46$, $p < .001$, a small effect (*Cramer's V* = 0.10, $p < .001$).

Within-group analysis showed that internalizing problems increased significantly with a small effect when family bereavement occurred within the past two years (see Table 3.2). In the non-bereaved, a significant decrease with a small effect of internalizing problems

Table 3.2 Comparison of family-bereaved at T2, T3, T4 (n = 70), including sibling bereaved (n = 15) and parental bereaved (n = 55), and non-bereaved (n = 1,213 internalizing and n = 1,222 externalizing problems) on pre and post internalizing and externalizing problems

	Internalizing problems						Externalizing problems						New clinical cases[a]	
	Pre		Post				Pre		Post					
	M[c]	*SD*	*M*	*SD*	*t*	*E.S.*[b]	*M*	*SD*	*M*	*SD*	*t*	*E.S.*[b]	Int	Ext
Parental bereavement	0.34	0.23	0.39	0.28	-1.72	0.19	0.31	0.20	0.35	0.24	-1.04	0.18	19%	9%
Sibling bereavement	0.37	0.28	0.52	0.41	-1.61	0.41	0.26	0.20	0.32	0.19	-0.92	0.31	22%	8%
Family bereavement	0.34	0.24	0.42	0.31	-2.35*	0.28	0.30	0.20	0.34	0.23	-1.35	0.19	22%	9%
Non-bereavement	0.33	0.24	0.29	0.25	6.2**	0.16	0.27	0.19	0.28	0.20	-1.04	0.05	5.5%	5.7%

* $p < .05$; ** $p < .01$.

[a] Percentage clinical cases at post test which were not yet clinical case at pretest.

[b] Effect size: *Cohen's d* corrected for correlation of pretest and posttest.

[c] *M* = mean.

was found for this period, $t(1213) = 6.2$, $p < .01$. The increase in internalizing problems after sibling bereavement was higher than after parental bereavement, but was not significant.

An independent *t*-test was conducted to test the changes in externalizing problems between both groups and this showed a significant increase in family-bereaved ($M = 0.04$, $SD = 0.25$) compared to non-bereaved ($M = -0.01$, $SD = 0.19$), $t(1180) = -1.99$, $p < .05$), with a small effect (*Cohen's d pooled* 0.12; 95% CI -0.36–0.12). This difference in increase in clinical cases with externalizing problems between family-bereaved and non-bereaved was 2.3%, which is very small, and not significant $X^2(1) = 2.17$, $p > .05$. Within both groups no differences were found in externalizing problems from pre to post (loss) (see Table 3.2).

Post (loss) mental health at age of 19

Two hierarchical multiple regression analyses were conducted separately for internalizing and externalizing problems at T4 to examine the effect of family bereavement during youth (0 to 19). In the first step, demographics (gender, SES) were added. In the second step, family-bereaved ($M = 3.03$, $SD = 0.81$) versus non-bereaved ($M = 3.17$, $SD = 0.70$) was added (see Table 3.3).

Table 3.3 Mental health problems, internalizing and externalizing problems, in family-bereaved as well as non-bereaved adolescents

	Post internalizing problems		Post externalizing problems	
Predictor	ΔR^2	β	ΔR^2	β
Step1	.04		.005	
Gender		-.19**		.03
SES T1		-.07**		-.07**
Step 2	.003		.004	
Family-bereaved yes/no		.05*		.06**
Total R^2	.04		.009	
n	1,580		1,581	

* $p < .05$; ** $p < .01$.

The results for internalizing problems showed that female gender ($B = -.19$, $SE = 0.01$, $p < .001$) and low SES ($B = -.07$, $SE = 0.01$, $p < .01$) significantly contributed to the variance, $F(2, 1661) = 34.88$, $p < .001$. Furthermore, family-bereaved versus non-bereaved explained an additional 0.3% of the variance, $F(3, 1660) = 25.02$, $p < .001$, indicating that

experiencing family bereavement is associated with more internalizing problems compared to non-bereaved adolescents. All variables explained 4.3% of the variance of internalizing problems by the age of 19.

Results concerning post (loss) externalizing problems showed approximately the same results as were found for internalizing problems, except that gender was not significant. SES contributed significantly to the variance, $F(2, 1661) = 4.32$, $p < .05$. Family-bereaved versus non-bereaved, explained an additional .4% of the variance $F(3,1626) = 5.11$, $p < .01$, ($B = .06$, $SE = 0.02$, $p < .01$) indicating that experiencing family bereavement is associated with more externalizing problems than in non-bereaved at T4.

Control variables

Gender and SES. As presented in Table 3.4, the hierarchical multiple regression analyses of internalizing problems for family-bereaved showed that the first step, gender and SES, explained 21% (versus 7% in non-bereaved); a significant part of the variance. SES at T1 was centred and was lower in non-bereaved ($M = -0.04$, $SD = 0.80$) than in bereaved ($M = -0.01$, $SD = 0.21$). Low SES predicted internalizing problems in family-bereaved but not in non-bereaved. Being female predicted internalizing problems in both groups. In both groups Gender and SES did not predict externalizing problems.

Predictors

Pre (loss) mental health problems. Adding pre (loss) levels of internalizing problems in step 2 explained an additional 18% of the variance in family-bereaved but much more in non-bereaved adolescents namely 30%. The first and second steps together explained 38% of the variance of internalizing problems in family-bereaved: adjusted R^2 is .35 and $F(3, 52) = 10.68$, $p < .001$, ($B = .67$, $SE = 0.15$, $p < .001$). In the non-bereaved, both steps explained in total 36% of the variance, with an adjusted R^2 of .36 and $F(3, 1000) = 144.25$, $p < .001$, ($B = .55$, $SE = 0.03$, $p < .001$).

Pre (loss) externalizing problems in family-bereaved adolescents did not explain variance in externalizing problems after bereavement $F(3, 52) = 1.26$, $p < .30$ ($B = .24$, $SE = 0.16$, $p > .05$). In the non-bereaved, externalizing problems at pre-test explained an extra 25% of the variance, $F(3, 1005) = 113.06$, $p < .001$ ($B = .50$, $SE = 0.03$, $p < .001$).

In sum: Pre (loss) scores on internalizing problems predicted post (loss) scores on internalizing problems in family-bereaved and in the non-bereaved adolescents. Pre (loss)

scores on externalizing problems did not predict externalizing problems after bereavement. In the non-bereaved, however, pre (loss) scores on externalizing problems predicted post (loss) scores on externalizing problems.

Pre (loss) family functioning. An independent paired sample *t*-test showed that family functioning within the family-bereaved did not significantly change after bereavement $t(41) = .34$, $p > .05$. In the non-bereaved, family functioning became significantly better over the same period $t(1090) = 2.13$, $p < .05$. This was a small effect (*Cohen's d pooled* 0.13; 95% CI 0.0102–0.25). The pre (loss) score on family functioning was significantly higher in the family-bereaved ($M = 1.85$, $SD = 0.37$) compared to the non-bereaved ($M = 1.68$, $SD = 0.39$), $t(1327) = -3{,}22$, $p < .001$).

An independent *t*-test was conducted to test the difference in changes in family functioning between the family-bereaved and non-bereaved subsample. The difference score on family functioning, post (loss) score minus pre (loss) score, was used. Change in family functioning in family-bereaved ($M = -.02$, $SD = 0.42$) was not different compared to non-bereaved ($M = -.05$, $SD = 0.38$) from pre- to post (loss) score over the same period $t(1131) = -0.04$, $p > .05$.

To examine whether family functioning before bereavement predicted mental health problems after bereavement, family functioning was added in the third step of the regression analysis. The pre (loss) score on family functioning did not predict internalizing problems after controlling for gender, SES and pre (loss) score on internalizing problems in family-bereaved $F(4, 51) = 8.60$, $p < .001$, ($B = .16$, $SE = 0.10$, $p > .05$), this was also true for non-bereaved adolescents, $F(4, 1003) = 144.25$, $p < .001$, ($B = .03$, $SE = 0.02$, $p > .05$).

Moreover, pre (loss) score on family functioning was not associated with post (loss) score on externalizing problems in the family-bereaved. In contrast, in the non-bereaved group the pre scores on family functioning predicted post (loss) scores on externalizing problems, indicating that dysfunctional family climate predicted externalizing problems. The additional variance explained was only 1%, $F(4, 1003) = 10.68$, $p < .001$, ($B = .08$, $SE = 0.01$, $p < .01$) (see Table 3.4).

Multiple bereavement. Adding multiple bereavement in step 4 of the hierarchical multiple regression analyses (Table 3.4) showed that the experience of more than one family bereavement ($n = 24$) did not predict internalizing problems after bereavement $F(5, 55) = 7.64$, $p < .001$, ($B = -.18$, $SE = 0.05$, $p > .05$). However, it did predict fewer externalizing problems, while controlling for pre (loss) score externalizing problems: $F(5, 50) = 1.90$, $p < .05$ ($B = -.28$, $SE = 0.04$, $p < .05$).

Table 3.4 Predictors of change in internalizing and externalizing problems in non-bereaved and family-bereaved

	Post internalizing problems		Post externalizing problems	
Predictor	ΔR^2	β	ΔR^2	β
Family-bereaved				
Step1	.21		.01	
Gender		-.31*		.10
SES T1		-.35**		.03
Step 2	.18		.06	
Pre loss internalizing or externalizing problems		.47**		.24
Step 3	.02		.02	
Pre loss family functioning		.16		.14
Step 4	.03		.08	
Multiple bereavement		-.18		-.28*
Total R^2	.43		.16	
n	70		70	
Non-bereaved				
Step 1	.07		.01	
Gender		-.25**		.05
SES T1		-.05		-.06
Step 2	.30		.25	
Pre loss internalizing or externalizing problems		.56**		.50**
Step 3	.01		.01	
Pre loss family functioning		.03		.08**
Total R^2	.37		.27	
n	1,007		1,007	

* $p < .05$; ** $p < .01$.

Discussion

The main aims of the present study were to examine the influence of family bereavement on the mental health of adolescents and to determine which pre-loss factors deteriorate mental health care problems. The main result shows that family bereavement has a clinically significant, medium sized effect on the increase of internalizing problems within 2 years in comparison to non-bereaved adolescents while accounting for pre (loss) internalizing problems. By the age of 19, family-bereaved adolescents experienced significantly more internalizing and externalizing problems than non-bereaved adolescents. The internalizing problems after family bereavement are predicted by the amount of internalizing problems before family bereavement occurred. This was not found for externalizing

problems. However, the experience of more than one family bereavement did predict fewer externalizing problems.

Internalizing problems

Family-bereaved adolescents developed more internalizing problems compared to their non-bereaved peers. Furthermore, the increase in the number of new clinical cases with internalizing problems in family-bereaved was four times as high, namely 22% in comparison to 5.5% in the non-bereaved adolescents. These findings are consistent with previous studies which found more internalizing problems in family-bereaved compared to non-bereaved (Cerel et al., 2006; Dowdney, 2000; Dowdney, 2005; Luecken & Roubinov, 2012; Worden, 1999). Moreover, by the age of 19 the difference between family-bereaved compared to non-bereaved in internalizing problems was robust. Earlier studies also found that internalizing problems, especially depression, increased within the second year after bereavement (Brent, Melhem, Donohoe, & Walker, 2009). Even after more than six years, 13% of parentally bereaved adolescents who participated in the control group of an intervention study reported internalizing disorders (Sandler et al., 2010). Although the studies cited above showed an increase in internalizing problems after bereavement, it was still uncertain how much could be accounted for by pre loss internalizing problems. In our study we were able to show a substantial increase in the amount of internalizing problems in adolescents who did not experience internalizing problems before bereavement. To our knowledge, so far one other study on bereavement has assessed pre-bereavement mental health including generalized anxiety, separation anxiety and depression. The results were mixed, parentally bereaved youth showed an increase in at least one anxiety symptom while controlling for pre-parental loss in comparison to non-bereaved youth but symptoms of depression did not (Kaplow, Saunders, Angold, & Costello, 2010). Research on effects of parental death on adult psychopathology is inconclusive, suggesting that it is unknown if family-bereaved children continue to have more internalizing problems during adulthood (Luecken, 2008).

Surprisingly the increase in internalizing problems after the loss of a sibling seemed substantially higher than after the loss of a parent. This finding was not significant however, probably due to low power of our study in view of its sample size. Despite the non-significant finding, these results are in line with the abovementioned study that also reported an increase in at least one depressive symptom from pre- to post- bereavement in adolescents who experienced losing a sibling or other bereavement, but not in youth losing

a parent (Kaplow et al., 2010). It is possible that specific factors are responsible for a higher impact of sibling loss on internalizing problems. For instance, siblings report feeling guilty because they did not die, so called survivor guilt (Lifton, 1967). Also parent's psychological distress after bereavement plays a role in the development of mental health problems (Kwok et al., 2005) and may be more problematic after losing a child in comparison to losing a spouse (Sanders, 1979).

In the present study we found that low SES predicted internalizing problems in the family-bereaved. When SES was already low before family bereavement, adverse social economic consequences might be more difficult to handle and put an adolescent at an increased risk for internalizing problems (Dowdney, 2000; Kaplow et al., 2010). Therefore special attention should be given to the family-bereaved adolescents growing up in families with low SES. Being female was associated with significant internalizing, but not externalizing, problems in both groups.

We found that an increase in internalizing problems among the family-bereaved as well as in the non-bereaved group is predicted by the amount of pre (loss) internalizing problems, after controlling for gender and SES. A history of internalizing problems before family bereavement puts an adolescent at a higher risk of internalizing problems in the future. This finding is comparable to the finding in a previous study, which showed that a retrospective account of a history of depression before parental bereavement increased the risk for depression in the 9 months following the death of a parent, which in turn increased depression risk between 9 and 21 months (Brent et al., 2009). Future research is needed on the selectivity and specificity of these measures by retrospective inquiry for internalizing problems before family bereavement, so professionals within schools, hospitals and mental health care institutions can identify adolescents at risk for internalizing problems.

Externalizing problems

We hypothesized that externalizing problems would increase after family bereavement compared to non-bereaved youth, but this was not supported by the results. Family-bereaved and non-bereaved did not experience a significant change in the number or extent of externalizing problems from pre- to post (loss) score. The change in clinical cases was 2.3% more cases in family-bereaved compared to non-bereaved and this was not significant. These findings are not in line with the estimated 10 to 21% of bereaved children who develop clinical levels of externalizing disorders (Lifton, 1967; Worden & Silverman, 1996). Furthermore, pre (loss) externalizing problems did not predict externalizing problems

after family bereavement. This is in contrast to the finding in non-bereaved adolescents, that pre (loss) externalizing problems predicted post (loss) externalizing problems, which explained 25% of the change in variance. In the non-bereaved, externalizing problems seem stable whereas this is not the case in the family-bereaved. However, we found that by the age of 19, family bereavement between 0 and 19 years significantly predicted more externalizing problems. Changes in externalizing problems after bereavement may be bidirectional. For instance, one study found an increase of externalizing problems because of emotion regulation problems (Luecken & Roubinov, 2012). Other studies found that some adolescents report that externalizing problems diminished after family bereavement because they felt more mature (Davies, 1991) and experienced a greater appreciation of life (Brewer & Sparkes, 2011). For example, incidence of substance abuse and alcohol abuse were found to be lower in adults who were parentally bereaved during childhood (Stikkelbroek, Prinzie, de Graaf, Ten Have, & Cuijpers, 2012).

Multiple bereavements

Almost 30% of family-bereaved adolescents experienced more than one family bereavement. Surprisingly, this factor predicted less externalizing problems controlling for gender, SES, externalizing problems at pre loss and family functioning. This finding is not in line with a previous study showing that after experiencing more than one family bereavement the adolescents were more vulnerable to symptoms of grief, such as explosive emotions, acting out, temper tantrums and delinquent activity (Oltjenbruns, 2001). A possible explanation for our finding might be, that increasing externalizing behaviour is rather normative in the adolescent years, and is decreased or buffered by the grief and loss that has occurred in these families. Multiple bereavements did also not predict an increase in internalizing problems. As internalizing problems already increased after the first bereavement a further increase could be difficult to detect because of a ceiling effect.

Family functioning

Family functioning did not change significantly after family bereavement. The difference in change in family functioning in family-bereaved compared to non-bereaved was not significant. Furthermore, poor family functioning only predicted externalizing problems in the non-bereaved, but seemed less relevant, compared to previous levels of internalizing/externalizing problems, because it only explained 1% of variance of change. In the family-

bereaved, family functioning did not predict internalizing or externalizing problems after bereavement. Taking into account that family-bereaved experienced significantly poorer pre (loss) family functioning than the non-bereaved, another explanation needs to be considered. The pre (loss) score on family functioning might already have been affected in some families before bereavement as a result of the impact of the illness that led to the death of the family member. In support of this explanation an extensive systematic review found that children of cancer patients, who experienced poor family functioning, were at risk for maladjustment (Krattenmacher et al., 2012). Also, the small sample size in our subgroup may have prevented the finding of predictive factors in the family-bereaved group. The change in family functioning in the family-bereaved group was established in intervention research as a relevant factor in overcoming family bereavement without mental health problems (Dowdney, 2000; Luecken & Roubinov, 2012).

Strengths and limitations

Certain limitations of this study need to be addressed. First, some findings were not significant but have to be interpreted with caution because of a potential lack of power due to a small size of the family-bereaved subgroup. Although 131 individuals suffered from family bereavement during their life of whom 70 during adolescence, this is still a small sample if 20% to 25% of them are expected to develop mental health problems after family bereavement on the basis of previous research (Cerel et al., 2006; Dowdney, 2000; Dowdney, 2005; Luecken & Roubinov, 2012; Worden, 1999). However, 7% (n = 9) of the family-bereaved did not participate in the assessment pre or post bereavement, which could have been associated with the burden of family bereavement. Examples are reluctance to answer potentially painful questions during the assessment or having to move house. This suggests that mental health problems after family bereavement might be even more prevalent than found in this study. Another important factor that may contribute to increasing levels of mental health problems following family bereavement is the mental health of the parent pre- to post bereavement. This could not be taken into account in the present study. The psychological functioning of a parent after the bereavement may have been impaired, resulting in less ability to support the emotional wellbeing of the child. Parental functioning predicts the adjustment of the child (Kalter et al., 2002). Furthermore, parental distress after bereavement can reduce the capacity for positive parenting (Kwok et al., 2005).

Other characteristics such as the gender of the deceased parent, cause of death and self-esteem also seem important to consider in future studies with larger samples sizes.

The cause of death, whether accidental death, illness, suicide or violent death, has been found to be associated with outcome of parental bereavement in terms of mental health (Brent et al., 2009).

Notwithstanding the limitations, the present study has several strengths. Strengths include the relatively large, representative community sample and longitudinal data. The data on mental health and family functioning were collected before the bereavement occurred, which made prospective analyses possible. It was also possible in our study to adjust for demographic characteristics that might have affected mental health problems. In addition, research on the bereavement process in adolescents thus far was limited to the duration of 2 years after experiencing the death of a parent (Balk & Corr, 2001), whereas we were able to examine mental health problems over a period of 8 years.

Conclusions

Family bereavement puts adolescents at risk for internalizing problems within 2 years and mental health problems by the age of 19, in comparison to non-bereaved peers. The present study identified a history of internalizing symptoms and low social economic status of the family as pre-bereavement predictors of mental health problems after family bereavement. These predictors could be used in further research to identify possibilities for selective prevention after occurrence of a family bereavement in adolescents. Awareness among professionals regarding the risks for aggravation of mental health problems after family loss is needed.

Acknowledgments

This research is part of the TRacking Adolescents' Individual Lives Survey (TRAILS). Participating centres of TRAILS include various departments of the University of Groningen, the Erasmus Medical Center of Rotterdam, the Free University of Amsterdam, the University of Nijmegen, and the Trimbos-institute. TRAILS is financially supported by grants from the Dutch Organisation for Scientific Research (GB-MW 940-39-011, GB-MAG 480-01-006, ZonMw 100-001-011), the Ministry of Justice and by the participating centers.

Acknowledgements of authors' contributions

Yvonne Stikkelbroek designed the study, conducted the statistical analyses, drafted the initial manuscript, revised the manuscript and approved the final manuscript as submitted. *Denise*

Bodden designed the study, revised the manuscript and approved the final manuscript as submitted. *Ellen Reitz* designed the study, conducted the statistical analyses, revised the manuscript and approved the final manuscript as submitted. *Wilma Vollebergh* designed the study, coordinated the data collection, revised the manuscript and approved the final manuscript as submitted. *Anneloes van Baar* designed the study, revised the manuscript and approved the final manuscript as submitted.

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Part B

Focus on mechanisms: emotion regulation

Lisa, aged 13 years, started high school last year. She looked forward to it and had everything going for her. She found it hard to make new friends in her new school. She felt teased at times. Last year she had problems with an old friend named Ellis. Since they went to high school Ellis acted annoyed with her. Lisa did not know what to do. She worried about the friendship with Ellis. She started ruminating about the arguments with Ellis. Kept repeatedly thinking of solutions. Especially when she had nothing to do. It kept her awake at night. Should she tell her parents of Ellis? – but then her mother would be worried. She felt tired and dreary and avoided to speak to Ellis. After a while she heard that Ellis attempted suicide and she felt very guilty. She did not know what to do.

Chapter 4

Adolescent depression and negative life events, the mediating role of cognitive emotion regulation

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Submitted for publication.

Abstract

Background: Depression during adolescence is a serious mental health problem. Difficulties in regulating evoked emotions after stressful life events are considered to lead to depression. This study examined if depressive symptoms were mediated by various cognitive emotion regulation strategies after stressful life events, more specifically, the loss of a loved one, health threats or relational challenges.

Methods: We used a sample of 398 adolescents (M_{age} = 16.94, SD = 2.90), including 52 depressed outpatients, who all reported stressful life event(s). Path analyses in Mplus were used to test mediation, for the whole sample as well as separately for participants scoring high versus low on depression, using multi-group analyses.

Results: Health threats and relational challenging stressful life events were associated with depressive symptoms, while loss was not. More frequent use of maladaptive strategies was related to more depressive symptoms. More frequent use of adaptive strategies was related to less depressive symptoms. Specific life events were associated with specific emotion regulation strategies. The relationship between challenging, stressful life events and depressive symptoms in the whole group was mediated by maladaptive strategies (self-blame, catastrophizing and rumination). No mediation effect was found for adaptive strategies.

Conclusion: The association between relational challenging, stressful life events and depressive symptoms was mediated by maladaptive, cognitive emotion regulation strategies.

Introduction

Depression during adolescence is a serious problem because of its high prevalence (Cohen et al., 1993; Fergusson, Horwood, & Lynskey, 1993; Hankin et al., 1998), considerable burden of disease (Hoeymans, Gommer, & Poos, 2006), suicide risk (Ryan, 2005), other comorbid psychiatric disorders (Herbert et al., 1996) and the high risk of recurrence (Curry et al., 2011; Ryan, 2005). Although knowledge about the etiology of depression has increased in the last decade, it is still difficult to explain and predict who becomes depressed, because of the many factors involved (Hankin, 2012). A well-established predictor of depressive symptoms is the experience of a stressful life event (Kendler, Karkowski, & Prescott, 1999), like a romantic break up. An intriguing question is what mechanisms are involved that may lead different types of stressful life events to contribute to the development of depressive symptoms and ultimately depression. Difficulty in emotion regulation is considered to contribute to depression (Abravanel & Sinha, 2014; Campbell-Sills & Barlow, 2007; Mennin, Holaway, Fresco, Moore, & Heimberg, 2007). Emotion regulation is seen as a potential mediator of depressive symptoms after stressful life events have occurred (Moriya & Takahashi, 2013). From a clinical viewpoint it is necessary to establish which factors actually mediate the occurrence of depressive symptoms after specific types of stressful life events, as such factors could then be addressed effectively in prevention and treatment efforts.

Adolescence is a challenging developmental phase with many physical and psychological changes, which may generate stress. Stressors are recognized as very important in the etiology and maintenance of internalizing problems (Grant et al., 2006). Three different types of stressful life events have been identified, namely loss, health threats and relational challenges (Garnefski, Boon, & Kraaij, 2003; Lazarus, 2006). Stressful life events are associated with a larger increase in depressive symptoms than other types of stress, such as academic stress (Charbonneau, Mezulis, & Hyde, 2009; Flynn & Rudolph, 2010; Flynn, Kecmanovic, & Alloy, 2010; Hammen, 2006; Hankin, Mermelstein, & Roesch, 2007; Rudolph, 2008). In children, negative life events were found to be a significant predictor of depression, putting children at risk for future depressive episodes (Nolen-Hoeksema, Girgus, & Seligman, 1992; Stikkelbroek, Bodden, Reitz, Vollebergh, & van Baar, 2015). Stressful life events during childhood have repeatedly been found to be associated with an increased risk of developing mental disorders during adulthood (Collishaw et al., 2007; Comijs et al., 2007; Cuijpers et al., 2011). Furthermore, stressors can be followed by depressive symptoms, and depressive symptoms in themselves can generate stressful life events, resulting in a reciprocal relationship (Abela, Nueslovici, & Chan, 2004; Grant

et al., 2006; Waaktaar, Borge, Fundingsrud, Christie, & Torgersen, 2004). Garnefski and colleagues (Garnefski et al., 2003) found no difference in type of stressful life event and the association with depressive symptoms in adolescents aged 14 to 18. For clinically depressed adolescents, however, it is unclear as yet whether this is also true.

The dual process model of cognitive vulnerability to depression hypothesizes that associative thought processing (automatic processing) induces depressive symptoms when no correction occurs by explicitly reflective processing (Beevers, 2005). This is especially the case when the associative processing is negatively biased with thoughts about oneself. Furthermore, life stress appears to deplete cognitive resources, which are necessary for reflective processes to correct associative processing (Beevers, 2005). This dual process of self-referent association and cognitive reflection is considered to be of importance for the regulation of emotions.

Difficulty in regulating evoked emotions is often thought to lead to depression (Campbell-Sills & Barlow, 2007; Gross & Muñoz, 1995; Mennin et al., 2007). In adults, emotion regulation plays a central role in the etiology and maintenance of clinical levels of psychopathology (Berenbaum, Raghavan, Le, Vernon, & Gomez, 2003; Greenberg, 2002; Mennin & Farach, 2007). Emotion regulation is a complex process with (un-)conscious, cognitive, and self-regulatory components. Emotion regulation strategies can be adaptive or maladaptive. Maladaptive emotion regulation has repeatedly been linked to various mental disorders, including the onset of depressive symptoms (Ehring, Fischer, Schnülle, Bösterling, & Tuschen-Caffier, 2008; Garnefski & Kraaij, 2006; Joormann & D'Avanzato, 2010; Martin & Dahlen, 2005; Schroevers, Kraaij, & Garnefski, 2007). Maladaptive emotion regulation is also a risk factor for the recurrence of depression in adults (Rude & McCarthy, 2003). Furthermore, findings suggest that the strength of the relationship between maladaptive emotion regulation strategies and psychopathology may be a function of clinical severity (Aldao, Nolen-Hoeksema, & Schweizer, 2010). Some specific maladaptive cognitive emotion regulation strategies such as self-blame, rumination and catastrophizing, are associated with higher levels of depressive symptoms in adolescence, while adaptive strategies such as positive reappraisal, positive refocusing and putting things into a broader perspective, are associated with less depressive symptoms (Garnefski et al., 2003; Kraaij et al., 2003).

Only a few studies have established the relationship between stressful life events and emotion (dys)regulation in adults (Abravanel & Sinha, 2014) and adolescents (Moriya & Takahashi, 2013). The type of life event influences the use of specific cognitive emotion regulation strategies, with health threat being associated with self-blame and relational challenge with other-blame in adolescence (Garnefski et al., 2003).

As pointed out, stressful life events have an impact on emotion regulation, which in turn influences the degree of depressive symptoms. Therefore, emotion regulation can be considered a mediator in the relationship between stressful life events and depressive symptoms (Goodman & Southam-Gerow, 2010; Kelly, Schwartz, Gorman, & Nakamoto, 2008). Studies on emotion regulation as a mediator of depressive symptoms in adolescents are scarce. One study reported that emotion regulation strategies were found to mediate the relationship between interpersonal stress and depressive symptoms in undergraduate students (Moriya & Takahashi, 2013). It is unclear if this mediation is also present when adolescents have high levels of depressive symptoms, or whether the use of specific emotion regulation strategies mediates the relation between certain stressful life events and depressive symptoms.

The aim of this study is to examine if the relation between stressful life events and depressive symptoms is mediated by cognitive emotion regulation strategies and whether these potentially mediating effects differ per type of stressful life event (Figure 4.1). We used a multi-sample approach, including a community sample and clinically referred depressed outpatients. Mediation was studied for the whole sample, as well as for the depressed and non-depressed adolescents separately. We expected to find that [1] the relationship between stressful life events (loss, health threat or relational challenge) and depressive symptoms is mediated by cognitive emotion regulation strategies; [2] the model for mediation would be specific for type of stressful life event: self-blame would be important after health threat and other-blame after relational stress, and no mediation would be present after loss; [3] the model would also be specific in that the pathway from stressful life events via cognitive emotion regulation to depressive symptoms would be more pronounced in adolescents with high levels of depressive symptoms compared to adolescents with low levels of depressive symptoms.

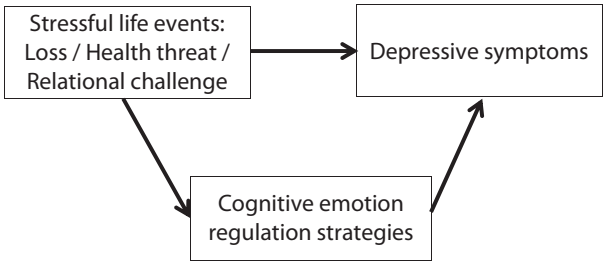

Figure 4.1 Mediation model being tested; cognitive emotion regulation strategies as mediator of depressive symptoms after a stressful life event.

Methods

Participants

In a total of 653 adolescents (of whom 84 were outpatients), those who rated no life event as stressful (n = 35) were excluded. Adolescents in the community sample (N = 569) receiving psychological treatment or social counseling (n = 40) were also excluded because of a potential effect on emotion regulation strategies. If answers on gender (n = 3), age (n = 4), life events or scores for whole scales were missing, cases were also excluded from the analyses (n = 173), which amounted to 39.2% from the community and 38.1% from the outpatient sample. Attrition analyses showed that the excluded adolescents (n = 255, M_{age} = 15.85, 31.8% boys) did not significantly differ from the included adolescents on the relevant scales, namely age, gender, depressive symptoms, life events and cognitive emotion regulation strategies.

The result was a final sample of 398 adolescents aged 11 to 22 years (68.8% girls, 92.5% Dutch) including 52 (13%) clinical depressed outpatients. This sample was divided into two groups with low or high scores on depression, based on the official Dutch cut-off point (< 12 vs. ≥ 12) for clinical depression on the Children's Depression Inventory 2 (CDI-2). These groups will be referred to as non-depressed and depressed. The non-depressed group consisted of 289 adolescents (66.8% girls, M_{age} = 16.94, 97.2% enrolled in education), whereas the depressed group consisted of 109 adolescents (74.3% girls, M_{age} = 17.09, 49.5% enrolled in education).

Data collection

Two samples were used in this study. The first sample consisted of adolescents from the general population who were recruited by Master's degree students in schools and sports associations. The adolescents were asked to participate in the research. After written informed consent forms were obtained from the participants and their parents, a self-report questionnaire was completed.

The second sample participated in an effectiveness trial comparing Cognitive Behavioral Therapy to usual care (for more information, see Stikkelbroek, Bodden, Dekovic, & van Baar, 2013). Clinically referred adolescents suffering from depression were recruited from 14 Dutch mental health care institutions between 2011 and 2014. A psychologist informed adolescents and parents about the study and when both gave written informed

consent, self-report questionnaires were completed pre-treatment using online or paper-and-pencil questionnaires.

Measures

Depressive symptoms. The degree of *depressive symptoms* was measured with the Child Depression Inventory-2 (Bodden, Stikkelbroek, & Braet, 2010; Kovacs, 2011), a revision of the CDI (Braet & Timbremont, 2002; Kovacs, 1992). The CDI-2 is a self-report questionnaire for children (7 to 17 years) that reflects affective, behavioral, and cognitive symptoms of depression. Each of the 28 items offers 3 assertions: non-depressed (score 0, e.g., "I am sad once in a while"); mildly depressed (score 1, e.g., "I am sad many times"); and clearly depressed (score 2, e.g., "I am sad all the time"). The participants had to choose the assertion that applied most during the past two weeks. Total scores could range from 0 to 56, and a score of 12 or above (based on the CDI) is considered a clinically relevant score (Braet & Timbremont, 2002). In this sample, 27.39% (n = 109) had a clinically relevant score. Reliability was very good for both the official target population of adolescents aged up to 17 years (n = 213, α = .93), and for adolescents older than 17 (n = 185, α = .91).

Cognitive emotion regulation strategies were investigated with the Cognitive Emotion Regulation Questionnaire (Garnefski, Kraaij, & Spinhoven, 2002). The CERQ consists of 36 items, reflecting 9 conceptually distinct adaptive or maladaptive strategies. Items refer to what someone thinks in response to a life event. The four maladaptive subscales are: Self-blame (thoughts of putting the blame of what you have experienced on yourself), Other-blame (thoughts of putting the blame of what you have experienced on others), Catastrophizing (thoughts of explicitly emphasizing the terror of an experience) and Rumination (thinking about the feelings and thoughts associated with the negative event).

The five adaptive subscales are: Putting into perspective (thoughts of playing down the seriousness of the event or emphasizing the relativity when comparing it to other events); Positive refocusing (thinking about joyful and pleasant issues instead of thinking about the actual event); Positive reappraisal (thoughts of attaching a positive meaning to the event in terms of personal growth); Acceptance (thoughts of accepting what you have experienced and resigning to yourself what has happened); and Refocus on planning (thinking about what steps to take and how to handle the negative event).

Each subscale contains 4 items measured on a 5-point Likert scale ranging from 1 (almost never) to 5 (almost always), with a higher score indicating more use of the specific adaptive strategy. Because extreme scores on Acceptance could be maladaptive the score

was transformed into a categorical variable high (score above 14), low (score less than 10) and medium (Garnefski & Kraaij, 2006).

Research on the CERQ subscales indicated that internal consistencies were good, ranging from .67 to .81, and good validity (Garnefski, Kraaij, & Spinhoven, 2001). In the present study, alphas ranged from good .70 to very good .82.

Stressful life events. For this study, we constructed the Life Event Scale (Bodden & Stikkelbroek, 2010), a 23 item self-report questionnaire about three types of life events, based on the distinction of psychological stress made by Lazarus (Lazarus, 2006); Loss (1 item: death of a loved one including pets), Health threat (8 items: serious (mental) illness, suicide attempt, sexual abuse, psychological abuse, alcohol or drug abuse, crime and accidents concerning the self, parent, sibling or friends), and Relational (or situational) challenges (14 items: parental divorce, step-parents, moving, changing schools, romantic break-up, police contact (parent or self), redundancy (parent or self), pregnancy, school failure, being bullied, conflict with parents or friends, being expelled from school). Participants were asked if they had experienced the life event, yes or no. If yes, respondents were asked to rate how stressful the event was from not stressful (0) to very stressful (3). Only adolescents with at least a score of two were included. The amount of Health threats and Relational challenges were both summed into a single score, both items were highly positively skewed. Loss was dichotomous.

Data analytic strategy

Missing data were imputed using Relative Mean Substitution (Raaijmakers, 1999). Descriptive statistics were calculated, and Pearson correlations were computed for all variables included in the models. Multivariate Analysis of Variance (MANOVA) was used to test for differences in depressive symptoms and cognitive emotion regulation strategies based on gender or on condition. To examine the correlations between the three stressful life event variables, the nine proposed mediators and the outcome measure of depression, we applied path analyses using the software package Mplus 7 (Muthén & Muthén, 2010). Models were tested first for the whole sample and thereafter separately for participants scoring high versus low on depression using multi-group analyses. Within the models, the correlation between the three stressful life event variables was taken into account, as well as the correlation between the proposed mediators. The comparative fit index (CFI, preferably .95 or higher), the root mean square error of approximation (RMSEA, preferably .08 or lower), and the standardized root mean square residual (SRMR, preferably .09 or lower) served as model fit indices (Iacobucci, 2010).

To examine the hypothesized mediation of cognitive emotion regulation strategies in the association between the type of stressful life events and depression, we used the Model Indirect approach using Mplus 7 with a bootstrap procedure. To assess the possible moderating effect of the level of depression, multi-group analyses were conducted within Mplus 7. This was done by testing whether the model fit ($\Delta\chi^2$) was significantly better for the model in which the paths of interest were allowed to differ between non-depressed and depressed, compared to the model in which the paths of interest were constrained to be equal (Lammers, Kuntsche, Engels, Wiers, & Kleinjan, 2013). Next, differences between both groups for the relations between model variables were tested per direct path, also using the chi-square difference test. This was done by constraining each path of interest separately while all other paths were unconstrained, and comparing this model to the model in which the path of interest, as well as all other paths, was unconstrained. To test the differences in the indirect effects between both groups, the MODEL TEST command was used. This command permitted testing of linear restrictions on the parameters using the Wald chi-square test (Muthén & Muthén, 2010).

Results

The percentage of adolescents with high scores (≥ 12) on depressive symptoms was 27.39%. The percentages of life events reported by the total sample (N = 398) adolescents were 24.87% for loss; 33.17% for health threats, and 60.55% for relational challenges.

A MANOVA on the total sample showed gender differences in cognitive emotion regulation strategies ($F(9,388) = 2.754$, $p = .004$), specifically girls scored lower on Other blame than boys ($F(1,396) = 6.642$, $p = .010$) and girls scored higher on Rumination than boys ($F(1,396) = 8.548$, $p = .004$). This analysis was repeated for both subgroups and also showed gender differences in the non-depressed group ($F(9,279) = 2.441$, $p = .011$), specifically girls scored lower on Other blame than boys ($F(1,287) = 10.872$, $p = .001$). An ANOVA showed no gender differences in depressive symptoms in the total group, nor in the subgroups.

A MANOVA using both the total sample and the subgroups showed no differences in cognitive emotion regulation strategies between adolescents who did or did not experience loss. An ANOVA using both the total sample and the subgroups showed no differences in depressive symptoms between adolescents who did or did not experience loss.

Another MANOVA showed group differences in the three types of stressful life events, which occurred more often in the depressed subgroup ($F(3,394) = 24.410$, $p <$

.001), specifically for health threats ($F(1,396) = 12.419$, $p < .001$) and relational challenges ($F(1,396) = 72.475$, $p < .001$).

Associations among variables

Correlations, means and standard deviations for the total sample and all model variables are reported in Table 4.1, and separately for depressed and non-depressed adolescents in Table 4.2.

Within the *total sample*, age did not correlate significantly with depressive symptoms. Health threatening and relational challenging stressful life events showed weak to moderate correlations with depressive symptoms. Except for acceptance, all cognitive emotion regulation strategies, correlated weakly to strongly with the number of depressive symptoms. Weak to moderate correlations were found for relational challenging stressful life events and seven out of nine cognitive emotion regulation strategies; self-blame, other-blame, catastrophizing, rumination, putting into perspective, positive refocusing and acceptance.

Within the *non-depressed group*, age did not correlate significantly with depressive symptoms. Relational challenging stressful life events were weakly correlated with more depressive symptoms. Weak correlations between relational challenging stressful life events and several strategies were found, namely; self-blame, other-blame, catastrophizing, rumination, positive reappraisal, acceptance and refocus on planning. Of these strategies, only self-blame, catastrophizing, positive reappraisal and refocus on planning in turn correlated weakly with depressive symptoms. Stressful health threatening life events correlated weakly with other-blame, which did not significantly correlate with depressive symptoms.

In the *depressed group*, age did not correlate significantly with depressive symptoms. Relational challenging and also health threatening stressful life events showed a weak to moderate correlation with the degree of depressive symptoms, as well as with self-blame. All strategies, except for other-blame and acceptance, were weak to moderately correlated with depression.

Path analyses

The model fit indices for the mediation model within the whole sample were satisfactory (CFI = .95, RMSEA = .09, SRMR = .05). Multi-group analysis was used to test differences in depression level. The Chi-squared difference test indicated that the model differed for

Table 4.1 Correlations total group (*N* = 398)

			1	2	3	4	5	6	7	8	9	10	11	12	13	*M*	*SD*
1	Depressive symptoms	*r*		**.505**	**.120**	**.430**	**.319**	**-.275**	**-.304**	**-.413**	.007	**-.278**	.049	**.254**	**.454**	9.608	8.854
		p		**.000**	**.016**	**.000**	**.000**	**.000**	**.000**	**.000**	.888	**.000**	.326	**.000**	**.000**		
2	Self-blame	*r*			**.222**	**.433**	**.497**	**.119**	-.086	-.004	**.296**	**.166**	.042	**.176**	**.360**	9.475	3.350
		p			**.000**	**.000**	**.000**	**.017**	.085	.929	**.000**	**.001**	.404	**.000**	**.000**		
3	Other-blame	*r*				**.442**	**.168**	.068	**.106**	.048	**.171**	**.124**	**-.128**	.063	**.128**	6.771	2.806
		p				**.000**	**.001**	.174	**.034**	.342	**.001**	**.013**	**.010**	.207	**.011**		
4	Catastrophizing	*r*					**.432**	**-.177**	-.097	**-.174**	.066	-.043	-.019	**.106**	**.276**	6.739	2.726
		p					**.000**	**.000**	.053	**.000**	.190	.390	.709	**.035**	**.000**		
5	Rumination	*r*						.056	-.028	**.161**	**.241**	**.323**	**.145**	**.112**	**-.141**	10.477	3.782
		p						.262	.574	**.001**	**.000**	**.000**	**.004**	**.026**	**.005**		
6	Putting into perspective	*r*							**.494**	**.641**	**.452**	**.480**	.003	-.060	**-.141**	12.269	3.927
		p							**.000**	**.000**	**.000**	**.000**	.949	.229	**.005**		
7	Positive refocusing	*r*								**.545**	**.330**	**.425**	-.032	-.065	**-.109**	11.912	3.870
		p								**.000**	**.000**	**.000**	.522	.198	**.030**		
8	Positive reappraisal	*r*									**.400**	**.715**	-.023	-.043	-.076	12.779	3.890
		p									**.000**	**.000**	.648	.395	.132		
9	Acceptance	*r*										**.369**	.021	.048	**.131**	1.015	.737
		p										**.000**	.674	.345	**.009**		
10	Refocus on planning	*r*											-.053	-.039	-.011	12.799	3.612
		p											.296	.441	.827		
11	Age	*r*												**.121**	**.143**	16.937	2.895
		p												**.016**	**.004**		
12	Stressful health threats	*r*													**.434**	.538	.919
		p													**.000**		
13	Stressful relational challenges	*r*														1.294	1.491
		p															

Significant results are printed in bold.

Table 4.2 Correlations depressed group ($N = 109$) and non-depressed group ($N = 289$)

			1	2	3	4	5	6	7	8	9	10	11	12	13	*M*	*SD*
1	Depressive symptoms	*r*		**.372**	-.079	**.210**	**.212**	**-.218**	**-.279**	**-.340**	.061	**-.244**	-.059	**.368**	**.240**	21.743	7.721
		p		**.000**	.416	**.028**	**.027**	**.023**	**.003**	**.000**	.530	**.011**	.545	**.000**	**.012**		
2	Self-blame	*r*	**.181**		.095	**.384**	**.506**	.046	-.155	-.140	.158	-.017	.062	**.309**	**.271**	11.881	3.656
		p	**.002**		.328	**.000**	**.000**	.633	.107	.146	.100	.863	.520	**.001**	**.004**		
3	Other-blame	*r*	.078	**.228**		**.489**	**.201**	.031	.122	.110	.108	.136	-.110	-.160	-.038	7.440	3.512
		p	.186	**.000**		**.000**	**.036**	.749	.207	.256	.264	.158	.254	.096	.696		
4	Catastrophizing	*r*	**.172**	**.257**	**.383**		**.464**	**-.326**	**-.202**	**-.272**	-.006	-.157	-.073	.009	.156	8.513	3.219
		p	**.003**	**.000**	**.000**		**.000**	**.001**	**.035**	**.004**	.950	.103	.452	.927	.106		
5	Rumination	*r*	.070	**.389**	.099	**.303**		-.050	-.124	-.013	-.038	.114	.055	.050	.155	12.330	3.687
		p	.237	**.000**	.092	**.000**		.607	.200	.897	.695	.238	.572	.606	.107		
6	Putting into perspective	*r*	-.044	**.382**	**.147**	.048	**.220**		**.489**	**.650**	**.470**	**.465**	.161	.025	-.145	10.651	3.857
		p	.458	**.000**	**.012**	.413	**.000**		**.000**	**.000**	**.000**	**.000**	.094	.793	.133		
7	Positive refocusing	*r*	-.063	**.141**	**.167**	**.141**	**.133**	**.445**		**.572**	**.256**	**.468**	-.055	.002	-.115	10.275	4.098
		p	.282	**.017**	**.005**	**.016**	**.024**	**.000**		**.000**	**.007**	**.000**	.572	.982	.234		
8	Positive reappraisal	*r*	**-.220**	**.343**	.101	.092	**.421**	**.593**	**.470**		**.395**	**.713**	.113	-.056	-.048	10.661	3.945
		p	**.000**	**.000**	.086	.118	**.000**	**.000**	**.000**		**.000**	**.000**	.240	.564	.620		
9	Acceptance	*r*	-.064	**.412**	**.200**	.109	**.358**	**.470**	**.382**	**.443**		**.289**	.017	.091	.114	1.028	.726
		p	.276	**.000**	**.001**	.064	**.000**	**.000**	**.000**	**.000**		**.002**	.859	.348	.236		
10	Refocus on planning	*r*	**-.178**	**.454**	**.173**	**.158**	**.528**	**.445**	**.361**	**.695**	**.413**		.136	-.092	-.078	11.551	3.463
		p	**.002**	**.000**	**.003**	**.007**	**.000**	**.000**	**.000**	**.000**	**.000**		.159	.340	.418		
11	Age	*r*	-.030	**.172**	-.031	**-.162**	**.270**	**.166**	-.073	**.228**	**.198**	**.195**		.092	.090	16.530	2.519
		p	.616	**.003**	.601	**.006**	**.000**	**.005**	.219	**.000**	**.001**	**.001**		.342	.352		
12	Stressful health threats	*r*	.024	-.014	.154	.062	.070	-.038	-.033	.056	.026	.041	**.161**		**.435**	.798	1.070
		p	.688	.815	.009	.297	.237	.520	.581	.347	.658	.493	**.006**		**.000**		
13	Stressful relational challenges	*r*	**.287**	**.195**	**.150**	**.129**	**.290**	.004	.057	**.130**	**.153**	**.163**	**.245**	**.384**		2.248	1.701
		p	**.000**	**.001**	**.011**	**.028**	**.000**	.942	.337	**.027**	**.009**	**.005**	**.000**	**.000**			
	M		5.031	8.568	6.519	6.069	9.779	12.879	12.529	13.578	1.010	13.270	17.090	.439	.934		
	SD		2.990	2.728	2.626	2.172	3.581	3.784	3.599	3.561	.743	3.560	3.015	.836	1.227		

The depressed sample is displayed in the top half of the table and the non-depressed sample is displayed in the bottom half; significant results are printed in bold.

non-depressed and depressed participants ($\Delta\chi^2$ (80) = 158.45, $p < .001$). The results of the model are described for participants with high and low depression scores separately below (see Figure 4.2 for the model and Figure 4.3 for the indirect effects). Gender was included in the model, but showed no direct significant effects on depressive symptoms or on any cognitive emotion regulation strategy.

Direct associations between type of life events and depression. Within the total sample and within the non-depressed subgroup, only relational challenging stressful life events were associated with depressive symptoms (β = .231, $p < .001$ and β = 338, $p < .001$, respectively). The depressed group showed a significant association of health threatening stressful life events with depressive symptoms (β = .285, $p = .003$). This association was also significantly different compared to the non-depressed group ($\Delta\chi^2$ (1) = 11.55, $p < .001$). Loss was not associated with depressive symptoms in the total sample, or in either subgroup.

Direct associations between type of life events and cognitive emotion regulation strategies. Within the total sample, relational challenging stressful life events were associated with various strategies, namely self-blame, other-blame, catastrophizing, rumination, putting into perspective and acceptance (Figure 4.2). Within the non-depressed group, direct associations between relational challenging stressful life events and other-blame (β = .122, $p = .039$), positive reappraisal (β = .130, $p = .034$) and refocus on planning (β = .168, $p = .004$). Within the depressed group, direct associations between relational challenging stressful life events and self-blame (β = .195, $p = .049$), catastrophizing (β = .209, $p = .041$) and rumination (β = .240, $p = .011$) were found.

Health threatening stressful life events were not significantly associated with any cognitive emotion regulation strategy within the whole sample, nor within the subgroups. Loss was negatively associated with catastrophizing within the non-depressed group (β = -.136, $p = .015$).

Direct associations between cognitive emotion regulation strategies and depression. Within the whole sample more depressive symptoms were significantly associated with: self-blame, catastrophizing, rumination, positive reappraisal and refocus on planning (Figure 4.2). In the non-depressed group, self-blame (β = .252, $p < .001$), less positive reappraisal (β = -.269, $p = .003$) and less refocusing on planning (β = -.245, $p = .004$) were significantly associated with depressive symptoms. In the depressed group, no significant associations between degree of depressive symptoms and use of any cognitive emotion regulation strategy was found. The correlations between strategies and depressive symptoms did not differ significantly between depressed and non-depressed subgroup. Acceptance was not significantly associated with the degree of depressive symptoms within either subgroup.

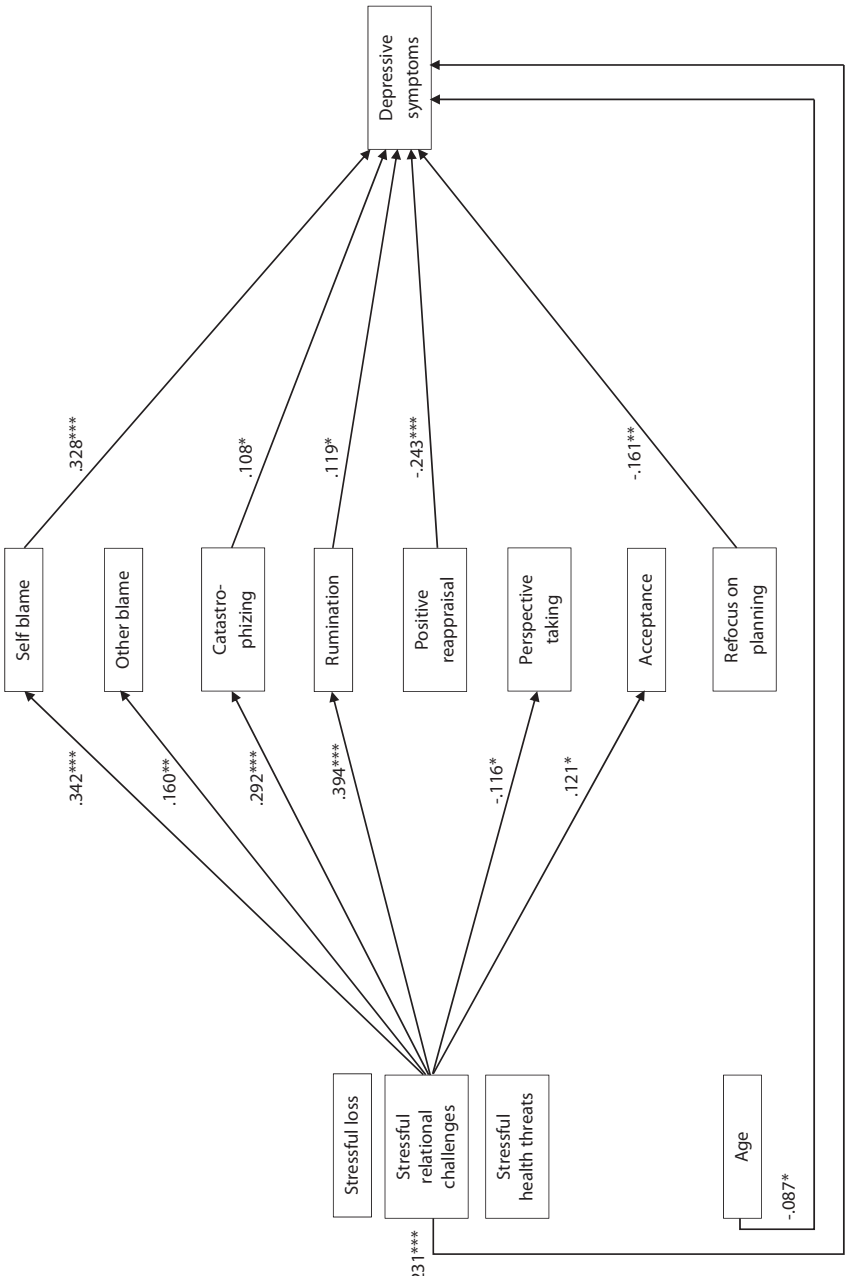

Figure 4.2 Direct effects for the total sample.
Standardized estimates of the direct effects on the cognitive emotion regulation and depressive symptoms. Only significant effects (* $p < .05$, ** $p < .01$, *** $p < .001$) within the total sample ($N = 398$) are shown.

Indirect associations. Within the whole sample, significant indirect paths from relational challenging stressful life events to depressive symptoms were found via self-blame, catastrophizing and rumination (Figure 4.3).

Indirect paths were found in the non-depressed group, from relational challenging stressful life events to depressive symptoms via self-blame and refocusing on planning. Within the depressed group, no indirect paths were identified. However, the Wald test of parameter constraints showed no significant differences between the non-depressed and depressed group for these indirect paths.

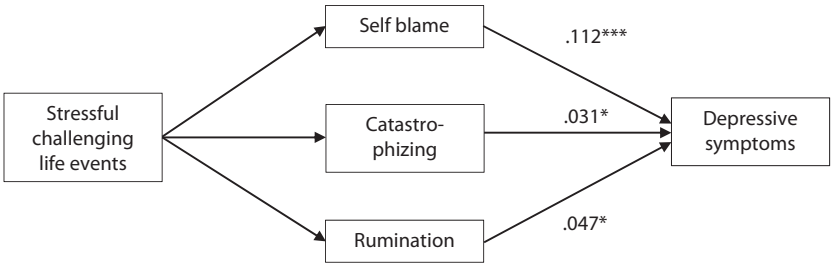

Figure 4.3 Mediation model.
Standardized estimates of the indirect effects on the depressive symptoms (N = 398). Only significant effects are shown (* $p < .05$, *** $p < .001$). Estimates apply to the total sample (N = 398).

Discussion

The findings of this study support the general hypothesis that certain stressful life events were related to the level of depressive symptoms and that this relationship was mediated by maladaptive cognitive emotion regulation strategies. These findings are important for clinical practice to increase understanding of the association between specific types of stressful life events and the use of cognitive emotion regulation strategies. In addition, the results confirm the dual process model on associative and reflective processing in adolescents and depression (Beever, 2005). The important role of self-referent association ,maladaptive cognitive emotion regulation strategy namely self-blame, as a mediator of depressive symptoms was confirmed.

The main results can be summarized as follows: (I) Health threatening and relational challenging stressful life events were associated with depressive symptoms, while stressful loss related life events were not; (II) more frequent use of maladaptive cognitive emotion regulation strategies was related to more depressive symptoms; (III) more frequent use of

adaptive cognitive emotion regulation strategies was related to less depressive symptoms; (IV) specific life events were associated with specific emotion regulation strategies; (V) only the association between relational challenging stressful life events and depressive symptoms was mediated by maladaptive cognitive emotion regulation strategies (self-blame, catastrophizing and rumination); and (VI) adaptive cognitive emotion regulation strategies were not identified as mediators in the total sample.

These results deserve some further interpretation and reflection. The relationship between cognitive emotion regulation strategies and depressive symptoms was established in our study. More use of maladaptive (self-blame, catastrophizing, rumination) and less use of adaptive cognitive emotion regulation adaptive strategies (positive reappraisal, refocus on planning) were significantly associated with more depressive symptoms in the whole sample. This finding is in line with earlier findings that maladaptive emotion regulation was linked to the onset of depressive symptoms (Ehring et al., 2008; Garnefski & Kraaij, 2006; Joormann & D'Avanzato, 2010; Martin & Dahlen, 2005; Schroevers et al., 2007). Maladaptive cognitive emotion regulation could representative of the self-referent association of the dual process model and adaptive cognitive reflection is considered to be of importance for the regulation of emotions.

Deficient emotion regulation is also a risk factor for recurrence of depression (Rude & McCarthy, 2003). Our findings suggest that using maladaptive strategies can be more harmful, than the absence of using adaptive strategies. These findings are relevant for clinical practice to enhance prevention and treatment in order to detect and address specific mechanisms at work in depression.

One specific and adaptive cognitive emotion regulation strategy, acceptance, was not significantly associated with depressive symptoms, as was also reported in a meta-analysis band colleagues (Aldao et al., 2010). Increase of acceptance of a problem or risk is a common objective in various treatments such as Mindfulness, and Acceptance and Commitment Therapy (Hofmann & Asmundson, 2008). In acceptance-based treatments, acceptance is promoted in order to reduce experiential avoidance (Eifert & Forsyth, 2005; Hayes, Strosahl, & Wilson, 1999). However, the role of acceptance might differ during the process of handling stressful life events and therefore it might also have been disguised in our study. A high score on acceptance immediately after a stressful life event could, for instance, be related to learned helplessness. Timing in relation to the occurrence of stressful life events should be taken into account in future research on acceptance. In addition, acceptance may be more of an end state that is based upon other regulation strategies, instead of reflecting an active and dynamic cognitive emotion regulation strategy.

Stressful loss was not found to be associated with higher levels of depressive symptoms. This finding that the death of a loved one was generally not associated with elevated levels of depressive symptoms should be interpreted with caution. Earlier studies found that a substantial number of 75% to 80% of children do not develop mental health problems after the death of a parent or sibling, but these studies also found a significant increase in internalizing symptoms in these cases (Cerel, Fristad, Verducci, Weller, & Weller, 2006; Dowdney, 2000; Dowdney, 2005; Luecken & Roubinov, 2012; Worden & Silverman, 1996). Another study found a significant increase in depression in the second year after bereavement (Brent, Melhem, Donohoe, & Walker, 2009). In our study however, lapse of time after loss could not be accounted for. In a community sample, the comparison between family bereaved and non-bereaved showed a robust difference in internalizing problems by the age of 19 (Stikkelbroek et al., 2015). No long-term effects could be assessed in the current study. Furthermore, a broad definition of loss was used, which included pets. The kind of loss might also be of importance for the impact on mental health.

Health threatening stressful life events were only associated with depressive symptoms in the depressed group and not in the non-depressed group. Although the level of depressive symptoms was high in the depressed adolescents, health threats still accounted for substantially more depressive symptoms. These findings are in line with a review on depressive symptoms in epileptic youth, showing an elevated risk for depression in this specific group with health problems (Hankin, 2006). So it seems that health threats are particularly important for depressive symptoms in adolescents.

An association between relational challenging stressful life events and depressive symptoms was established for the total sample, and seen in both the depressed as well as the non-depressed group. This association was not found in earlier research conducted with secondary school students (Garnefski, Legerstee, Kraaij, van den Kommer, & Teerds, 2002). This discrepancy can be explained by the use of a larger multi-group sample in this study with higher levels of depressive symptoms, which made detection of the association possible. This shows that the use of multiple samples is indeed important in future research on cognitive emotion regulation (Aldao et al., 2010).

Our findings confirm the existence of a specific association between relational challenges and cognitive emotion regulation. Loss or health threatening stressful life events showed no specific association with any of the cognitive emotion regulation strategies within the whole group, suggesting that the type of stressful event influenced the use of specific cognitive emotion regulation. Relational challenging stressful life events were associated with maladaptive strategies as well as with two adaptive strategies: putting

experiences into perspective and acceptance. The non-depressed group showed a significant association between relational challenging stressful life events and three adaptive strategies, namely positive reappraisal, refocus on planning, and acceptance. In the depressed group, this association was not found, suggesting that non-depressed and depressed adolescents differ in their use of maladaptive and adaptive cognitive emotion regulation strategies. However, no significant difference between groups in the strength of this association was found. These results must thus be interpreted with caution, and studies with larger groups are needed to rule out power issues in interpreting these differences.

The mediating role of maladaptive cognitive emotion regulation strategies was established, Self-blame, catastrophizing and rumination could be identified as mediators between stressful relational challenging life events and depressive symptoms. However, depressed and non-depressed adolescents did not differ significantly in these mediation relationships, which may be due to the size of the depressed sample. Still, this is an important finding, which could be useful for clinical practice. Experiencing relational challenging stressful life events and blaming oneself, emphasizing the terror of experiences or dwelling on feelings and thoughts about the events, may put adolescents at risk for depressive symptoms.

Strengths and limitations

This study is innovative for several reasons. First, according to the literature, testing mediational models on the etiology of adolescent depression was needed (Grant et al., 2006). Second, the use of the multi-sample approach, including severely depressed adolescent patients, is scarce and should be used more often (Southam-Gerow & Kendall, 2002), as it is essential for the study of psychopathology (Aldao et al., 2010; Grant et al., 2006). Third, a rigorous criterion for life events was used, namely stressful life events reported by the adolescent as upsetting. Previous research used the number of life events as a variable, without the upsetting criterion, thereby ignoring whether the life events actually impact the life of participants in a negative fashion. Fourth, not only being upset but also the type of life event was taken into account as an important variable affecting depressive symptoms, as well as the cognitive emotion regulation strategies. Fifth, to our knowledge, we were the first to test the mediating role of cognitive emotion regulation in the association between stressful life events and depressive symptoms in adolescents and to test differences in mediation between low and high levels of depressive symptoms.

This study also has several limitations. First, cross-sectional data were used and therefore no temporal conclusions could be drawn. Future research is needed to test mediational models in a longitudinal design. Second, the profile of different mediators within one individual could not be taken into account. For example, the mediation of depressive symptoms by rumination may be more prominent if the use of self-blame is high and positive refocusing is low. Even more useful for clinical practice would be the identification of patterns in how the various emotion regulation strategies are used (Dixon-Gordon, Aldao, & De Los Reyes, 2015).

Third, the relationship between associative (maladaptive strategies) and reflective processing (adaptive strategies) could not be taken into account, while this may be a function of clinical severity (Aldao et al., 2010). Further research on specific correlations between cognitive emotion regulation strategies is needed and of importance to determine which strategy should be addressed in interventions.

Fourth, a lack of power could underlie the fact that no mediating paths were found in the depressed group, and that no significant differences in the strength of the mediational paths between the non-depressed and depressed adolescents were found. A larger sample than $N = 109$ is needed to identify possible mediators in the depressed group.

Fifth, the time between the last stressful life event and the measurement of depressive symptoms was not taken into account. In a longitudinal design this variable should be included because depressive symptoms could increase instantly or gradually after some time, through use of specific cognitive regulation strategies (Calvete, Orue, & Hankin, 2013).

Despite the mentioned limitations, our study contributes to current scientific knowledge by showing that depressive symptoms are mediated by maladaptive cognitive emotion regulation strategies (self-blame, rumination and catastrophizing) uniquely after stressful relational challenging life events. Mediation was not found after losing a loved one or experiencing a health threat. Adaptive cognitive emotion regulation strategies, for instance acceptance, were not identified as mediators.

These findings are important for clinical practice. Use of specific maladaptive cognitive regulation strategies after relationally challenging stressful life events can aggravate depressive symptoms. To prevent depression after negative life events, maladaptive cognitive emotion regulation strategies should be reduced in adolescents.

Acknowledgements of authors' contributions

Yvonne Stikkelbroek designed the study, obtained funding, coordinated the recruitment of participants and data collection, conducted the statistical analyses, wrote the initial manuscript, revised the manuscript and approved the final manuscript as submitted. Denise H. M. Bodden designed the study, obtained funding, coordinated the recruitment of participants and data collection, conducted the statistical analyses, revised the manuscript and approved the final manuscript as submitted. Marloes Kleinjan conducted the statistical analyses, revised the manuscript and approved the final manuscript as submitted. Mirjam Reijnders conducted the statistical analyses, revised the manuscript and approved the final manuscript as submitted. Anneloes van Baar designed the study, revised the manuscript and approved the final manuscript as submitted.

Acknowledgments

This research is part of the Adolescent Depression study of the University of Utrecht. We would like to thank Maria Kovacs and MHS for their generosity in letting us use the CDI-2. We are grateful for the contribution of the Mental Health Institutions and their professionals, as without them data collection would be impossible: Accare, Altrecht, Ambulatorium, Bascule, Curium, GGZ-centraal, Herlaarhof, Lentis, Orbis, Perspectief, Praktijk Appelboom, Traverse, and Triversum. We also thank the students for collecting data in the community sample. This research is funded by ZonMw - the Dutch Organisation for Health Research and Development, grant number 80-82435-98-10117.

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Part C

Focus on treatment: CBT versus TAU

Lisa, aged 14 years, went to the general practitioner with her mother. She was tired and was not able to go to school at times. The doctor advised counseling by a child psychologist. The psychologist talked with Lisa about important topics in her life like school, bullying and friends. Lisa felt worse afterwards because she still thought there was no solution for her problems. After several weeks Lisa stopped visiting the psychologist although her mother tried to force her to continue.

Chapter 5

Effectiveness and cost effectiveness of Cognitive Behavioral Therapy (CBT) in clinically depressed adolescents: Individual CBT versus Treatment As Usual (TAU)

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BMC Psychiatry, *13* (2013), 314.
doi:10.1186/1471-244X-13-314

Abstract

Background: Depressive disorders occur in 2 to 5% of the adolescents and are associated with a high burden of disease, a high risk of recurrence and a heightened risk for development of other problems, like suicide attempts. The effectiveness of cognitive behavior therapy (CBT), cost-effectiveness of this treatment and the costs of illness of clinical depression in adolescents are still unclear. Although several Randomized Controlled Trials (RCT) have been conducted to establish the efficacy of CBT, the effectiveness has not been established yet. Aim of this study is to conduct a RCT to test the effectiveness of CBT and to establish the cost-effectiveness of CBT under rigorous conditions within routine care provided by professionals already working in mental health institutions.

Method/design: CBT is investigated with a multi-site, RCT using block randomisation. The targeted population is 140 clinically referred depressed adolescents aged 12 to 21 years old. Adolescents are randomly assigned to the experimental ($N = 70$, CBT) or control condition ($N = 70$, TAU). Four assessments (pre, post, follow up at 6 and 12 months) and two mediator assessments during treatment are conducted. Primary outcome measure is depression diagnosis based on a semi-structured interview namely the K-SADS-PL. Secondary outcome measures include depressive symptoms, severity and improvement of the depression, global functioning, quality of life, suicide risk, comorbidity, alcohol and drug use, parental depression and psychopathology, parenting and conflicts. Costs and treatment characteristics will also be assessed. Furthermore, moderator and mediator analyses will be conducted.

Discussion: This trial will be the first to compare CBT with TAU under rigorous conditions within routine care and with a complex sample. Furthermore, cost-effectiveness of treatment and cost-of-illness of clinical depression are established which will provide new insights on depression as a disorder and its treatment.

Trial registration: Dutch Trial register (NTR) number 2676. The study was financially supported by a grant from ZonMw, the Netherlands organization for health research and development, grant number 157004005.

Background

Depressive disorders in adolescents are among the most prevalent disorders with a high burden of disease (Hoeymans, Gommer, & Poos, 2006) and high risk of recurrence (Curry et al., 2011; Ryan, 2005). Before entering adulthood, 14 to 25% of the adolescents have experienced at least one episode of a depressive disorder (Ryan, 2005). Besides the high prevalence (Cohen et al., 1993; Fergusson, Horwood, & Lynskey, 1993; Hankin et al., 1998; McGee et al., 1990), comorbid psychiatric diagnoses are often present (Goodyer & Cooper, 1993; Herbert et al., 1996; Mitchell, McCauley, Burke, & Moss, 1988). In addition, a heightened risk exists for development of social problems, juridical problems, learning problems, substance abuse, negative life events, physical problems, teen pregnancies and suicide (Portzky & Van Heeringen, 2009; Ryan, 2005). Therefore, it is important that depression is treated in an early stage with an effective treatment (Birmaher, Brent, & AACAP Work Group on Quality Issues, 2007; Ryan, 2005).

In the international literature, there is no consensus on the degree of effectiveness of psychotherapeutic interventions in depressed adolescents. In a meta-analysis, which included studies with a large diversity of investigated interventions, only a modest effect size of 0.34 was found (Weisz, McCarty, & Valeri, 2006). Other meta-analyses calculated medium (0.72) (Michael & Crowley, 2002) to large (1.27) effect sizes (Lewinsohn & Clarke, 1999). In a meta-analysis solely directed at Cognitive Behavioral Therapy (CBT) a medium effect size of 0.53 was found (Klein, Jacobs, & Reinecke, 2007). Although the effect size for CBT is promising, it also reflects the need for improved treatment of depression, as a large group of depressed adolescents will not recover after CBT treatment.

In addition, it is often discussed that effectiveness studies in depressed adolescents lack generalizability for clinical practice, because the study samples do not match the complex and severe cases in routine mental health care (Weisz et al., 2006). In this study, this issue is addressed by comparing CBT to treatment as usual within a referred clinically depressed group of adolescents.

Within this study an individual revision of the group CBT program "Coping with Depression course for Adolescents" (CWD-A) (Clarke, Lewinsohn, & Hops, 1990) will be investigated. Group CBT was adapted into an individual CBT format because it is much better applicable within mental health care than group CBT, for instance children can start treatment immediately. Several RCT's were conducted with an American population, but not with clinically referred adolescents. Results repeatedly have shown that the CWD-A was more effective than control conditions (Clarke et al., 1995; Clarke et al., 2001) and treatment

as usual (Clarke et al., 2002; Clarke et al., 2005). As only one research group investigated the CWD-A, it is regarded as probably efficacious (David-Ferdon & Kaslow, 2008).

The costs of depression in adolescents have not been studied before. Knowledge about costs of depression is essential to motivate an increase in budgets for treatments. A recent cost-of-illness study on children with anxiety disorders shows that both the costs of school absence, as well as productivity loss of the parents are substantial (Bodden et al., 2008). Given the high degree of comorbidity of anxiety and depression and the fact that both disorders are internalising disorders, the same high costs are expected in adolescents with depression. Lynch and colleagues (Lynch et al., 2005) investigated cost-effectiveness of a group based prevention course "Coping with Stress" in adolescents with a subclinical depression. It was concluded that group CBT was more cost effective in comparison to treatment as usual. However, intervention related costs like productivity costs, expressed as school absence, were not taken into account. Including these costs could indicate that cost-effectiveness is even higher.

Within intervention research in depressed adolescents, little is known about possible moderators and mediators of treatment. A lot of authors mention the necessity to investigate factors that may be involved as such (David-Ferdon & Kaslow, 2008; Weisz et al., 2006).

In conclusion, the efficacy of CBT for the treatment of clinically depressed adolescents is established, but the effectiveness is not yet clear. Cost effectiveness of CBT in comparison to Treatment As Usual (TAU) and potentially important moderators and mediators have not been investigated yet. Effectiveness, cost effectiveness, and information on moderators and mediators are essential for the enhancement of the treatment for depression in adolescence in order to reduce the burden of adolescent depression and recurrence.

Methods and design

Aim of the study

The aim of this study is to investigate the effectiveness and the cost-effectiveness of the individual CBT program the "D(o)epression course" in a sample of referred adolescents with a Depressive Disorder according to DSM-IV-TR [American Psychiatric Association, 2000] in a randomized controlled trial. We expect that CBT will be more effective than TAU (without CBT). Furthermore, cost-effectiveness of CBT and the cost of illness of clinical depression in adolescents will be established. Potential moderators (comorbidity, severity of depression, age, ethnicity, gender, suicidal thoughts and psychopathology in

parents) and mediators (negative automatic thoughts, cognitive emotion regulation and attribution style) for the effectiveness of CBT will be studied. The role of non-specific treatment variables (therapeutic alliance, client expectancy, client satisfaction, treatment adherence) will be taken into account as well (see Figure 5.1).

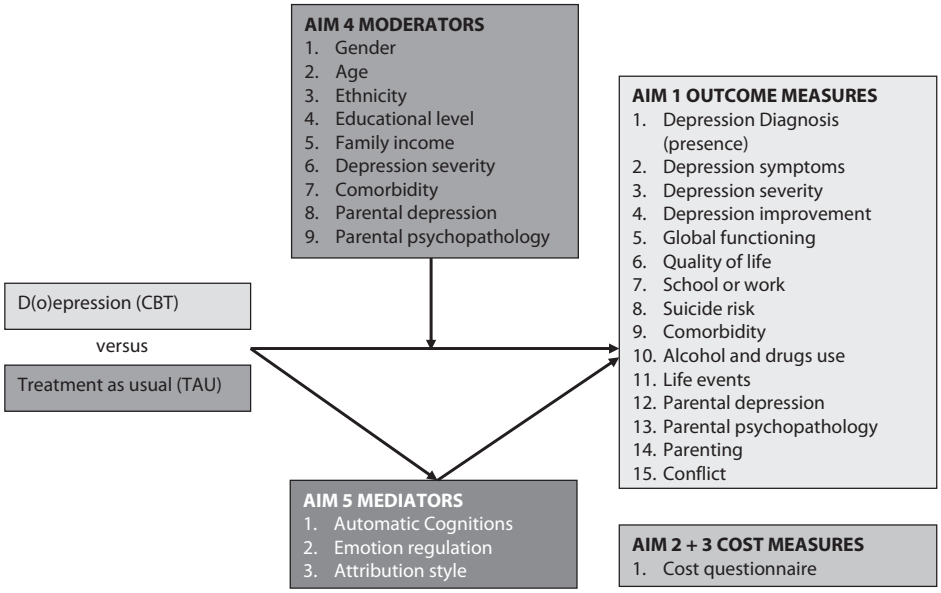

Figure 5.1 Aims, conditions, potential moderators and mediators evaluated in this study.

Design

This study is designed as a multi-site, randomized controlled clinical trial in which individual CBT will be compared to Treatment as usual (TAU). Four multiple informant (adolescent, parent, therapist) assessments are done: prior to treatment (pre-test assessment), immediately after treatment (post-test assessment or after 15 sessions), 6 months after treatment (6 month follow-up) and 1 year after treatment (1 year follow-up). To investigate potential mediators two temporary assessments are conducted, each after 5 therapy sessions.

All sessions will take place within routine outpatient care within second order public mental health clinics to enhance external validity. All treatments in both conditions are delivered by psychologists with at least a master's degree-level and two years of experience within professional mental health care. These professionals are trained before delivering the treatments to enhance treatment integrity.

Adolescents who are diagnosed with a depression according to the K-SADS-PL (Kaufman et al., 1997; Reichart, Wals, & Hillegers, 2000), who meet inclusion criteria and do not meet the exclusion criteria are randomly assigned to either individual CBT or TAU. Random assignment per adolescent is executed using computer generated block randomisation and stratified per mental health centre. See Figure 5.2 for patient's flow chart.

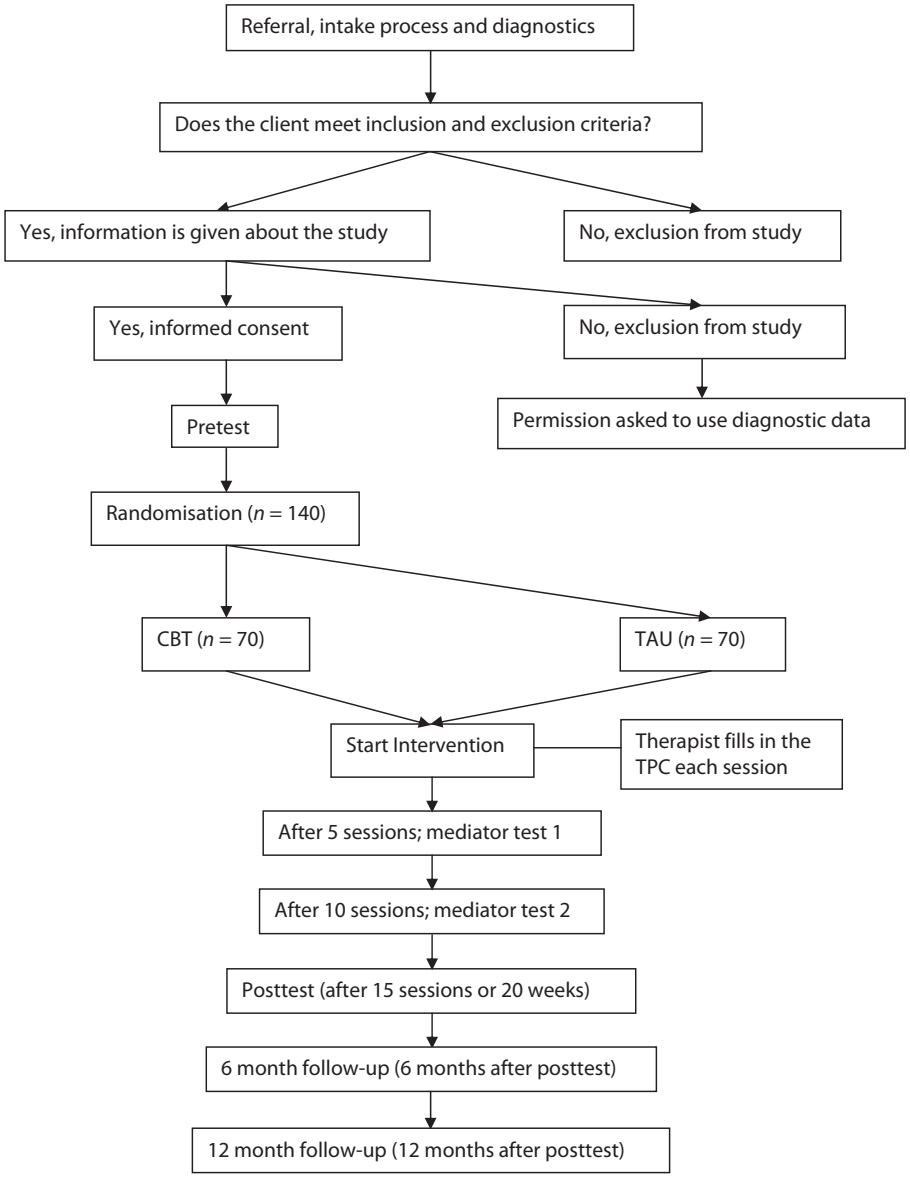

Figure 5.2 Participant's flow through the study.

The design of this study is according to the guidelines specified by the Task force on promotion and dissemination (1995) and approved by the independent Medical Ethics Committee (METC) of the Utrecht Medical Centre at Utrecht University.

Sample size

Based on previous research (Klein et al., 2007) an effect size (Cohen's *d*) of 0.53 is expected. Power calculations indicated that 70 adolescents per condition (assuming an alpha of .05, a statistical power, 1-beta, of 0.80 and a drop-out of 20%; power calculations in STATA) are required to detect a difference in depression diagnosis. In total 140 adolescents will be included.

Study sample

In total 140 referred clinically depressed adolescents aged 12 to 21 (n = 140) and their parents will be included in this study. If the adolescent is 18 years or older, parents will only be approached after the adolescent's permission. The inclusion criteria for the depressive adolescents are: (1) a primary diagnoses of Depressive Disorder (regardless the severity: mild, moderate or severe) or Dysthymic disorder, (2) age 12 to 21 years, and (3) referred to one of the participating mental health institutions. The exclusion criteria are: (1) acute suicide risk, (2) drug abuse (as primary diagnosis), (3) pervasive developmental disorder (as primary diagnosis), (4) bipolar disorder (as primary diagnosis), (5) day care or admission to the clinical setting and (6) not fluent in Dutch, Turkish, Arabic or Berber language. If medication is used (for the depression or another disorder), the dosage should be kept constant during the intervention, unless medication is the control treatment.

Participants in both groups will be compared afterwards for their match on the following characteristics: age, ethnicity, gender, educational level parents and severity of the depression. If significant differences between two groups appear, these variables will be controlled for in analyses.

Recruitment

The participants are recruited from fourteen different specialized mental health care institutions spread all over the Netherlands. An experienced psychologist within the mental health centre informs the adolescents and their parents about the study. After written

informed consent by the adolescent and his/her parents, a trained independent researcher carries out an interview to check for the inclusion and exclusion criteria.

Intervention

The experimental treatment is a protocolled individual CBT program, the D(o)epressie course. It consists of 15 weekly sessions of 45 minutes, two parent sessions after 3 and 9 weeks and a meeting with the parent at the end of treatment. The D(o)epressie course is, as the CWD-A, based on the social learning theory about the aetiology of depressions by Lewinsohn (Lewinsohn, Antonuccio, Steinmetz, & Teri, 1984). According to this theory, there is a connection between the number of positive interactions between a person and his environment on one hand, and depression on the other. A triggering event such as a stressful life event causes a negative spiral of less positive interactions leading to more negative thoughts and a deteriorating depressed mood. The aim of the intervention is to reduce depressive complaints in adolescents with a depressive disorder. Since depressive episodes are multi-factorial determined, the focus of the intervention is broad. The intervention contains representative components of CBT (McCarty, Weisz, & Hamilton, 2007) namely: psycho-education (information about depression and the rationale for the aetiology of the complaints and the treatment of them), setting attainable goals (translate large goals into realistic short term goals), self monitoring (registration of the mood, activities and thoughts), activation (planning frequent, joyful activities), improving social skills and communication skills (improvement and stimulation of social behavior), relaxation techniques, cognitive restructuring (identifying and changing unrealistic negative thoughts about the self, others and events), role play and problem solution skills (teaching the creation of solutions for problems via brainstorm, choosing, trying and evaluating) and relapse prevention. Exercises are executed within the sessions and are generalized into daily life by means of homework assignments. In the parent sessions, parents will receive psycho education and information on CBT. Therapists are not allowed to conduct treatments in both conditions.

The control treatment consists of TAU for clinical depression. After a short telephone survey we concluded that TAU in the Netherlands consists of: Interpersonal Therapy (IPT), family therapy, parent counseling, medication, mindfulness training, acceptance commitment therapy (ACT), psychodynamic therapy (short duration), (non-directive) counseling, creative therapy and running therapy, and CBT. However, in this study CBT is not allowed within TAU. The content of TAU and the treatment techniques used, are monitored.

Instruments

In Table 5.1, concepts, source and time of assessment of all used instruments are presented. The adolescent and parent complete the self-report questionnaires online at home. Both, the adolescent and the parent have a separate login code to secure privacy. The parents fill in a paper version of the cost diary at home. The therapist completes the questionnaires at the office.

Primary outcome measures

The primary outcome measure is the presence of the depression diagnosis, as measured by the Kiddie-Schedule for Affective Disorders and Schizophrenia, present and lifetime version (K-SADS-PL) (Kaufman et al., 1997; Reichart et al., 2000), a widely used semi-structured diagnostic interview. The K-SADS-PL assesses a wide range of diagnoses (present and life time) including their severity. The view of the adolescent, the parent and the independent clinician are taken into account. Concurrent validity of the K-SADS-PL is supported (Kaufman et al., 1997). Also the interrater agreement is high (range 93% to 100%) and test–retest reliability is excellent for present and lifetime diagnoses of major depression (0.77 to 100) (Kaufman et al., 1997). Convergent validity of the depression screen criteria and the diagnoses generated with the K-SADS-PL was confirmed but divergent validity is only partly supported within an inpatient sample (Lauth et al., 2010).

Secondary outcome measures

A broad range of secondary outcome measures will be assessed namely total symptoms of major depressive disorder or dysthymic disorder, severity and improvement of depression, global functioning, quality of life, suicide risk, comorbidity, alcohol and drug use, parental depression and psychopathology, parenting and conflicts. Costs, moderators, mediators and treatment characteristics will be assessed as well.

The degree of depressive symptoms are measured with a self report measure, the Child Depression Inventory-2 (CDI-2) (Bodden, Stikkelbroek, & Braet, 2010; Kovacs, 2011). The CDI-2 is a revision of the CDI (Braet & Timbremont, 2002; Kovacs, 1992) and was translated in Dutch. It was expanded with a version for the parents (CDI-P) (Kovacs, 2011) as well. The severity of the depression is rated by the independent clinician on the K-SADS-PL (see above) and by the therapist on the Clinical Global Impression-severity scale (CGI-S) (Guy, 1976). Improvement of depression, in reference to the severity of

Table 5.1 Instruments at different assessments and informants

				Source			Test				
	Domain / concept	Instrument	Items	A.	P.	T.	Pre	Med	Post	Fu1	Fu2
Primary outcome	Depression diagnosis	K-SADS		x	x		x		x	x	x
Secondary outcomes	Depression symptoms	CDI-II	28/17	x	x		x	x	x	x	x
	Depression severity	KSADS	1	x	x	x	x	x	x	x	x
		CGI-S	1				x		x		
	Depression improvement	CGI-I	1			x	x	x	x		
	Global functioning	CGAS	1			x	x	x	x		
	Quality of life	EuroQol	6	x	x		x	x	x	x	x
	School or work	SQ	7	x			x		x	x	x
	Suicide risk taxation	SRT	6	x			x		x	x	x
	Comorbidity	KSADS		x	x		x		x	x	x
		YSR	69	x	x		x		x	x	x
		CBCL	74	x	x		x		x	x	x
		SCARED	5				x		x	x	x
	Alcohol and drug use	AD	7	x			x		x	x	x
	Personality	Big 5	30	x			x		x		
	Life events	LES	23	x	x		x		x	x	x
	Parental depression	BDI-II	21		x		x		x	x	x
	Parental	ASR	69		x		x		x	x	x
	Psychopathology	SCARED	4		x		x		x	x	x
	Parenting			x	x		x		x		
	Responsivity	NOV	8		x		x		x		
	Consistency	PDI	8								
	Positive parenting	APQ	6								
	Harsh discipline	SOG	8								
	Psychological control	PCS	8								

	Behavioral control	VTH	6								
	Competence	NOSI	5		x		x		x		
	Attachment	PARA	13	x	x		x		x		
	Conflict	NRI	6	x	x		x		x	x	x
Cost-effectiveness	Costs	Cost questionnaire			x		x		x	x	x
	Quality of life	EuroQol		x	x		x	x	x	x	x
Moderators	Demographic	Gender	8/12	x	x		x		x	x	x
	Characteristics adolescent	Age									
		Ethnicity		x	x		x		x	x	x
		Education									
		Income									
	Depression severity	K-SADS		x	x		x		x	x	x
	Comorbidity	YSR		x			x		x	x	x
		CBCL			x		x		x	x	x
	Parental depression	BDI			x		x		x	x	x
	Parental Psychopathology	ASR			x		x		x	x	x
Mediators	Negative automatic thoughts	CNCEQ	16	x			x	x	x	x	x
	Cognitive Emotion regulation	CERQ	36	x			x	x	x	x	x
	Attribution style	CASQ	24	x			x	x	x	x	x
Treatment characteristics	Expectancy of treatment	PETS	7	x	x		x				
	Previous treatment	VEHI	8	x	x		x		x	x	x
	Satisfaction with treatment	SSS	4	x	x				x		
	Cooperation with treatment	CWT	5			x		x	x		
	Relationship with therapist	RWI	13	x				x	x		
	Treatment Integrity	observations							x		
	Therapy Procedures Checklist	TPC	51			x	Each session				
	Preferred treatment		1			x	x				

Abbreviations: A, adolescent; FU1, Follow-up1; FU2, Follow-up2; Med1, mediatortest1; Med2, mediatortest2; Post, posttest; P, parents; Pre, pretest; T, therapist.

the depression at the start of the treatment, is also rated by the therapist on the Clinical Global Improvement scale (CGI-I) (Guy, 1976). Global functioning of the adolescent is measured by an independent clinician and therapist on the Children Global Assessment Scale (CGAS) (Bunte, Schoemaker, & Matthys, 2010; Shaffer et al., 1983). The Dutch version of the EuroQol Questionaire (EQ-5D adolescent and parent version) (The EuroQol Group, 1990) is used to establish quality of life as expressed in quality adjusted life years (QALYs). Apart from the K-SADS-PL, suicide risk is also assessed with a newly developed self-report questionnaire, which focuses on frequency of suicidal thoughts, wishes, plans and actions over the past two weeks.

Comorbidity and psychopathology is assessed with the K-SADS-PL, but also with the Youth Self Report scale (YSR) for adolescents and the Child Behavior Check List (CBCL) for parents (Achenbach, 1991; Verhulst, van der Ende, & Koot, 1996). Comorbidity between depression and anxiety is very high (Birmaher & Brent, 2007) therefore anxiety symptoms are also assessed separately with the Scared-5 (Birmaher et al., 1999).

Personality of the adolescent is assessed with the Quick Big Five Personality Inventory (QBF) (Vermulst & Gerris, 2005). For this study, we also constructed the Life Event Scale (LES) (Bodden & Stikkelbroek, 2010b), which is a self-report measure about life events (including drug abuse, bereavement, maltreatment and suicide attempts), their date of occurrence and their impact on the adolescents well being.

Psychopathology of both parents is measured with the Adult Self-Report (ASR) (Achenbach & Rescorla, 2003). The degree of depressive symptoms in parents is assessed with the Dutch version of the Beck Depression Inventory, second edition (BDI-II-NL) (Beck, Steer, Ball, & Ranieri, 1996; Van der Does, 2002).

Parenting, in particular consistency, responsiveness, positive parenting, harsh discipline, psychological control and behavioral control is assessed with subscales of different instruments filled in by both the adolescent and the parent. The Parenting Dimensions Inventory (PDI) (Deković, Janssens, & As, 2003; Slater & Power, 1987) was used to measure consistency, the degree to which the parent shows predictable discipline behavior. The Nijmeegse Rearing Questionnaire (NOV) (Gerris, 1993; Gerrits, Dekovic, Groenendaal, & Noom, 1996) measures responsiveness, the degree to which the parent is responsive for the needs, signals and condition of the child, and attachment, the degree to which the parent feels emotionally connected to the child. Positive parenting is measured with 6 items from the Alabama Parenting Questionnaire (APQ) (Shelton, Frick, & Wootton, 1996). The Ghent Parental Behavior Questionnaire (SOG) (Van Leeuwen & Vermulst, 2004) assesses physical harsh discipline or physical punishment. Psychological control

is assessed using the Psychological Control Scale (PCS) (Barber, 1996), which measures the degree in which the parent tries to control the child in an intrusive way. The degree in which parents monitor their children, that is behavioral control is measured with 6 items of the (Monitoring questionnaire, VTH) (Brown, Mounts, Lamborn, & Steinberg, 1993). Competence, the parents' perspective on their ability to address rearing practices, is established with the subscale competence of the Nijmeegse Parental Stress Index (NOSI) (Abidin, 1982; De Brock, Vermulst, Gerris, & Abidin, 1992).

Attachment from child to parent is measured using 13 items of the Psychological Availability and Reliance on Adult (PARA) (Schuengel & Zegers, 2003). The degree of conflicts (quarrels, irritations and antagonism in the child–parent relationship) was measured with 6-item Network of relationship inventory (NRI) (Furman & Buhrmester, 1985).

The economic evaluation is done by registration of costs in a cost diary based on the Trimbos Institute and Institute of Medical Technology Assessment Questionnaire on Costs Associated with Psychiatric Illness (TiC-P) (Roijen, Straten, Tiemens, & Donker, 2002) and PRODISQ (Koopmanschap, 2005). The registered costs are directly related to health care or indirect health care (out-of-pocket costs, costs of informal care) and direct costs outside health care (monetary value of production losses caused by absence and reduced productivity). The costs will be considered separately from the perspective of mental health and from society. The mental health costs are the costs, which are credited to the mental health care budget, the decision-maker's perspective. The societal costs are the costs of direct (mental) health care as well as indirect costs such as lost productivity, school absent and out-of-pocket costs.

Potential moderators that are analysed are severity of the depression, comorbidity, parental depression and psychopathology and demographic variables. Demographic information is gathered by adding questions about gender, age, ethnicity, education level and family income to the self-report questionnaires.

Three mediators are investigated namely negative automatic thoughts (CNCEQ) (Maric, Heyne, van Widenfelt, & Westenberg, 2011), cognitive emotion regulation (CERQ) (Garnefski, Kraaij, & Spinhoven, 2001) and attribution style (CASQ) (Thompson, Kaslow, Weiss, & Nolen-Hoeksema, 1998). The Cognitive Negative Cognitive Error Questionnaire (CNCEQ) measures cognitive errors namely the underestimation of the ability to cope, personalizing without mind reading, selective abstraction, over generalizing and mind reading. The Cognitive Emotion Regulation Questionnaire (CERQ) measures a broad set

of cognitive emotion regulation strategies which are used in response to the experience of threatening or stressful life events; Self-blame, Other-blame, Rumination, Catastrophizing, Positive refocusing, Planning, Positive reappraisal, Putting into perspective and Acceptance. The Children's Attributional Style Questionnaire (CASQ) is a self-report measure with three dimensions of attribution; internal- external, stable-unstable and global- specific.

Several non-specific treatment variables will be investigated. The client's credibility, expectancy and involvement regarding treatment are assessed with the Parent Expectancies for Therapy Scale (PETS) (Kazdin & Holland, 1991) which was revised for adolescents. Previous treatments for depression, including complementary and self-help treatments, are administered with the inventory of History of Treatments (VEHI) (Bodden & Stikkelbroek, 2010a). Satisfaction with treatment is measured with the Service Satisfaction Scale (SSS) (Bickman et al., 2010). The Cooperation With Treatment scale (CWT) (Tolan, Hanish, McKay, & Dickey, 2002) is used to assess the degree of cooperation with treatment as observed by the therapist. The quality of the therapeutic alliance is assessed with the Therapy Alliance Scale for Adolescents (TASC) (Shirk & Saiz, 1992). The content of treatment is assessed in both conditions with the Therapy Procedure Checklist (TPC) (Weersing, Weisz, & Donenberg, 2002). Treatment integrity will be established by recording two randomly chosen sessions that are observed and rated.

Statistical analyses

Missing values will be imputed. Intent-to-treat as well as completer analyses will be conducted. The effect of the intervention is analyzed with a chi-square test on the dichotomous primary outcome measure, presence of the depression diagnosis (K-SADS-PL). The cost-effectiveness analyses will be based on the comparison of costs and effects in both conditions and will be done according the international guidelines (Ramsey et al., 2005). The cost-effectiveness analyses will be done separately from the perspective of mental health and society over a period of 6 months and 1 year. The effects of societal costs will be expressed in years to live, corrected for quality of life (QALYs). The costs of CBT versus CAU will be expressed in 1) incremental costs per QALY and 2) incremental costs per adolescent with a depression in full remission.

The secondary continuous outcome measures will be analyzed with repeated measures MANCOVA using the pre-test as a covariate as is recommended for an RCT with pre-, post- and follow-up measurements (Rausch, Maxwell, & Kelley, 2003). For each questionnaire, the effect size (Cohen's *d*) from pre- to post-treatment is defined as $(M_{pre} - M_{post})/SD_{pooled}$,

where $SD_{pooled} = [(SD_{pre}^{2} + SD_{post}^{2})/2]$. CBT versus TAU pre-post effect sizes are calculated as follows $[(M_{CBT\ post} - M_{TAU\ post})/SD_{pooled\ post}] - [\ (M_{CBT\ pre} - M_{TAU\ pre})/SD_{pooled\ pre}]$. Furthermore, analyzes will be conducted to establish clinical significance and the reliable change index (Jacobson & Truax, 1991).

Moderators will be analysed by multi-group analyses for dichotomous variables. The continuous variables will be analysed using hierarchic regression analyses. Mediator effects will be analyzed using hierarchical regression analyses and structural equation modelling.

Discussion

As Weisz (Weisz et al., 2006) pointed out, it is not enough to replicate studies to increase our knowledge of effective treatment of adolescent depression. It is necessary to be innovative and to go further and "pushing the boundaries of what has been done" (Weisz et al., 2006). In this study the design is innovative in several regards.

First, the target population consists of referred clinically depressed adolescents and the treatment is conducted within routine mental health care services with routine care professionals, in the Netherlands. Therefore, CBT is investigated under real life conditions.

Second, the control condition is an active condition, namely treatment as usual (TAU) within routine clinical care, not a waiting list condition or just one specific treatment such as medication. TAU being the control condition is a more rigorous test of effectiveness of CBT. As a secondary spin off, the collected data will also enable a detailed description of TAU without CBT.

Third, long term effects of CBT versus TAU will be examined, up to one year post treatment. This is important because of possible sleeper effects (Trowell et al., 2007) and recurrence of depressive symptoms.

Fourth, cost-effectiveness was investigated for a group CBT program "Coping with Stress", but only in adolescents with a subclinical depression and as a prevention program (Lynch et al., 2005). Cost-effectiveness of CBT versus TAU in adolescents with clinical depression to our knowledge is not yet investigated. Also productivity losses have never been taken into account. The cost-effectiveness is of increased importance because of diminishing budgets in mental health care. Perhaps even more important, in this study the costs of clinical depression in adolescents are determined.

Fifth, although it is very important to know why a treatment works and for whom it works, few studies actually addressed this topic. In this study potential mediators and moderators will be investigated.

As a result of the design, we anticipate several problems, which may become limitations of this study if not properly addressed. To ensure the quality of the study, these problems and their solutions, which are undertaken to minimize the limitations, are discussed.

First, content of TAU and the techniques used are difficult to monitor. Assessment of the therapeutic procedures used during each session by the therapist, provides detailed information on the components of the treatment. Also two sessions are recorded at random, observed and rated in detail to assess content of treatment and techniques used.

Second, comparing CBT to an active control condition may lead to a lower mean effect size than CBT versus a non-active control condition (Weisz et al., 2006). The TAU condition in this study is heterogeneous and it contains also evidence-based treatments such as Interpersonal therapy. As a result the ES can be even smaller, so we increased the power accordingly.

Third, to include 140 adolescents within 18 months, cooperation with a large group of mental health institutions is necessary. Furthermore, we try to minimize the effort the adolescent and their parents have to put into the study by using online assessments of the self-report questionnaires, while ensuring secrecy. Since the K-SADS-PL is assessed in vivo, not only self-report, but also observations by an independent clinician are taken into account.

Fourth, non-response may be a huge problem because of the multiple assessments and informants. Online assessment enables the researchers to monitor the progress per assessment per informant. They can react immediately to non-response and increase the response rate accordingly. This transparent logistic process of data collection, data transportation and data file construction reduces the risk of mistakes, missing data and contributes to the quality of the data (Farrell, Kenyon, & Shakur, 2010).

Fifth, as it is not allowed to conduct CBT within the TAU condition it is inevitable that TAU is changed in this regard. This is a methodological problem, which may lead to bias, but cannot be solved properly. Although we are fully aware of this methodological problem we accept it because of the advantages of an RCT in a naturalistic setting. The preferred choice of treatment by the multidisciplinary team for every included depressed adolescent is registered and enables us to take into account the preferred choice of treatment.

Sixth, the total amount of face-to-face contact within TAU can be different from CBT. Also the time period in which the treatment is completed can differ within TAU and CBT. The amount of face-to-face contact in minutes and the time period of the treatment will be taken into account as potential moderating factors.

Acknowledgements of authors' contributions

Yvonne Stikkelbroek designed the study, obtained funding, drafted the initial manuscript, revised the manuscript and approved the final manuscript as submitted. *Denise H. M. Bodden* designed the study, obtained funding, revised the manuscript and approved the final manuscript as submitted. *Maja Deković* designed the study, revised the manuscript and approved the final manuscript as submitted. *Anneloes L. van Baar* designed the study, obtained funding, revised the manuscript and approved the final manuscript as submitted.

Acknowledgements

We would like to thank Gregory Clarke for the permission to make use the CWD-A protocol and Maria Kovacs for her generosity, to let us use the CDI-2. Caroline Braet, Jan Buitelaar, Pim Cuijpers, Carmen Dirksen, Maaike Nauta, Jet Roobol, Mark Reinecke and John Weisz for their comments and help in establishing this study. We are grateful for the contribution of the Mental Health Institutions and their professionals without them this study would be impossible; Accare, Altrecht, Ambulatorium, Bascule, Curium, GGZ-centraal, Herlaarhof, Lentis, Orbis, Perspectief, Praktijk Appelboom, Traverse, and Triversum.

This research is funded by ZonMw – the Dutch Organisation for Health research and Development, grant number 80-82435-98-10117.

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After another half year the functioning of Lisa deteriorated and school results were bad. She could not bear the way she felt and started to drink alcohol frequently and smoked marijuana at times. Her parents were worried but she would not talk to them. They wanted her to seek help for her problems. Lisa was then diagnosed with a Major Depression and was treated with CBT by an experienced therapist. Lisa did not expect much of the treatment. She liked the therapist but found it very difficult to talk about herself. Making homework for the therapy was very hard for Lisa and she failed most of the times. Practicing skills in the sessions made her curious and helped her to understand others and to act differently. Her parents reported that Lisa became more assertive and open. It took Lisa a long time to feel better. She tried to focus on nice things and it helped her to overcome annoying events. If she feels bad nowadays she trusts that it will pass. She does not need to use alcohol or drugs anymore.

Chapter 6

Effectiveness and moderators of individual Cognitive Behavioral Therapy (CBT) versus Treatment As Usual (TAU) in clinically depressed adolescents

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Abstract

Objective: We examined if manualized Cognitive Behavioral Therapy (CBT) was more effective than Treatment As Usual (TAU) for clinically depressed adolescents within routine mental health care.

Method/design: This multisite Randomized controlled trail included 88 clinically depressed adolescents (aged 13 and 21 years). Adolescents were randomly assigned to CBT or TAU. Multiple assessments (pretreatment, post treatment and 6 month follow-up) were done using multiple assessment methods (semi-structured interviews, questionnaires and ratings) and multiple informants (adolescent, parent and therapist). The primary outcome was depressive disorder or dysthymic disorder based on the KSADS. Treatments involved manualized CGT, consisting of 15 sessions, and TAU.

Results: CBT and TAU showed a significant reduction of affective diagnoses at posttest (76% versus 76%) and after 6 months follow-up (90% versus 79%). Intention to treat analyses also showed a significant reduction in self-reported and parent-reported depressive symptoms at post-treatment and at six-month follow-up. No significant differences between both treatments were found in outcome measurements. Except for parent reported externalizing symptoms, which decreased significantly, more in TAU. Discontinuation of treatment and adverse events were more frequent in CBT than in TAU. No prediction or moderation effects were found for age, gender, child and parent educational level, suicidal criteria, comorbidity, and severity of depression.

Conclusion: CBT did not outperform TAU in clinical practice in the Netherlands. Both treatments were found to be suitable to treat clinically referred depressed adolescents.

Introduction

Depression is identified as a rapidly growing epidemic disease that will be the leading cause of the global burden of disease in 2030 (World Health Organization, 2011). Even more worrisome, the highest incidence rate of depression is found during adolescence. Depression is the predominant cause of illness and disability for youth aged 10 to 19 years (World Health Organization, 2011). Depressive disorders are a serious threat for adolescent mental health because of the high prevalence rate (Cohen et al., 1993; Fergusson, Horwood, & Lynskey, 1993; Hankin et al., 1998; McGee et al., 1990), high burden of disease (Hoeymans, Gommer, & Poos, 2006), high suicide risk and high rate of recurrence (J. Curry et al., 2011; Ryan, 2005). In addition, depressed adolescents showed an increased risk for social problems, delinquency, learning problems, substance abuse problems, physical problems, teen pregnancies, as well as for experiencing negative life events and to commit suicide (Goodyer & Cooper, 1993; Portzky & Van Heeringen, 2009; Ryan, 2005). Therefore, it is important that depressive disorders are treated effectively in an early stage (Birmaher, Brent, & AACAP Work Group on Quality Issues, 2007; Ryan, 2005).

Besides medication, Cognitive Behavior Therapy (CBT) and Interpersonal therapy are identified as the psychological treatments of choice (McDermott et al., 2010; National Collaborating Centre for Mental Health (UK), 2005). Different meta-analyses on the effectiveness of a broad range of investigated psychological interventions for adolescent depression showed effect sizes ranging from modest (0.34) (Weisz, McCarty, & Valeri, 2006) to large (1.27) (Lewinsohn & Clarke, 1999). In a meta-analysis solely directed at the effectiveness of CBT in depressed youth, a medium effect size of 0.53 was found (Klein, Jacobs, & Reinecke, 2007). A review of Watanabe and colleagues (2007) showed that 50% of the adolescents is depression diagnosis free after CBT compared to 35% in the TAU condition. Furthermore, a recent network meta-analysis (a novel approach that integrates direct and indirect evidence from randomized controlled studies) showed that CBT was significantly more effective than control conditions in treating depression in youth (including placebo, waitlist, and treatment-as-usual) (Zhou et al., 2015). However, most studies included in these meta-analyses are efficacy studies, conducted in "ideal" and controlled circumstances. Such studies lack generalizability to "real-world" clinical practice, because their samples do not match the complex and severe cases seen in routine mental health care (Weisz et al., 2006).

Although CBT is one of the most intensively studied psychological treatments of which efficacy is repeatedly established against a broad range of control conditions, it is

still unclear if CBT can outperform an active treatment condition within routine mental health care. It is suggested that highly structured and manualized CBT can be beneficial when confronted with complex client conditions (Nilsen, Eisemann, & Kvernmo, 2013). However, the effectiveness of CBT in clinically depressed adolescents referred to routine mental health care still needs to be established.

For this study, the CBT program "Coping with Depression course for Adolescents" (Lewinsohn, Antonuccio, Steinmetz, & Teri, 1984) designed for groups, was translated to Dutch and adapted to an individual version, the "D(o)epression course". (Clarke, Lewinsohn, & Hops, 1990; Stikkelbroek, Bodden, Dekovic, & van Baar, 2013). Several RCT's have repeatedly shown that CWD-A is more effective than inactive control conditions (Clarke, Rohde, Lewinsohn, Hops, & Seeley, 1999; Clarke et al., 2002; Clarke et al., 2009; Lewinsohn, Clarke, Hops, & Andrews, 1990; Rohde, Clarke, Mace, Jorgensen, & Seeley, 2004; Rossello & Bernal, 1999; Rosselló, Bernal, & Rivera-Medina, 2008) and treatment as usual (Clarke et al., 2002; Clarke et al., 2005). When comparing the results of several studies on CWD-A with an active control condition for adolescents diagnosed with a depression, a moderate effect size of 0.35 was found (Cuijpers, Muñoz, Clarke, & Lewinsohn, 2009). CWD-A is regarded as probably efficacious because studies were conducted by only one research group, solely within the American population and not with clinically referred adolescents (David-Ferdon & Kaslow, 2008). Research on clinically referred adolescents is necessary to enhance generalizability to clinical practice.

In addition, knowledge about possible moderators of treatment is desperately needed, but scarce (David-Ferdon & Kaslow, 2008; Weisz et al., 2006). A systematic review of randomized or controlled depression studies concluded that predictors and moderators were investigated in only a few studies (n = 13) since 2000, and outcomes provided little consistent knowledge about moderators (Nilsen et al., 2013). It was concluded that gender, age, comorbidity, externalizing problems did not predict or moderate treatment results in depressed adolescents. Only one study out of 13 investigated ethnicity and found that it predicted drop out, poor response, and slow response. Severity of depression and comorbid anxiety seem to be potential predictors of worse treatment outcome (Nilsen et al., 2013). Another literature review on CBT treatment studies on depressive youth found that treatment outcome was predicted by age, general functioning, and number of diagnoses and moderated by family income and severity of depression (J. Curry et al., 2006). Inconsistency in findings may result from moderator relationships that are specific for one population, one outcome, one treatment or one specific moderator, but do not hold automatically in other circumstances (Kraemer, 2013). Despite this restriction, the

study of potential moderators, such as age, gender, educational level of the child and the parent, suicidal criteria, as well as comorbidity and severity of depression, is relevant within routine mental health care, because it can reveal essential knowledge for the usefulness of CBT in specific populations.

In conclusion, the efficacy of CBT as treatment of clinically depressed adolescents is well-established, but the effectiveness in routine mental health care in comparison to other psychotherapies is not yet clear. Also, potentially important moderators have not been studied in effectiveness trials. In this study, a randomized controlled trial was conducted investigating the effectiveness of the individual CBT program the "D(o)epression course" compared to TAU in a sample of clinically referred adolescents with a Major Depressive Disorder or Dysthymic disorder according to DSM-IV-TR (American Psychiatric Association, 2000). The aims of this study are to investigate the (1) effectiveness and (2) potential moderators (age, gender, educational level of the adolescent and the parent, suicidal criteria, comorbidity and severity of depression) of CBT versus TAU (see Figure 6.1). CBT was expected to be more effective than TAU (without CBT). No specific hypotheses were formulated concerning the moderators due to inconclusive findings on moderators in previous research (J. F. Curry, 2009; Nilsen et al., 2013).

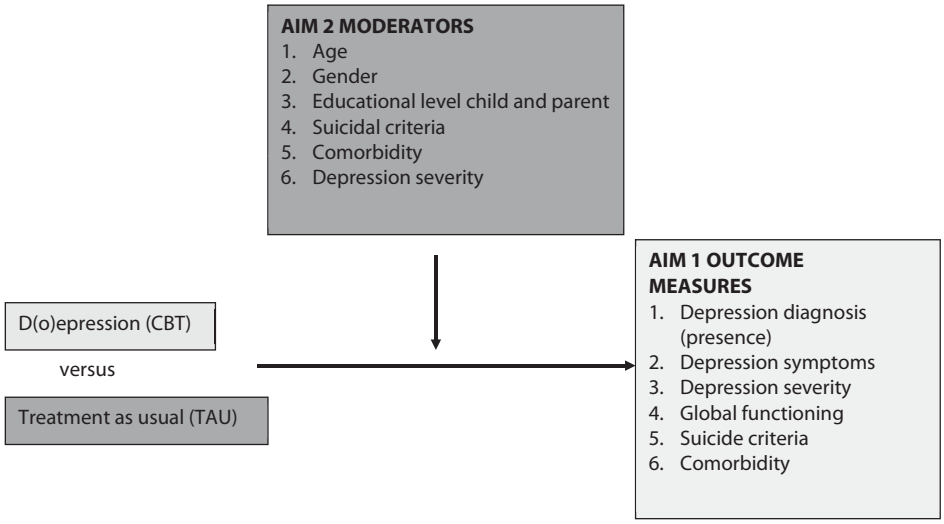

Figure 6.1 Aims and potential moderators evaluated in this study.

Method

Study design

This study was designed as a multi-site (N = 14), randomized controlled clinical trial in which individual CBT was compared to Treatment as usual (TAU). Randomization was conducted after pre-treatment assessment and was executed per adolescent by computer generated block randomization and stratified per mental health care center. The study design is described in detail elsewhere (Stikkelbroek et al., 2013). The study design was approved by the independent Medical Ethics Test Committee (METC) of the Utrecht Medical Centre at Utrecht University, number 10/446. The trial was registered with the Dutch Trial register (NTR) number 2676.

The following assessments took place; prior to treatment (pretreatment assessment), within treatment (mediator assessments), immediately after treatment or after 15 sessions (post-treatment assessment), 6 months after treatment (6-month follow-up) and 1 year after treatment (1 year follow-up). In this paper, we will present the post treatment and 6 months follow-up results. Assessments were multi-method (semi-structured interviews, questionnaires and ratings) and involved multiple informants (adolescent, parent and therapist). Semi-structured interviews were conducted by independent research assistants who were blind to condition. Questionnaires were completed online using Survalyzer (an online questionnaire server) at home by the adolescent and the parents using a separate login code to secure privacy. The therapist completed the questionnaires at the office.

The primary outcome measure was depression diagnosis based on the semi-structured diagnostic interview, the Kiddie-Schedule for Affective Disorders and Schizophrenia, present and lifetime version (Lauth et al., 2010). Secondary outcomes included depressive symptoms, comorbidity, suicide criteria, global functioning and severity of depression.

Based on previous research an effect size (Cohen's d) of 0.53 was expected (Klein et al., 2007). Power calculations indicated that 70 adolescents per condition (assuming an alpha of 0.05, a statistical power, 1-beta, of 0.80 and a drop-out of 20%; power calculations in STATA) would be required to detect a difference in depression diagnosis.

Sample characteristics

In total 103 referred clinically depressed adolescents aged 12 to 21 and their parents (n = 71) were included in this study between 2011 and 2014. For a presentation of patient flow through the trial, see Figure 6.2.

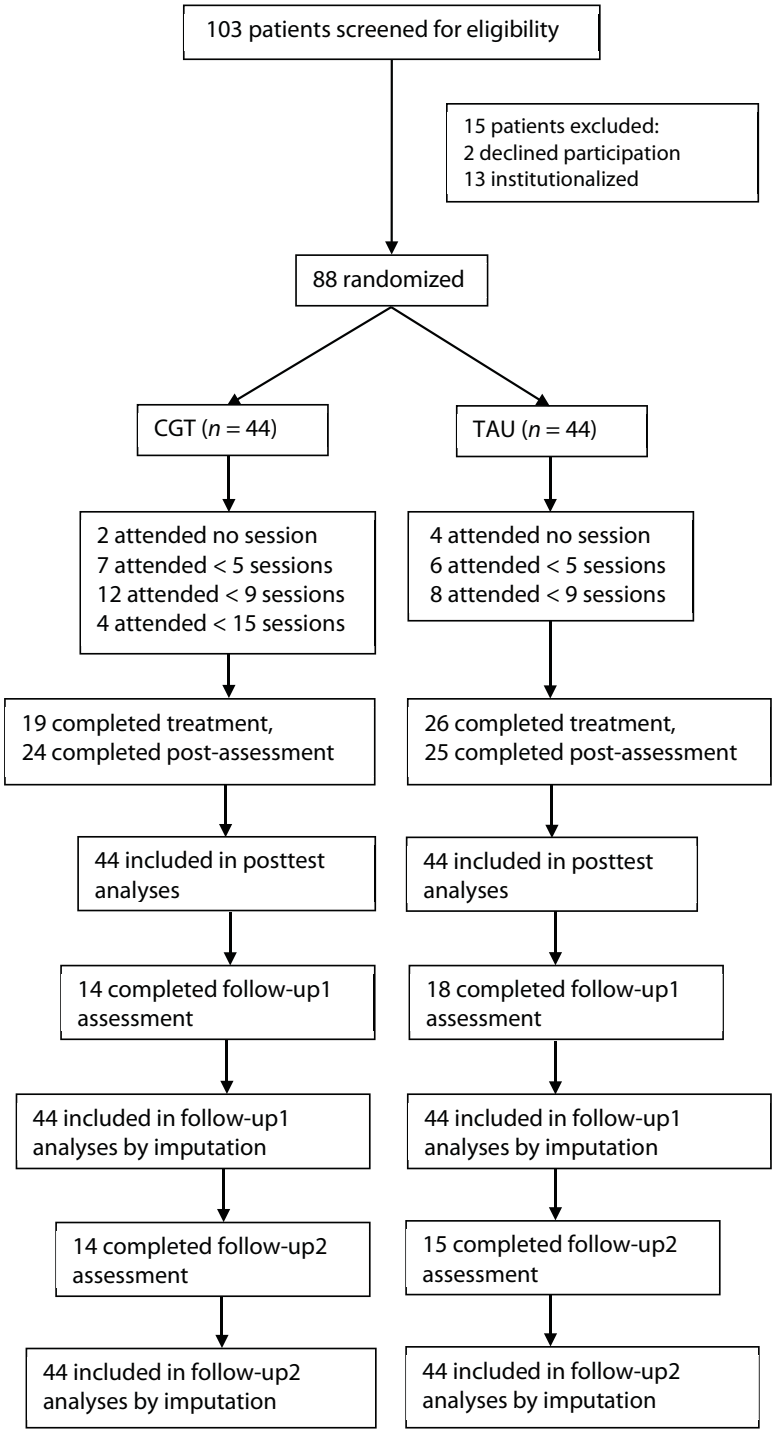

Figure 6.2 Participants flow chart.

The participants were recruited from 14 different public mental health clinics geographically spread out over the Netherlands, from December 2011 to December 2014.

Sample characteristics are shown in Table 6.1 and based on pre-treatment data. The mean age of the participants was 16.6 years (*SD* = 2.1) and 71% was younger than 18 years. Most participants (92%) were of Dutch origin and 2.3% of other European countries, 1.4% of Iran, 1.4% African and 2.9% unknown. The majority (82%) of the adolescents was female.

Participation of parents was not always possible because some adolescents (n = 14) above the age of 18 did not consent to the involvement of parents in the treatment or in the study (n = 14). We included the parent who filled out most questionnaires during the study and had the most complete assessments. In total 71 parents were included, of which

Table 6.1 Sample characteristics at baseline and pre-treatment comparison between CBT and TAU

Characteristics at baseline	*n*	CBT	*n*	TAU	Test statistic
Female, *n* (%)	44	34 (77.3)	44	38 (86.4)	$\chi^2 = 1.22$
Age, mean (*SD*)	44	16.9 (2.2)	44	16.3 (2.0)	$t = -1.27$
Dutch nationality, *n* (%)	41	39 (95.1)	43	42 (97.7)	$\chi^2 = 0.40$
Education level parents, *n* (%)	35		32		$\chi^2 = 16.73$**
Primary education		1 (2.9)		0 (0.0)	
Secondary education		0 (0.0)		7 (21.9)	
Low level		14 (40.0)		9 (28.1)	
Middle level		18 (51.4)		10 (31.3)	
High level		2 (5.7)		6 (18.7)	
University					
Education level children, *n* (%)	37		40		$\chi^2 = 4.22$
Secondary education					
Special education		2 (5.4)		1 (2.5)	
Middle level		16 (43.2)		14 (35.0)	
High level		17 (46.0)		24 (60.0)	
University		2 (5.4)		1 (2.5)	
History of mental health service use, mean (*SD*)	35	2.8 (0.7)	40	2.7 (0.6)	$t = -1.20$
Depression (CDI-II child version) mean (*SD*)	34	27.1 (8.7)	36	24.1 (6.7)	$t = -1.62$
Depression (CDI-II parent version), mean (*SD*)	28	26.9 (8.0)	29	24.8 (6.4)	$t = -1.11$
Depression severity (CGI-S) mean (*SD*)	37	4.16 (0.9)	37	3.92 (1.3)	$t = -0.95$
Global functioning (CGAS), mean (*SD*)	37	4.5 (3.9)	40	3.6 (3.2)	$t = -1.19$
Suicide risk (SRT), mean (*SD*)	37	49.5 (9.7)	35	49.4 (8.1)	$t = -0.08$
Number comorbid diagnoses, mean (*SD*)	41	0.83 (1.09)	44	1.25 (1.82)	$t = -1.28$

Note. CDI-II = Child Depression Inventory-II; CGAS = Children Global Assessment Scale; SRT = Suicide Phenomena Assessment; CBT = Cognitive-Behavioral Therapy; TAU = Treatment as Usual.
* $p \leq .05$, ** $p \leq .01$.

10 had a child aged 18 or above. All participating parents were biological parents, their mean age was 48.4 (*SD* = 5.3) and 18.6% (*n* = 11) was father.

An experienced psychologist within the mental health center screened adolescents and parents with the CDI-2, informed the adolescents and their parents about the study. After written informed consent by the adolescent and his/her parents, a trained independent research assistant carried out the semi-structured diagnostic interview and checked whether the adolescent met the inclusion and exclusion criteria. The inclusion criteria were: (1) a primary diagnosis of Major Depressive Disorder or Dysthymic disorder, (2) age 12 to 21 years, and (3) referred to one of the participating mental health care institutions. The exclusion criteria were (1) acute suicide risk (2) substance abuse, pervasive developmental disorder, or bipolar disorder which required a different treatment approach (3) day care or admission to an inpatient clinical setting and (6) not fluent in Dutch, Turkish, Arabic or Berber language. If medication (for the depression or another disorder) was used in the CBT condition, the dosage at pre-treatment was kept constant during the intervention. If the adolescent was 18 years or older, parents were only approached after the adolescent's permission.

Interventions

CBT. The experimental treatment consisted of the D(o)epression course (Stikkelbroek, Bouman, & Cuijpers, 2005), which is an individual CBT protocol based on the CWD-A (Clarke et al., 1990). This treatment consisted of weekly sessions of 45 minutes with the adolescent. By the end of treatment a meeting with the parent(s) was scheduled to evaluate the treatment.

In line with the CWD-A, the D(o)epression course is based on the social learning theory which explains the etiology of depression and was developed by Lewinsohn and colleagues (1984). This theory states that there is a connection between the number of positive interactions between a person and his environment on one hand, and depression on the other. A triggering event such as a stressful life event may cause a negative spiral of less positive interactions, which in turn leads to more negative thoughts and a deteriorating depressed mood. The intervention aims to reduce depressive complaints in adolescents with a depressive disorder. The focus of the intervention is broad, since depressive episodes are considered to be multi-factorially determined. The intervention contains representative CBT components (McCarty, Weisz, & Hamilton, 2007; Weersing, Rozenman, & Gonzalez, 2009) namely: psycho-education (information about depression and the rationale for the etiology of the complaints and the treatment of them), setting attainable goals (translate

large goals into realistic short term goals), self-monitoring (registration of the mood, activities and thoughts), activation (planning frequent, joyful activities), improving social skills and communication skills (improvement and stimulation of social behavior), relaxation techniques, cognitive restructuring (identifying and changing unrealistic negative thoughts about the self, others and events), role play and problem solution skills (teaching the creation of solutions for problems via brainstorm, choosing, trying and evaluating) and relapse prevention. Exercises and homework were used to incorporate new skills and generalize them into daily life. The parents received psycho education and information on CBT after session three and nine.

Treatment integrity was enhanced, by a standardized training in delivering the D(o)epression course and routine intervision and supervision within the mental health care center by a senior CBT therapist. Supervision by an expert in conducting treatment with this manual was given on demand within the mental health center by a registered and experienced psychotherapist.

The control treatment consisted of TAU for clinical depression delivered by qualified therapists specialized in different therapies. TAU within public child mental health care consists of a broad range of different treatments: Interpersonal Therapy (IPT), family therapy, parent counseling, medication, mindfulness training, acceptance commitment therapy (ACT), psychodynamic therapy (short duration), (non-directive) counseling, creative therapy and running therapy, and CBT. However, in this study, CBT was not allowed within TAU. TAU treatment could continue after 15 sessions.

To enhance external validity, all sessions took take place within routine outpatient care in public mental health care institutions.

Treatment integrity was established by rating video and audio recordings of two randomly chosen sessions per treatment. Two trained psychologists did ratings. A treatment integrity scale was developed containing three factors, namely quality of the therapist (e.g. empathy, motivating client, instigating interaction, avoiding depressive talk), content of treatment (e.g. following protocol, attaining goals, instigate exercise like role play, modeling, providing feedback) and structure of the session (e.g. setting agenda, following time schedule, efficient use treatment time). Items were rated on a three-point scale (0 = absent, 1 = minimal, 2 = largely, 3 = maximal). Interrater reliability was established by rating the same sessions (n = 8) by the observers and a supervisor specialized in this protocol. The Intraclass Correlation Coefficient (ICC) was .92, which indicates excellent interrater reliability. The mean score on the treatment integrity was 2.68 (*SD* = 0.75).

Therapists

All treatments were delivered by psychologists with at least one year of experience within professional mental health care and CBT. Therapists were not allowed to conduct treatments in both conditions.

In the CBT condition, 37 therapists participated and in the TAU condition, 37 other therapists participated. Their mean age was 42.78 (*SD* = 11.47), 68.2 % was female, most (98.6%) were white Caucasian and had on average 16.3 (*SD* = 7.16) years of experience. No differences were found on these therapist characteristics between both conditions.

The therapists within the CBT condition were in general CBT oriented (*n* = 27, 72.97%), eclectic (*n* = 9, 24.3%) or cognitive oriented (*n* = 1, 2.7%). Of these therapists, nine (23.4%) were registered as a CBT therapist. The therapists in the CBT condition received a two day training in delivering the D(o)epression course by the first author.

The overall orientation of TAU therapists was eclectic (*n* = 12, 32.4%), cognitive (*n* = 12, 32.4%), psychodynamic (*n* = 9, 24.3%), family based (*n* = 2, 5.4%) or they had another orientation (*n* = 2, 5.4%). Therapists in the TAU condition did not have CBT as a primary orientation of treatment.

Instruments

The *primary outcome measure* was presence of a major depression or dysthymic diagnosis, assessed by a semi-structured diagnostic interview, the Kiddie-Schedule for Affective Disorders and Schizophrenia, present and lifetime version (K-SADS) (Kaufman et al., 1997; Reichart, Wals, & Hillegers, 2000). The K-SADS assesses a wide range of diagnoses (present and life time). The view of the adolescent, the parent and the independent clinician were taken into account in the final diagnosis, expressed as diagnosis present (yes) or absent (no). In previous research, the concurrent and convergent validity of the KSADS was supported (Kaufman et al., 1997; Lauth et al., 2010), the interrater agreement was high (range: 93% to 100%) and test–retest reliability alpha coefficients were excellent (.77 to 1.00) (Kaufman et al., 1997).

As *secondary outcome measures* depressive symptoms, severity and global functioning, suicide criteria, and comorbidity were used.

The *degree of depressive symptoms* was measured by means of self-report using the Child Depression Inventory-II (CDI-2-C) (Bodden, Stikkelbroek, & Braet, 2010; Kovacs, 2011). The CDI-2 is a revision of the CDI (Braet & Timbremont, 2002; Kovacs, 1992), which was translated in Dutch (Bodden et al., 2010). The CDI-2-C consists of 28 items,

which assess cognitive, affective and behavioral symptoms of depression in the past two weeks. Each item has three graded alternatives of which one is chosen (e.g., "0 = I feel like crying once in a while, 1 = I feel like crying many days, 2 = I feel like crying every day"). Higher scores reflect more depressive symptoms. The reliability of the CDI-2-C total score was good in the current study (α = .82).

The CDI-2 also provides a parent version (CDI-2-P) (Kovacs, 2011), which contains 17 items. Parents have to indicate how often the adolescent has experienced cognitive, affective and behavioral symptoms in the past two weeks on a Likert scale ranging from 0 (not at all) to 4 (most of the time). The reliability of the total scale in de current study was good (α = .78.).

The *severity of depression* was rated by the therapist on the one item Clinical Global Impression-severity scale (CGI-S) with a scale range from 1 (no complaints) to 7 (most severe depressive complaints) (Guy, 1976).

Global functioning of the adolescent was assessed by the therapist on the Children Global Assessment Scale (CGAS) (Bunte, Schoemaker, & Matthys, 2010; Shaffer et al., 1983). The therapist rated the overall quality of functioning of the adolescent in several contexts namely at home, at school, with friends and during leisure time. The scale contains one item and the scores range from 0 (extremely impaired functioning) to 100 (very good functioning).

Suicide criteria are assessed with the Suicide Criteria Assessment (SRA). The scale was constructed based on the Suicidal Ideation Questionnaire (Reynolds, 1987) and the Columbia-Suicide Severity Rating scale (Posner et al., 2011). The scale contains five questions including "I thought about killing myself" or "I thought about planning to kill myself". These questions tap into different aspects of suicidal criteria such as the frequency of thoughts, wishes, plans and urges to perform action within the past two weeks on a scale from 0 (not at all) to 2 (nearly every day). The reliability of the SRA is good (α = .89).

Comorbid psychopathology was assessed on two levels namely on diagnosis level with the K-SADS (present or absent) and on symptom level with Youth Self Report scale (YSR) for adolescents and the Child Behavior Check List (CBCL) for parents (Achenbach, 1991; Verhulst, van der Ende, & Koot, 1996). The YSR and CBCL use a three point Likert scale (0 = not true, 1 = somewhat or sometimes true, and 2 = very true or often true). A higher score indicates more symptoms of psychopathology. The YSR and the CBCL allow a distinction between internalizing and/or externalizing psychopathology and specific psychopathological problems (such as affective problems, anxiety problems, somatic problems, attention deficit/hyperactivity problems, oppositional defiant problems

and conduct problems). Reliabilities for the YSR externalizing problems (α = .86) and internalizing problems (α = .79) were good, as were the reliabilities of the CBCL scale for externalizing (α = .85) and internalizing (α = .87) problems.

Demographic information was gathered by questions about age, gender, ethnicity, education level and family income.

Statistical analysis

All missing values were imputed at item and assessment level, except for the semi-structured interview. Imputations were generated in R version 3.2.1 (R Core Team, 2015) with package MICE version 2.22 (Buuren & Groothuis-Oudshoorn, 2011). The imputation routine was tailor made to the analysis problem and the predictor matrix and imputation method are optimized for efficiency. Initially, for each incomplete variable, the 10 best predictors were selected. Where needed, this selection has been extended to conform to make the imputation model compatible to the analysis model. The experimental condition was always included as a predictor. Ten imputed datasets were generated with 25 iterations for the algorithm to converge.

Predictive mean matching (Little, 1988) was used as the imputation routine for continuous and categorical data. Predictive mean matching draws imputation from the observed data and is known to preserve patterns and relations that are present in the data (Vink, Frank, Pannekoek, & Buuren, 2014). Variables that contain bonafide missings, such as items that are not applicable for a particular respondent, were imputed with a custom adaptation of predictive mean matching. The analyses were pooled based on Rubin's rules (Rubin, 2004) following the work from (Li, Meng, Raghunathan, & Rubin, 1991). Intent-to-treat as well as completer analyses were conducted on the secondary measures.

Pre-treatment differences were analyzed with chi-square tests for dichotomous variables and *t*-test for continuous variables. Within group effects were examined by looking at the percentage of adolescents that did not meet all criteria of the depressive or dysthymic disorder as indicated by the K-SADS. Continuous variables were analyzed using paired *t*-tests. To calculate the effect sizes within the conditions, the formula described in Dunlap, Cortina, Vaslow, and Burke (1996) was used. The criteria used to interpret the effect sizes were: .10 is small, .30 is medium and .50 is a large effect (Field, 2009). Clinical significance was established by examining the percentage of adolescents falling below the clinical cut-off score (14) of the CDI-2 for the adolescent version and 17 for the parent version (Kovacs, 2011).

Between group effects were analyzed with chi-square tests on the percentages of adolescents that did not meet all criteria of the depressive or dysthymic as indicated by the K-SADS. Between group effects for continuous variables at post-treatment and follow-up1 were conducted, using ANCOVAs with pre-treatment scores as a covariate to control for pre-treatment differences, as recommended (Rausch, Maxwell, & Kelley, 2003; Vickers & Altman, 2001). TAU versus CBT effect sizes were computed as described by Hedges and Olin (2014) using a statistical software package named Comprehensive Meta-analysis, version 3.3.070.

Moderation was analyzed by multi-group analyses for dichotomous variables and linear regression analyzes for adolescent or parent reported continuous variables. Moderation was studied by separate linear regression analyses for condition on adolescent or parent reported depressive symptoms at post-treatment and at follow-up1 while controlling for pre-treatment depressive symptoms and adding a potential predictor and the interaction variable. The tested potential predictors and moderators were adolescent age, adolescent gender, adolescent and parent education level, suicidal criteria, adolescent and parent reported comorbid externalizing problems, and therapist rated depression severity.

Results

Sample

The level of depressive symptoms reported by the adolescent (N = 70) at pre-treatment was high (M = 25.6; SD = 7.8), considering the cut-off score (14) participants fell high above the level of clinical significance (Kovacs, 2011). More than half of the participants had at least one-comorbid diagnoses (56%, n = 49). Most frequent disorders were Social phobia (n = 21, 25%), Generalized Anxiety Disorder (n = 23, 27%), Specific Phobia (n = 7, 8%), Panic Disorder (n = 5, 6%), Separation Anxiety Disorder (n = 4, 5%), Post-Traumatic Stress Disorder (n = 6, 7%), Attention Deficit Disorder (n = 11, 13%) and Oppositional Defiant Disorder (n = 3, 4%). On the K-SADS, 72% reported thinking about death and 58% about suicidal ideation. Half of the sample had previous experience with mental health services (53%).

Pre-treatment differences are reported in Table 6.1. Groups did not differ significantly in gender, age, ethnicity, history of mental health care use, inter- or externalizing problems (YSR/CBCL), depressive symptoms (CDI-2), pre-treatment number of diagnoses (K-SADS), suicide criteria (SRT), global functioning (CGAS) or severity of depression

(CGI-S). The chi-square test showed that only parental level of education in the CBT condition was significantly higher than in the TAU condition. Overall, randomization can be viewed as succeeded.

Treatment received

The number of treatment sessions in both conditions between pre- and post-treatment assessment was not different (M_{TAU} = 12.8, *SD* = 5.5; M_{CGT} = 12.7, *SD* = 4.8). At pre-treatment, 9% of the adolescents in the CBT condition and 13.6% in the TAU condition already received antidepressants. Treatments conducted within TAU were eclectic 40.9% (*n* = 18), IPT 25% (*n* = 11), Eye Movement Desensitization and Reprocessing 11.4% (*n* = 5), Solution focused therapy 2.3% (*n* = 1), Family therapy 2.3% (*n* = 1), group counseling 2.3% (*n* = 1), medication only 2.3% (*n* = 1) and some did not start treatment 13.6% (*n* = 6). Within the TAU condition 11% (*n* = 5) changed to treatment with medication only during treatment.

Drop-out and adverse events

In CBT more adolescents (57%, *n* = 25) dropped out of treatment compared to TAU (41%, *n* = 18) but not significant on a chi-square test. Different reasons led to discontinuation of treatment. In TAU, the reasons for discontinued treatment were elevation of depressive symptoms (38.8%, *n* = 7), lack of motivation (33.8%, *n* = 6), and reason unknown (27.7%, *n* = 5). In the CBT condition, discontinuation of treatment occurred because of change to another psychological intervention (28%, *n* = 7), reason unknown (24%, *n* = 6), elevation of depressive symptoms (20%, *n* = 5), change to medication (16%, *n* = 4) and lack of motivation (12%, *n* = 3).

Adolescents who discontinued CBT or TAU treatment did not differ on gender or education level. However, an independent-samples *t*-test showed a significant higher level of pre-treatment depressive symptoms on the CDI-2 in the CBT participants who discontinued treatment (M_{CGT} = 29.3, *SD* = 9.0) compared to participants that discontinued TAU (M_{TAU} = 22.9, *SD* = 6.9), $t(29) = -2.2$, $p = .04$, partial eta squared = 0.4).

Three adverse events occurred in the CBT condition (and none in the TAU condition), that is two suicide attempts (4.5%) before session 5, and one participant committed suicide (2.2%) between follow-up1 and follow-up2, after a therapist and parents observed good response to CBT and a maintenance dosage of medication as recommended by the Dutch clinical guidelines (Buitelaar et al., 2009).

Treatment effectiveness

Primary outcome. Within the CBT condition, 73% (n = 16) of the adolescents did not meet criteria for depressive or dysthymic disorder on the K-SADS at post-treatment, this percentage increased to 88% (n = 14) at 6 months follow-up. Within the TAU condition, these percentages were 81% (n = 21) and 77% (n = 13) respectively.

Secondary outcome. Paired-samples t-tests, two sided, were conducted to measure change within the CBT and TAU condition on secondary outcome measures reported by adolescent, parent or therapist and between pre- and post and pre and follow-up1 assessment.

A statistically significant decrease was found on depressive symptoms (CDI-2) reported by the adolescent within both conditions, respectively within the CBT condition pre-post ($t(96) = 5.9$, $p < .001$) and pre- to follow-up1 ($t(54) = 9.2$, $p < .001$) and the TAU condition pre-post ($t(39) = 4.06$, $p < .001$) and pre-follow-up1 ($t(34) = 8.14$, $p < .001$). The effect sizes varied from moderate to large, see Table 6.2. Also a clinically significant reduction in depressive symptoms (below the cut off score on the CDI-2) at post-treatment was reached in 41.6% (n = 18) of the cases within the CBT condition and 31.8% (n = 14)

Table 6.2 Within and between condition pooled pre-treatment and pre-follow-up1 effect sizes (*g*) for Adolescent (*n* = 88) and Parent (*n* = 88) Questionnaires

	Pre-treatment			Pre-6-month follow-up		
Scale	CBT (*g*)	TAU (*g*)	CBT-TAU (*g*)	CBT (*g*)	TAU (*g*)	CBT-TAU (*g*)
CDI-II-C	0.92***	0.69***	0.20	1.37***	1.37***	0.09
CDI-II-P	0.47**	0.71**	-0.18	0.91***	1.15***	-0.15
YSR INT	0.70***	0.83***	0.01	1.31***	1.22***	0.15
YSR EXT	0.19	0.34	-0.25	0.96**	0.60**	-0.17
CBCL INT	0.10	0.55**	-0.55	0.67***	1.00***	-0.32
CBCL EXT	0.05	0.11	-0.29	0.09	0.44*	-0.29
SRT	0.48**	0.26	0.08	0.05***	1.13***	-0.40
CGAS[a]	0.58**	1.07***	-0.27	-	-	-
CGI-S[a]	0.77**	1.14***	-0.26	-	-	-

Note. CDI-2 = Child Depression Inventory II; C = child report; P = Parent; YSR = Youth Self Report scale; INT = internalizing problems; EXT = externalizing problems; CBCL = Child Behavior Check List; SRT = Suicide Phenomena Assessment; CGAS = Children Global Assessment Scale; CGI-S = Clinical Global Impression-severity scale; CBT = Cognitive-Behavioral Therapy; TAU = Treatment As Usual.

[a] No 6-month follow-up measurement of the CGAS and CGI-S.

* $p < .05$, ** $p < .01$, *** $p < .001$.

within the TAU condition. At follow-up1, 61.4% (n = 27) within the CBT and 47.7% (n = 21) within the TAU condition had a CDI-2 score below the clinical cut-off score.

Internalizing symptoms (YSR) reported by the adolescent were also significantly reduced within both treatments, respectively within the CBT condition pre-post ($t(62)$ = 4.56, $p < .001$) and pre- to follow-up1 ($t(44) = 7.66$, $p < .001$) and TAU condition pre-post ($t(61) = 4.53$, $p < .001$) and pre-follow-up1 (t (46) = 5.96, $p < .001$).

Parents also reported a significant decrease in adolescent depressive symptoms within the CBT condition from pre to post ($t(21) = 3.48$, $p = .002$) and pre to follow-up1 ($t(15) = 5.99$, $p < .001$), with a moderate and large effect size respectively. A significant decrease was also found within the TAU condition, pre-post ($t(18) = 3.81$, $p = .001$) and pre-follow-up1 ($t(22) = 7.22$, $p < .001$), with large effect sizes. A clinically significant reduction at post-treatment was reached in 35.9% within the CBT condition and 39.8% within the TAU. At follow-up, 52.5% within CBT and 61.81% within TAU condition had a CDI-2 score below the clinical cut-off score.

Ratings from the therapist showed that depression severity decreased while global functioning of the adolescent increased from pre to post-treatment, with large effect sizes within both conditions.

Comorbid suicide criteria reported by the adolescent within CBT ($t(132) = 2.97$, p = .004) dropped significantly at post treatment but not in the TAU condition. At follow-up1 within both conditions a decrease in suicide risk was found, respectively CBT ($t(48) = 4.55$, $p < .001$) and TAU ($t(243) = 5.79$, $p < .001$). Comorbid externalizing problems reported by the adolescent decreased significantly from pre- to follow-up1, within CBT ($t(38) = 2.98$, $p = .005$) as well as in TAU($t(130) = 3.34$, $p = .001$). Only parents in the TAU condition reported a significant decrease of externalizing symptoms from pre to follow-up1 ($t(13)$ = 2.46, $p = .021$), so parents in the CBT condition reported no significant change.

Effectiveness of CBT versus TAU

Primary outcome

Intent to treat analyses were performed. Chi-square tests were done to measure differences in the percentage of adolescents who did not meet all the criteria for depressive or dysthymic disorder. No significant difference was found between TAU and CBT at post-treatment, $\chi^2(1) = 0.44$, $p = .509$ nor at follow-up1, $\chi^2(1) = 0.11$, $p = .743$. Treatment completer analyses ($N_{TAU} = 23$, $N_{CBT} = 19$) showed the same results.

Secondary outcomes

Between groups comparisons were conducted, using ANCOVAs with pre-treatment scores as a covariate, see Table 6.2. No main effect of condition was found on self-reported and parent reported depressive symptoms at post-treatment, nor at follow-up. The effect sizes for pre-post and pre-follow-up1 scores between the conditions were respectively small and very small, see Table 6.2. Also, no main effects of condition were found at post-treatment or follow-up1 on the following variables; adolescent and parent reported internalizing and externalizing symptoms, adolescent reported suicide criteria, therapist rated depression severity and therapist rated global functioning. Effect sizes varied between almost zero for adolescent reported internalizing problems at post-treatment to moderate (0.55) for parent reported internalizing problems at post-treatment.

Predictors and moderators

Potential predictors and moderators were analyzed with linear regression analyses. The following variables were included: adolescent age, adolescent gender, adolescent and parent education level, suicidal criteria, adolescent and parent reported comorbid externalizing problems, and therapist rated depression severity. No significant predictors or moderators were identified.

Discussion

In this study, CBT was compared to an active treatment condition namely TAU, under rigorous conditions within routine care institutions and with a referred clinical sample of adolescents diagnosed with depression or dysthymia. Results can be summarized as follows. Both treatments showed a significant increase of the percentage of adolescents who did not met the criteria for a depressive or dysthymic disorder and a significant decrease of self-reported and parent reported depressive symptoms with large effect sizes. There were no significant differences on depression diagnosis level nor on adolescent and parent reported depressive symptom level between the two conditions at post-treatment or at follow-up 6 months after treatment. Also, no significant differences were found between CBT and TAU on adolescent reported externalizing comorbid symptoms, suicide criteria, therapist reported depression severity and global functioning. More adverse events occurred in CBT compared to TAU. No predictors or moderators of treatment were found for age, gender, educational level adolescent and parent, comorbidity and severity of depression.

The finding that treatments in both conditions showed a decrease in number of depression diagnoses and clinical significant symptom reduction in this specific sample is reassuring.

The outcome of CBT treatment in a large RCT, Treatment Adolescent Depression Study (TADS), conducted with a community recruited sample (n = 327) was found to be less when severity of depression and comorbidity were high (Curry, 2009). This could implicate that the outcome of treatment of a more complex sample would be less but we found a large effect size (ES = 0.92) at post-treatment for CBT.

We hypothesized that CBT would outperform TAU, but it did not. Previous research showed that the efficacy of the treatment group manual CWD-A versus TAU was established in several RCT's (n =3) (Cuijpers et al., 2009). However, the finding of this study is in line with the results of a recent meta-analysis showing that evidence-based protocols did not outperform usual care in clinically referred samples or in youths with a diagnosis, including depression (Weisz et al., 2013).

Several explanations for these contradictory findings can be given. *First*, in our study, the control condition was TAU. In general, the quality of TAU is considered an important influential factor on the results of a RCT and specifically for effectiveness of CBT (van de Wiel et al., 2007). In our study, TAU had a high quality. The therapists who performed TAU treatments in this study were highly qualified and were experienced in tailoring the treatment to the individual's needs. Furthermore, the TAU consisted of a substantial amount of evidence-based treatments for depression, for instance IPT and anti-depressant medication or a combination of both. It is known that CBT does not outperform these evidence-based treatments. For example, CBT did not outperform IPT (Zhou et al., 2015) and medication outperformed CBT as acute treatment (March et al., 2007). Besides, TAU in routine mental health care is also considered to be a stronger standard to test manualized protocols against than other control conditions (Weisz et al., 2013).

Second, the treatment dose could not be kept equal in both conditions after post-treatment. Some TAU treatments continued after 15 sessions in contrast to the CBT treatment, which ended after 15 sessions. Continuation of CBT after 15 sessions was a reason to drop-out of the study. It is possible that TAU needed more sessions to reach the level of decrease in depressive symptoms between post-treatment and follow-up after 6 months was possibly due to extra sessions. Another possibility is that the amount of reduction in depressive symptoms could partly be due to a natural course of depression in participants in both treatment conditions. Spontaneous reduction of depressive symptoms can occur even without treatment after 8 months, the mean duration of a major depressive disorder (Birmaher et al., 2007).

Third, the amount of comorbid diagnoses was substantial in both conditions and interfered with CBT treatment delivery. In this study, the CBT manual did not allow adaptations to address comorbidity. In the TAU condition the therapists were free to treat comorbid diagnoses, next to treating the depression. The content of TAU treatments compared to CBT may target behavior problems, which may be related to irritable mood as a characteristic of depression and therefor important to the treatment of depression. For example, parents in the TAU condition reported a significant decrease of externalizing symptoms at post-treatment and parents in the CBT condition did not.

Furthermore, one-third of the adolescents discontinued CBT treatment and changed to another psychological treatment. TAU seemed better equipped to address comorbidity by adding other psychological treatment elements. Previous research found that the highly flexible CBT treatment containing different components used in the TADS study did not result in a better response rate namely 48% after 12 weeks and 65% after 18 weeks on the CGI-I (March et al., 2007). However, discontinuation of CBT treatment in the TADS study was much lower than in the present study namely 15% after 12 weeks and 19% after 18 weeks. Probably a tradeoff between inflexibility and discontinuation is inevitable.

Fourth, another explanation is the adaptation of the group based manual of CWD-A into an individual based manual without any peer interaction which could influence effectiveness. Group treatments are considered to work better than individual treatment in depressed teens (Weersing et al., 2009).

Since there were no differences on effectiveness, we still need to determine which treatment a therapist should be used when dealing with adolescent depression. There are several factors that can be viewed within this decision making.

Besides effectiveness, this study examined possible moderators of treatment, which could be indicative of selecting a specific treatment for a specific patient. Search for moderators is important in order to identify sources of individual differences in treatment response and guide differential treatment selection. No effect of moderators was established and thereby no specific group who benefited from CBT could be identified. The sample size may be accountable for this result (Curry, 2009). Apart from sample size another statistical reason should be considered. Kraemer (2013) pointed out that research on a heterogeneous population with major individual differences is more likely to find moderators with a sensitive measure for individual differences (Kraemer, 2013; Nilsen et al., 2013). The group within this study was rather homogeneous in regard to demographics and diagnoses.

Apart from moderators, cost-effectiveness of different treatments could also be a factor to take into account when a therapist chooses a specific treatment. The cost effectiveness of CBT versus TAU will be presented in a forthcoming paper and was not further examined at this paper.

Also, speed of symptom reduction within both conditions can be relevant for the selection of treatments. Depression in adolescents should be treated as soon as possible and aggressively in order to shorten the depressive period (Buitelaar et al., 2009). Reduction of the time to response has the potential to diminish the risk on suicide, functional impairment, substance abuse and problems at school and work as much as possible (Kratochvil et al., 2006). In future research, trajectories of treatment response should be analyzed.

Future research should also address mediators of outcome in CBT and TAU. For instance, reduction of negative thoughts by cognitive restructuring may mediate the relation between pre and post treatment depressive symptoms in the CBT condition.

A finding of serious concern was the high level of self-reported depressive symptoms at the time of referral. Of the adolescents 53% already received treatment before entering the mental health center. Although mental health treatment of children under 18 is free of charge in the Netherlands, a significant amount of depressed adolescents only sought treatment when depression was already severe. The dissemination and organization of effective treatment still needs attention to reach out to depressed adolescents in time.

This study also has several limitations. *First*, our sample size was not as big as was advised by our power calculation. We included 88 adolescents while the power calculation recommended 140 adolescents. Also, the effect size of TAU in the Netherlands was larger than TAU in studies conducted in other countries on which the power calculations were based. As a result the power of the study was not as high as preferred.

Second, the content of TAU was more difficult to monitor than expected. TAU therapists were instructed not to conduct CBT elements in TAU treatment. The therapists did not complete the assessments that monitored the use of therapeutic procedures as much as expected. Thereby, the use of CBT elements could not be ruled out for 100% and a more detailed description of TAU was not possible.

Third, the amount of participants with a low education level or with a different ethnic background was small. Even though this is representative for the population in youth mental health care in the Netherlands, the generalization of the findings is limited to this particular group.

Fourth, even if adolescents and parents decided to participate in the study they are hesitant to participate in the assessments. Although assessments were conducted online and were easy to monitor and to react to non-response it was difficult to reach full response by all participants.

Fifth, TAU was not limited to 15 sessions and after post-treatment the TAU treatment could continue. The total amount of face-to-face contact between post-treatment and followup1 was probably larger within TAU than in CBT. This could have influenced the increased effect size in TAU.

Sixth, the participating institutions in this study may have differed in various ways, including in priority and affinity to conduct research. This may have affected the findings (Weisz et al., 2013). We did not control for this factor.

Conclusion

Treatment of depression or dysthymic disorders in adolescents between 12 and 21 with CBT or TAU showed a significant reduction of depressive diagnoses and amount of depressive symptoms. CBT did not outperform TAU in this complex and severe sample. No moderators of treatment outcome were found. Drop out in CBT was higher than in TAU, due to need for medication and may be because of comorbidity. After 15 sessions of CBT 59.1% still had an elevated level of depressive symptoms. Further studies are needed to establish cost-effectiveness and to identify mediators in order to improve CBT effectiveness by permitting personalizing CBT to address comorbidity in a systematic way.

Acknowledgements of authors' contributions

Yvonne Stikkelbroek designed the study, obtained funding, coordinated the data collection, conducted the statistical analyses, drafted the initial manuscript, revised the manuscript and approved the final manuscript. *Gerko Vink* conducted the imputation of the data and revised the manuscript. *Marco Bottelier* coordinated the data collection and revised the manuscript. *Maaike Nauta* coordinated the data collection, revised the manuscript and approved the final manuscript. *Cathelijne Lont* coordinated the data collection and revised the manuscript. *Anneloes L. van Baar* designed the study, obtained funding, revised the manuscript and approved the final manuscript as submitted. *Denise H. M. Bodden* designed the study, obtained funding, coordinated the data collection, revised the manuscript and approved the final manuscript.

Acknowledgements

We would like to thank Gregory Clarke for the permission to use the CWD-A protocol and Maria Kovacs for her generosity, to let us use the CDI-2. We are grateful for the contribution of the Mental Health Institutions and their professionals without them this study would be impossible; Accare, Altrecht, Ambulatorium, Bascule, Curium, GGZ-centraal, Herlaarhof, Lentis, Orbis, Perspectief, Praktijk Appelboom, Traverse, and Triversum.

This research is funded by Dutch Organisation for Health research and Development (ZonMw), grant number 157004005. The study was registered in the Dutch Trial register (NTR) number 2676.

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Lisa felt not depressed any more after treatment. She felt confident and threw a birthday party. Her parents enjoyed seeing their daughter mingle with her friends. However, the risk of another depressive episode is still high. The chance that Lisa will experience challenging life events is evident, as she will face a lot of changes when growing into adulthood. Can assertiveness and opening up to others keep Lisa out of depression? What if focusing on nice things is not enough to regulate negative emotions? Is she merely avoiding negative emotions or is she effective in keeping out of the depressive cycle? Could Lisa profit more of CBT now she feels much better? Can her parents and friends be important to regulate the evoked emotions after experiencing challenging life events? Future will tell.

Chapter 7

General discussion and summary

Introduction

This dissertation focuses on three important themes related to the development and treatment of depressive symptoms in adolescents, namely life events, cognitive emotion regulation and CBT. Life events were studied as risk factors for adolescent depression, cognitive emotion regulation was examined as a mediating mechanism between risk factors and adolescent depression and the effectiveness of CBT was investigated as a treatment for adolescent depression in clinical practice and compared to TAU. Different samples were used, including two large community samples, as well as a sample of clinically depressed adolescents. In addition different study designs were used, including a large longitudinal adult population study (NEMESIS), a longitudinal study following adolescents from 12 to 20 years of age (TRAILS) and a randomized controlled trial (RCT) studying the effectiveness of CBT ('Doepressie'). Important results were found clarifying the relationships between depressive symptoms in adolescents and invasive life events, cognitive emotion regulation strategies and different forms of treatment.

Main findings

Looking into the role of life events in adolescent depression, the first study focused on the consequences of family bereavement. It was found that the devastating experience of the death of a parent during childhood was not associated with increased psychiatric diagnoses during adulthood. Most children seemed to cope well after family-bereavement and handled their emotions without developing internalizing problems. A small number of family-bereaved adolescents was found to be at risk for severe internalizing problems. Next, we identified that elevated levels of internalizing problems before bereavement, formed a risk factor for internalizing problems after bereavement. Another important risk factor that was found to increase the vulnerability in adolescents to develop depression was stressful relational life events, like conflicts between the adolescent and his/her parents or friends. In addition, in a clinical sample, it was found that depressed adolescents who experienced stressful health threats like serious illness of themselves, parents or sibling had more depressive symptoms than depressed adolescents without a health threating life event.

Another focus of this thesis is on processes that contribute to the actual development of depressive symptom after the occurrence of severe life events, namely cognitive emotion regulation strategies. Maladaptive strategies, like rumination, as well as adaptive strategies, like positive reappraisal, were found to be related to elevated depressive symptoms.

Maladaptive strategies were identified as mediators of depressive symptoms after stressful life events but adaptive strategies were not. Therefore it seems that stressful relational life events, put adolescents at risk for depression, and even more so when they use maladaptive cognitive emotion regulation strategies.

Regarding treatment of adolescents that had a clinical diagnosis of depression, it was found that both groups that were either treated with CBT or TAU, improved significantly. CBT did not outperform TAU. However, half of the treated adolescents still experienced elevated levels of depressive symptoms by the end of the treatment. Although it was feasible to use a manualized treatment in the CBT group in routine mental health, it was also found that discontinuation of treatment in the CBT group was higher than in TAU, which resulted in new ideas that could improve CBT for depressed adolescents.

This thesis covers these three themes and the results of the studies on these themes are discussed in greater detail below (see also Table 7.1). A model that incorporates these three themes can be found in Figure 7.1.

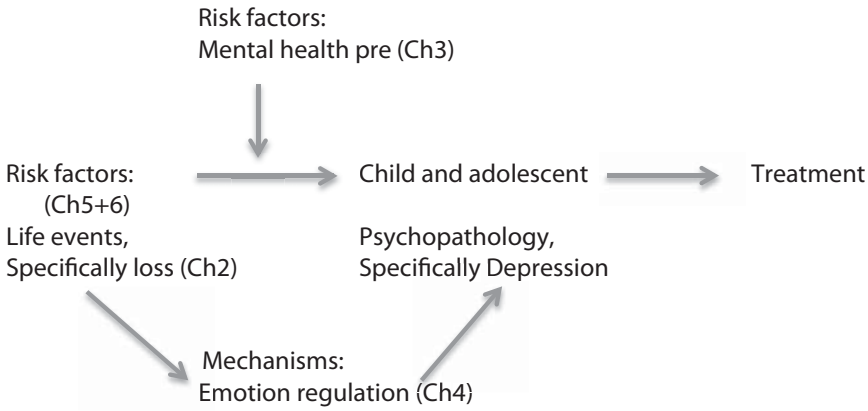

Figure 7.1 Model of the studies described in the chapters of this thesis.

Focus on risk factors: life events

The first focus in this thesis is on life events. In Chapter 2 and 3, two studies are described examining the role of life events, including family bereavement, on the onset of mental health problems during adolescence and adulthood. Family bereavement refers to loss of a sibling or parent.

Table 7.1 Overview of main characteristics

Chapter	Design	N	Age	Population	Measures	Core findings
2	Longitudinal	7,076	Range = 18–64	Population-based (NEMESIS)	Demographic variables, Mental disorders (CIDI), Parental death, Adversities	Few indications were found that there was a significant increase in mental disorders in adulthood among people who had lost a parent before the age of 16 (*N* = 541). Parental death was not associated with mental disorders (12 months; lifetime), age of onset, incidence of mental disorders, functional limitations or use of mental health services.
3	Longitudinal	2,230	*M* = 11.09 *SD* = 0.56	Population-based (TRAILS)	Demographic variables, Death within the Family, Multiple Bereavement within the Family, Mental Health Problems (YSR, ASR), Family Functioning (FAD)	Family-bereaved adolescents reported more internalizing problems within 2 years, post-loss internalizing problems were predicted by pre-loss internalizing problems, the increase of new clinical cases with internalizing problems in family-bereaved was four times as high (22%) as non-bereaved adolescents (5.5%), low SES predicted more internalizing problems in family-bereaved adolescents, Multiple family bereavements predicted fewer externalizing problems.

4	Correlational	398	Range = 11–22 *M* = 16.94 *SD* = 2.90	Clinical-community and Population-based	Demographic variables, Depressive Symptoms (CDI-2), Cognitive Emotion Regulation Strategies (CERQ), Stressful Life Events (LES)	Stressful relational challenging life events were associated with depressive symptoms. Health threats were associated with more depressive symptoms within the depressed group. More frequent use of maladaptive strategies was related to more depressive symptoms. More frequent use of adaptive strategies was related to less depressive symptoms. The association between relational challenging stressful life events and depressive symptoms was mediated by maladaptive cognitive emotion regulation strategies (self-blame, catastrophizing, rumination).
5 & 6	Longitudinal, RCT	103	Range = 12–21 *M* = 16.6 *SD* = 2.099	Clinical-community	Demographic variables, MDD or Dysthymic Disorder (K-SADS-PL), Depressive Symptoms (CDI-2), Severity of the Depression (CGI-S), Global Functioning (CGA-S), Suicide Criteria (SRA), Comorbidity (K-SADS; YRS; CBCL), Mental Health Service use (VEHI), Treatment Integrity (Observations)	Experimental treatment (CGT) was compared with Treatment as Usual (TAU) in treating adolescents with clinical depression. Both treatments were found to be equal in significant reductions of depression diagnoses and self reported depression post treatment and at 6 months follow up. No significant predictors or moderators of the treatment were found.

The findings of the first study (Chapter 2) indicate that the majority of people can overcome the loss of a parent during childhood without a significant increase in psychiatric disorders (including depressive disorders) during adulthood, increase of limitations in functioning or need for mental health services. Lifetime prevalence of substance abuse and alcohol abuse may be even somewhat lower.

However, our second study (Chapter 3), showed that family-bereavement during childhood and adolescence was associated with an increase in internalizing and externalizing problems at the age of 19 compared to non-bereaved adolescents. Findings from other research linking parental death to mental health problems during adulthood also showed mixed results (Luecken, 2008).

After the unexpected results of the first study, we raised the question if mental health problems after family bereavement could be predicted by pre-existing mental health problems instead of the bereavement itself (Chapter 3). The answer was yes for internalizing problems, but no for externalizing problems. Family bereavement was also associated with an increase of 22% new cases with clinically significant internalizing problems in comparison to 5.5% in the non-bereaved. These findings confirm the association between parental bereavement and mental health problems in adolescence (Cerel, Fristad, Verducci, Weller, & Weller, 2006; Dowdney, 2000; Dowdney, 2005; Luecken & Roubinov, 2012; Worden, 1999).

Furthermore, family functioning, specifically a dysfunctional climate, was already poor in the family before bereavement occurred compared to non-bereaved families. A large systematic review on children of cancer patients showed poor family functioning to be a risk factor for maladjustment (Krattenmacher et al., 2012). However, in our study family functioning did not predict internalizing or externalizing problems after family-bereavement.

Strengths and Limitations of studies on life events

Both studies have several strengths that will be discussed. Many epidemiological studies have investigated the association between several life events or adversities combined, including family bereavement, and on the association with mental health problems (Cuijpers et al., 2011). We used a more narrow perspective and focused solely on one specific life event, namely family-bereavement compared to non-bereavement, to identify specific risk factors in family-bereaved people. Besides, we used relatively large representative community samples in both studies, respectively $N = 7{,}076$ and $N = 2{,}230$, which allowed

generalizability to the general (western) population. Furthermore, a longitudinal design was used which enabled prospective analyses.

Mental disorders in adulthood after parental bereavement during childhood (study 1), was assessed with a well-validated standard diagnostic interview (Composite International Diagnostic Interview). The CIDI is a much more rigorous measure compared to the most commonly used self-report measures on psychopathology in bereavement research (Neimeyer & Hogan, 2001).

In our study on childhood mental health problems, longitudinal data on mental health and family functioning were collected before bereavement occurred and this enabled prospective analyses, which is an important step forward compared to the retrospective designs that were often used in childhood bereavement research (Balk & Corr, 2001; Luecken & Roubinov, 2012). In addition, research on the bereavement process in adolescents thus far was limited to the duration of 2 years after experiencing the death of a parent (Balk & Corr, 2001), whereas we were able to examine mental health problems over a period of 8 years.

Some limitations should also be considered. As these studies were not originally designed to study parental or family bereavement, specific information on potentially important predictors and moderators could not be taken into account, for instance gender of the deceased parent, cause of death (for instance suicide, traffic accident, violent death or illness), psychopathology of the deceased parent or psychopathology of the surviving parent. These are supposed to by related to mental health problems (Dowdney, 2000). Furthermore, in these studies, we could not account for specific bereavement related symptoms, such as persistent disruptive yearning or excessive bitterness, of the so-called Complicated Grief Disorder (CGD) (Prigerson et al., 2009). CGD, also referred to as Prolonged Grief Disorder (PGD), was identified as a distinct disorder in adults, questioning the validity of a depressive diagnoses as a proper classification of the symptoms associated with bereavement (Prigerson et al., 2009). Research on bereaved children and adolescents also identified PGD as a distinct syndrome, next to the occurrence of depressive symptoms and Post Traumatic Stress symptoms (Spuij et al., 2012). A longitudinal study showed that depressive episodes in bereaved youth under the age of 18 did not differ in length, severity and number of symptoms compared to non-bereaved depressed (Hamdan, Melhem, Porta, Payne, & Brent, 2012). These findings suggest that depression and PGD in bereaved may be two separate conditions. PGD is specifically linked to bereavement and in adolescents with depression no experience with bereavement may have occurred.

In our study on pre-bereavement mental health problems (n = 70), results must be interpreted with caution because of a potential lack of power. Nevertheless, nine

family bereaved adolescents discontinued to participate in one assessment pre- or post-bereavement. This discontinuation could have been associated with the family-bereavement and mental health problems. This suggests that mental health problems after family bereavement might be more prevalent than was found in this study.

Future research: life events

Both studies showed that a large proportion of the bereaved children did not develop mental health problems during childhood or adulthood. This information seems clinically relevant as part of the psycho-education for the parent, as well as for the child. Research on psycho-education about bereavement reactions and mental health problems for children in different age groups and parents could generate knowledge about how the psycho-education is perceived by family-bereaved and if it contributes to prevent mental health problems.

One fifth of family bereaved adolescents were found to be at risk for internalizing symptoms during childhood and panic disorder during adulthood. Although the death of a loved one is irreversible, the findings can inform us on the prevention of mental health problems after bereavement. Important may be for instance that we found that parentally bereaved experienced significantly more panic disorders for the first time during adulthood than non-bereaved. Furthermore, prevention research on family bereavement identified fear of abandonment as a mediator between bereavement and mental health problems in parental bereaved children (Wolchik, Ma, Tein, Sandler, & Ayers, 2008) and showed a slight rise in anxiety symptoms in girls over time (Sandler et al., 2010). It could be hypothesized that fear of abandonment after bereavement in childhood may precede and be associated with anxiety disorder, specifically panic disorder in adulthood. Parents or caretakers could be informed how to handle the fear of abandonment after bereavement.

We found that family functioning was already poor before bereavement compared to non-bereaved families. Although poorer family functioning did not predict mental health problems, it could be worthwhile to consider this as a predictor in future research. Research on parental bereavement showed that prevention of development of psychosocial problems following parental loss is possible by addressing caregiver warmth and effective discipline (Kwok et al., 2005; Lin, Sandler, Ayers, Wolchik, & Luecken, 2004) even after 6 years (Hagan et al., 2012). Prevention of mental health problems may be even more successful by addressing family functioning, specifically parenting, before bereavement. This may be possible if the decease of the family member is expected. Easily accessible online prevention interventions for parents are needed and should be investigated on their effectiveness.

Focus on mechanisms: cognitive emotion regulation

The second focus of this thesis is on cognitive emotion regulation as a potential mediator between stressful life events and depressive symptoms in depressed and non-depressed adolescents (Chapter 4) (see Table 7.1). We found support for the general hypothesis that certain stressful life events were related to the level of depressive symptoms and that this relationship was mediated by maladaptive cognitive emotion regulation strategies. The association between relational challenging stressful life events (such as parental divorce, moving, school failure, being bullied,) and depressive symptoms was mediated by maladaptive cognitive emotion regulation strategies (self-blame, catastrophizing and rumination). Adaptive cognitive emotion regulation strategies were not identified as mediators.

As expected, more frequent use of maladaptive cognitive emotion regulation strategies was related to more depressive symptoms. More frequent use of adaptive cognitive emotion regulation strategies was related to less depressive symptoms. Other research has often linked the use of maladaptive and less use of adaptive emotion regulation to depressive symptoms (Ehring, Fischer, Schnülle, Bösterling, & Tuschen-Caffier, 2008; Garnefski, Boon, & Kraaij, 2003; Martin & Dahlen, 2005; Schroevers, Kraaij, & Garnefski, 2007). However, we found no significant difference in use of maladaptive or adaptive cognitive emotion regulation strategies between depressed and non-depressed adolescents.

Stressful loss (such as death of a family member or pet) was not associated with higher levels of depressive symptoms in the total sample, the depressed as well as the non-depressed group. This finding questions once more the relationship between loss and depressive symptoms, who are at risk and why.

Relational challenging stressful life events were associated with depressive symptoms. This was in line with the finding that adolescents with clinical depressive symptoms have an attentional bias towards negative interpersonal stimuli (Gotlib, Krasnoperova, Yue, & Joormann, 2004). Also depressed adults who recovered from depression, showed higher negative affect when confronted with specific social stress (van Winkel et al., 2015). These latter findings suggest that more attention to negative interpersonal stimuli and a specific sensitivity to social stress may reflect an underlying vulnerability for depression.

Strengths and limitations of the study on cognitive emotion regulation

This study (Chapter 4) is important in order to establish a better understanding of specific mechanisms that can contribute to the etiology of adolescent depression. To our knowledge

this was the first study to test the mediating role of cognitive emotion regulation in the association between stressful life events and depressive symptoms in adolescents in a sample that includes healthy as well as severely depressed adolescent patients.

To make sure that all participants had used emotion regulation strategies, depressed as well as non-depressed adolescents were included in the analyses if life events were reported as upsetting. Previous research used the number of life events as a variable and did not take into account if the life event caused distress, which actually upset the adolescent, thereby ignoring whether the life events actually evoked strong emotions. Furthermore, different types of life events were taken into account as potentially affecting depressive symptoms, as well as different types of cognitive emotion regulation strategies. Therefore important differences between life events and cognitive regulation strategies could be detected in relation to depressive symptoms.

However, there were also several limitations in this study. The analyses were conducted on cross-sectional data and therefore no causal conclusions could be drawn. Also a lack of power could underlie the fact that no mediating paths were found in the depressed group, or that no significant differences were found in the strength of the mediational paths between the non-depressed and depressed adolescents. Furthermore, we did not ask the participants to report the use of cognitive emotion regulation strategies for a specific stressful life event. For example, it is possible that the same person used different cognitive emotion regulation strategies when dealing with loss related events compared to coping with stressful relation life events. Also the time passed since the stressful life event was not taken into account. Depressive symptoms could increase instantly or gradually after the stressful life event as a consequence of the use of specific maladaptive cognitive regulation strategies (Calvete, Orue, & Hankin, 2013). Similarly, a study showed that depressive symptoms did not increase immediately but only gradually after two years in family bereaved adolescents (Cerel et al., 2006).

Future research on cognitive emotion regulations

Maladaptive cognitive emotion regulation strategies were identified in this study as mediators of depressive symptoms after stressful relational life events. Further studies are needed on cognitive emotion regulation strategies as a mediator over time in a longitudinal design.

The relationship between adaptive and maladaptive cognitive emotion regulation strategies is still unclear. Research of Wigman and colleagues (Wigman et al., 2015) on

transdiagnostic concepts identified two dynamic processes in depressed compared to non-depressed youth, which may contribute to a better understanding of adaptive and maladaptive strategies and depression. First, negative mental states in depressed youth tend to accumulate and reinforce each other. Second, negative mental states also suppress a positive state of feeling, which in turn stimulates the negative mental state. Depressed adolescents seem to get into a loop of a more prominent negative mental state. This is in line with a study on a large community sample, which found that depressive symptoms predicted the negative cognitive style, but no association was found the other way round (Kindt, Kleinjan, Janssens, & Scholte, 2015).

Based on these findings, it could be hypothesized that even if adaptive cognitive emotion regulation strategies were used, the positive affect may be suppressed by depression. Our findings are in favour of this hypothesis because adaptive strategies were not identified as a mediator of less depressive symptoms after stressful life events. Furthermore the role of adaptive cognitive emotion regulation strategies may be different in adolescents with mild or severe depression. For instance, focussing on adaptive strategies may be important for decreasing a mild depression and an increase in positive affect, but in case of a severe depression, positive affect will be suppressed and positive adaptive strategies may not need to be focussed on.

Even more interesting is the identification of different cognitive emotion regulation profiles, which are combinations of single maladaptive and adaptive emotion regulation strategies. Profiles of emotion regulation strategies might contribute to a better understanding of depressive symptoms. For example, mediation of depressive symptoms by frequent use of rumination may be more prominent if the use of self-blame is high and positive refocusing is low, compared to low self-blame and little positive refocusing. Research on the interplay between different types of cognitive emotion regulation strategies is needed and important to determine which strategy should be addressed first in interventions.

A neuropsychological perspective might also shed light on the association between cognitive emotion regulation and depression. For instance, Platt and colleagues (Platt et al., 2015) compared depressed ($n = 15$) with non-depressed adolescents ($n = 15$) and found that they did not differ in acquiring the ability to use cognitive reappraisal, which was also reflected in fMRI images. In our study, positive reappraisal was found to be negatively associated with depression in the total sample. Cognitive reappraisal could be an important focus in treatment because depressed adolescents are able to acquire that ability. However, it remains uncertain if the use of cognitive reappraisal can reduce depressive symptoms.

With regard to prevention of depression, the type of stressful life event is important to consider. Stressful relational challenges were related to depression in the whole sample. This is in line with the outcome of other studies, showing that depression in puberty could be predicted by social adversity and that poor emotional control can be regarded as a risk factor of depression in girls. (Patton et al., 2008). Also, a large population based study (N = 13,434) established the association of negative and mostly interpersonal events with depressive symptoms but was not predicted by negative cognitive style (Kindt et al., 2015). These findings suggest that prevention of depression should address strategies for coping with stressful relational challenges. In depressed adolescents, health threat challenges were also found to be a specific risk factor for more severe depression that might need a specific approach in intervention.

Focus on treatment: CBT versus TAU

The third focus of the dissertation was on reduction of depressive disorders in adolescents by means of a psychological treatment, in particular Cognitive Behavioral Therapy (CBT). In Chapter 5 and 6, the design and the results of our RCT examining the effectiveness of CBT compared to TAU are described.

CBT is a well-studied treatment, which addresses behavior and cognitions (Weersing, Rozenman, & Gonzalez, 2009; Zhou et al., 2015). However effectiveness studies lack generalizability to clinical practice (Weisz, McCarty, & Valeri, 2006). In CBT as well as in TAU, a significant reduction of affective diagnoses and self-reported depressive symptoms was found in a sample with a high level of depression severity and low global functioning. However, the difference in symptom reduction between both conditions was not significant at post-treatment or at 6 month follow-up, with effect sizes of 0.20 and 0.09 respectively. This is in line with a recent meta-analysis of studies on children and adolescents with a broad range of psychopathology, which found that evidence based protocols did not outperform usual care in clinically referred samples or in youths with a diagnosis (Weisz et al., 2013). The finding in our study that depressive symptoms were significantly reduced in both conditions can be regarded as reassuring. However, improvement of treatment outcome is necessary as an elevated level of depressive symptoms was found at post-treatment and at follow-up1, respectively 58.4% and 68.2%. Furthermore, three adverse events occurred in CBT and discontinuation of treatment occurred more often in CBT (n = 25) compared to TAU (n = 18). May be a more flexible treatment is more feasible in this complex clinical sample. Treatment effects were not predicted or

moderated by age, ethnicity, gender, suicide phenomena, comorbidity and severity of depression.

Strengths and Limitations of the study on CBT versus TAU

The design of the RCT was innovative in several ways. CBT was investigated under real life conditions, thereby pushing the boundaries of RCT research out of the research laboratory into real world practice (Weisz et al., 2006). Therapists working within the participating mental health care institutions conducted the treatments. Furthermore, CBT was put to a rigorous test by the comparison with an active condition, namely routine mental health care without CBT (TAU). TAU is considered to be a stronger standard to test evidence-based protocols than other control conditions (Weisz et al., 2013). Also, long-term effects were measured 6 months after treatment. In such a way, possible sleeper effects of treatment could be taken into account. Possible moderators of treatment effect were also investigated.

Some limitations should be considered. First, the inclusion of participants was much more difficult than expected and we did not include the 140 participants that we aimed for. Second, it may have been possible that therapists in the TAU condition used CBT elements and did not report it. Third, the transparent logistic process of online data collection, and data file construction reduced the specific research problems such as missing data and contributed to the quality of the data. Unfortunately, it did not prevent nonresponse (Farrell, Kenyon, & Shakur, 2010). Fourth, the amount of face-to-face contact in minutes and the duration of the treatment within TAU after post-treatment was unclear and could have influenced the outcome at follow-up1.

Considerations concerning the sample are also important to discuss. The sample is a good representation of the population of adolescents and their families who seek treatment, so the generalizability is good. However, the sample is not a good representation of the Dutch population. More than half of the parents had a high educational level and almost all were of Dutch, white Caucasian background. Generalizability of the findings to depressed adolescents of other educational and ethnic backgrounds is thereby hampered.

Differences in priority and affinity with conducting research within the mental health care institutions, may have affected the findings (Weisz et al., 2013). For instance, the rate of inclusion differed per institution ranging from regular recruitment to almost no recruitment at all. Reasons for low recruitment were that no depressive adolescents were available, one forgot to approach potential participants, one had concerns about the burden of assessments or concerns about the delivered treatment.

Future research and implications of the study on CBT versus TAU

Further research on the data of this RCT should focus on time to response, that is the time passed until the depression had resided and the comparison between CBT and TAU in that respect. It is possible that CBT showed a faster response in the adolescents who completed the treatment and such a result might underpin the selection of CBT as a first choice of treatment. Also, the comparison between CBT and TAU on treatment costs could indicate which treatment should be selected in clinical care.

Almost half of the participants were still showed a high level of depressive symptoms after treatment. Thus, an increase in effectiveness of treatments is needed to reduce time to response, which has the potential to diminish the risk on suicide, functional impairment, substance abuse and problems at school and work as much as possible (Kratochvil et al., 2006). In order to increase treatment effectiveness it is necessary to answer the question: "Which treatment works for whom and why?". Although several large RCT trials such as TADS (J. Curry et al., 2011), ADAPT (Goodyer et al., 2007), and TORDIA (Brent et al., 2008) on treatment of adolescent depression were conducted, this question is still difficult to answer (J. F. Curry, 2014). This could be called "*depressing*". For instance, Weersing and colleagues (Weersing et al., 2009) pointed out that even after conducting 1,500 trials, information *why* therapy works, is scarce. There is some limited evidence that some components of CBT like cognitive restructuring mediate change in symptoms after treatment (Webb, Auerbach, & DeRubeis, 2012). The identification of mediators may be hampered because it is unclear if treatment components, like cognitive restructuring that are supposed to mediate the change in depression, are learned during treatment (J. F. Curry, 2014). It seems obvious that depressed adolescents can differ in type and amount of components that were acquired to a certain level. Future research on detecting possible mediators is necessary. Knowledge about mediators as mechanisms of change in CBT is urgently needed to adapt CBT in order to improve treatment effectiveness (J. F. Curry, 2014; Kazdin, 2007). CBT could be adapted by adding effective modules, changing the dose of effective modules and delineating ineffective modules.

Depressive disorders have been proven to be a recurrent disorder and successful treatment should also prevent future depressive episodes (J. Curry et al., 2011; J. F. Curry, 2014). Relapse is estimated to be about 34% to 75% within 1 to 5 years (Kennard, Ginsburg, Feeny, Sweeney, & Zagurski, 2005). Our study focused on acute treatment and showed that the reduction on diagnoses and symptoms was stable even after six months. The Follow-up2 data, one year after treatment, still have to be analysed to give us an indication

whether the results remain robust. This difference in long term outcome between CBT and TAU is also relevant, because a recently conducted large review showed that there is not enough evidence right now to conclude which type of treatment approach is most effective in preventing relapse or future depressive episodes in children and adolescents (Cox et al., 2014).

Clinical implications and considerations from a scientist-practitioner view

The findings from the different studies in this thesis are important for clinical practice.

First I will discuss clinical implications of our findings regarding family-bereavement. Child and family have to bear the tragic loss of a family member but also the concerns about development of mental health problems in the family members as a possible result of the mourning process. Bereavement counselors warn parents about disabling psychological problems later in life, if the mourning process does not proceed properly. Even if the bereaved child is happy at some point and is able to enjoy life, the parent may find this behavior suspicious. Parents may think that the child is avoiding or covering up grief. The finding that lifetime mental health problems are not inevitable could be very reassuring for adolescents, parents or adults who lost a parent before the age of 16 years. Our studies showed that there is no need to further aggravate the consequences of bereavement for the child by stigmatizing the child as a potential psychiatric case.

The finding that mental health problems before bereavement predict mental health problems after bereavement is of importance to professionals surrounding the child, like teachers or general practitioners. If adolescents already experienced internalizing problems before bereavement than the professional should be aware of an increase in internalizing problems and provide or arrange support in time.

If problems do occur after family-bereavement and the adolescent is referred for counseling than counselors should actively screen for symptoms of depression as well as PGD. The reason to check both is that treatment is different for each set of symptoms. For example, in contrast to PGB depression can be treated with anti-depressants.

In depressed adolescents, especially health risks in the adolescent or parent or friend, were found to be associated with a higher level of depression. This important risk factor could easily be overlooked and should be addressed in treatment for example by reducing the cognitive emotion regulation strategy catastrophizing.

Treatment selection and clinical judgment

Our findings did not answer the question "Which treatment should be considered as the first choice of treatment?". Still, the practitioner has to choose a treatment by clinical judgement. Some considerations based on the results of our studies in this thesis can inform the selection process.

The findings on relational stressful life events are of clinical importance with regard to selecting treatment type for the depressed adolescents. The treatment best suited to treat relational stressful life events is may be the best choice. For instance, Interpersonal therapy (IPT) (Mufson, Pollack Dorta, Moreau, & Weissman, 2004) has a specific focus on interpersonal functioning. CBT contains some components of improving social skills, but not exclusively (Weersing et al., 2009).

Cognitive emotion regulation was found to be a mediator between life events and depressive symptoms, more specifically maladaptive strategies mediated this relation. However, we did not study whether adaptive strategies can mediate change of depressive symptoms during treatment. Still, our findings may contribute to a better understanding of conducting treatment of depression with CBT. CBT treatment contains cognitive restructuring (Weersing et al., 2009). Cognitive restructuring is focussed on maladaptive strategies and tries to challenge clients to reflect on their thoughts in order to change them and induce the use of adaptive strategies. However after receiving cognitive restructuring, patients often call out desperately "I know my thought is not true, but it still feels like it". This entails a challenging situation for the therapist and client because it confirms hopelessness and indirectly strengthens the depression once more. The practitioner could then turn to other strategies, such as activation, to enhance the mood and retry cognitive restructuring when the depressed mood is diminished.

Our effectiveness study also showed that a broad range of comorbid psychopathology was common and this hampered the use of manualized treatment. Discontinuation of treatment was frequently seen in CBT. In these cases, treatment may have been a discouraging experience for the adolescents and might also have aggravated hopelessness and reduced expectations for positive outcome of other treatments as well. Hopelessness was identified as the most difficult to treat characteristic of depression (Kennard et al., 2005). In the case of comorbidity, a more flexible treatment than the D(o)epression course seems more feasible. If severity of the depression is high, as indicated by a high score on the CDI2, the D(o)epression course as a stand-alone intervention is not preferable, but a combination with medication should be considered (Buitelaar et al.,2009).

The chance that the treatment does not succeed in a sufficient reduction of the patient's problems is considerable. Failure to treat the adolescent's depression successfully can damage the confidence of the therapist in the treatment and thereby influence the selection of a treatment in the near future. Introduction of an open and systematic debate between therapists of cases of treatment failure could address this issue and enhance clinical judgements. Also, potential flaws in treatments and manuals can be uncovered in such a way. In addition the cases where the treatment did succeed should also be identified.

Personalizing treatment

Our studies showed that depressed adolescents were found to be heterogenic in many aspects, for example regarding kind of life events, number of comorbid diagnoses, use of certain cognitive emotion regulation strategies, and severity of the depression. These differences could, or even should, have consequences for the treatment planning. A big step forward in treatment of depression would be to personalize treatment in order to cope with comorbidity and treatment discontinuation. A promising strategy to handle comorbidity and at the same time disseminate evidence-based treatment into practice in a personalized way, is the Modular Approach to Therapy for Children with Anxiety, Depression, Trauma, or Conduct Problems (MATCH) (Chorpita & Weisz, 2009). MATCH contains clinical procedures similar to evidence based protocols for one specific mental health problem but flexibly selected and sequenced using a guiding clinical algorithm. A large RCT conducted within routine care showed that MATCH outperformed TAU even after 2-years, but evidence based treatments for single diagnoses did not outperform TAU (Chorpita et al., 2013). Furthermore, therapists were more satisfied with the modular approach design than the TAU or singular diagnoses treatment protocols (Chorpita et al., 2015). Another innovative approach is transdiagnostic treatment that aims to treat a range of emotional disorders (i.e., anxiety and depression) simultaneously by addressing emotion regulation (Trosper, Buzzella, Bennett, & Ehrenreich, 2009). The results of an open trial suggest that transdiagnostic treatment, the Unified Protocol-Youth, is potentially efficacious for adolescents suffering from multiple emotional difficulties (Queen, Barlow, & Ehrenreich-May, 2014).

Personalized treatment could also contain modules for parents. Risk for adolescent depression is associated with a broad range of parent and family factors such as less warmth, specific parental cognitive styles, or less autonomy granting (Sander & McCarty, 2005; Yap, Pilkington, Ryan, & Jorm, 2014). In our RCT for instance, parents only received

psycho-education and not a specific treatment module within the CBT condition and still a significant reduction in depressive symptoms was established. A recent study on referred depressed children (aged 7 to 13) compared individual CBT versus Behavioral Parent Training focusing solely on child conduct problem. That latter study showed a significant reduction in diagnoses and depressive symptoms at post-treatment in both groups (Eckshtain, Kuppens, & Weisz, 2015). This promising result indicates that further exploration of ways in which parents can contribute to treatment effectiveness is needed.

Treatment dissemination

Our RCT also revealed a specific point of concern. Adolescents sought treatment or were referred for treatment when depression was already severe (or at its' worst). Furthermore, almost half of the participants received no professional guidance prior to referral. In view of the stepped care principles, used in the multidisciplinary guideline on depression in youth (Buitelaar et al., 2009), the aim is to treat depression as soon as possible in order to keep the time to response as short as possible. The question is how to deliver services to depressed adolescents and their families at an early stage, in a non-stigmatizing and feasible way to, to reduce their hesitations to seek professional help. It is suggested that new technologies, like online interventions or games have the potential to reach out to depressed adolescents and possibly these should be included in treatment packages (Ebert et al., 2015). Face-to-face treatment, for instance, could be mixed with an online treatment: D(o)epressie blended (Stikkelbroek & van Dijk, 2013). At this moment, a pilot study is conducted investigating the feasibility of D(o)pressie blended and the effects of this treatment on diagnoses and symptoms. Blended treatment could diminish time to response to treatment by enabling the adolescents to work online on their depression treatment between sessions in an interactive way.

Treatment outcome

A general point of concern on effectiveness research of psychological treatments of adolescent depression is that the reported effect size in meta-analyses could be lower because of publication bias. A recent meta-analysis using data on depressed adults found that the efficacy of psychological interventions was overestimated in the published literature by publication bias, just as it has been for pharmacotherapy (Driessen, Hollon, Bockting, Cuijpers, & Turner, 2015). The effect size of psychological treatments was reduced by

25% when unpublished papers were also taken into account (Driessen et al., 2015). The trust of practitioners in scientific research on effectiveness is put to a test by these results. These results encourage practitioners to follow their own impressions of effectiveness of treatments, instead of research results.

However, the need to increase effectiveness of psychological treatment of adolescent depression by conducting research may be even more urgent than it already was.

Conducting an RCT

Retrieving knowledge by performing an RCT in clinical practice is difficult, time consuming, very costly and hard to complete. To conduct a methodologically sound study it is necessary to convert many threats. In our RCT inclusion of participants was problematic because of the diversity of the comorbidity and the severity of depression. The symptoms of depression like fatigue or hopelessness interfere with the motivation to participate in the research and with completing assessments. Practitioners wanted to contribute to the study, but they were also reluctant to ask depressed adolescents to participate in the study. For instance, we put a lot of effort into including depressed adolescents from different ethnic backgrounds in our study. We trained practitioners of different ethnic backgrounds working in mental health centres for specific ethnic minorities. We stayed in contact and assisted wherever possible, without success: only two participants were from an ethnic minority. Another point of concern was how to secure the blinding of the research assistants to the condition. This could be compromised with just one remark by the participant and could induce bias. However, bias could benefit outcome of CBT as well as TAU because we told all participants, therapists and research assistants that all treatments were used regularly.

Research and costs

Funding for research on psychological treatment of adolescent depression is scarce. Overall, the budget for evaluation of psychological treatments is insignificant compared to medical treatments. From a clinical as well as a public health perspective no justification exists for this difference (Falissard, 2015). Ian Goodyer made an appeal to psychiatry to do better and to make a stand for their own agenda on innovation and to persuade funding bodies and governments to contribute (Goodyer, 2015). Studies on costs of a clinical depression in adolescents are needed to deliver underpinned arguments to persuade funding bodies and government to act. Cost-effectiveness of CBT versus TAU should be studied in order

to use treatment budget effectively. The results of our cost-of-illness and cost-effectiveness studies will shed more light on these topics.

General conclusion

The findings of all the studies in this thesis indicate that a more personalized intervention is needed to address the aftermath of specific stressful life events and the use of maladaptive cognitive emotion regulation strategies, as well as to enhance effectiveness of treatments. Modular treatment may be a feasible way to treat a patchwork of problems and symptoms and to address cognitive emotion regulation in a flexible, but consistent way. For scientist-practitioners no reason to get depressed, we know what to do next!

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Samenvatting (Summary in Dutch)

Het onderzoek uit dit proefschrift was gericht op drie belangrijke thema's die gerelateerd zijn aan de ontwikkeling en behandeling van depressieve symptomen in adolescenten, namelijk levensgebeurtenissen, cognitieve emotieregulatie, en cognitieve gedragstherapie (CGT). Levensgebeurtenissen, in het bijzonder rouw en verlies, werden bestudeerd als een risicofactor voor depressieve symptomen in adolescenten. Cognitieve emotieregulatie werd bestudeerd als een mediator, het proces waardoor risicofactoren tot depressie zouden kunnen leiden. De effectiviteit van CGT bij depressieve jongeren werd onderzocht door CGT te vergelijken met reguliere zorg in de klinische praktijk. Data van verschillende steekproeven werden voor deze studies benut, waaronder twee grote steekproeven uit de algemene populatie maar ook de data van adolescenten met een depressieve stoornis. Daarbij werden verschillende designs van onderzoek toegepast, zoals een grote longitudinale studie onder volwassenen uit de algemene populatie (NEMESIS), een longitudinaal onderzoek waarin adolescenten gevolgd werden van hun 12e tot hun 20e jaar (TRAILS) en een gerandomiseerd gecontroleerd onderzoek (RCT) naar de effectiviteit van CGT ('Doepressie'). De studies die in het proefschrift gebundeld zijn leverden belangrijke resultaten op die bijdragen aan het verhelderen van de relatie tussen depressieve symptomen in adolescenten en invasieve levensgebeurtenissen, cognitieve emotieregulatiestrategieën en verschillende type behandelingen.

Algemene bevindingen

De rol van levensgebeurtenissen bij het ontstaan van depressies tijdens de adolescentie werd onderzocht door eerst te focussen op de consequenties van een overlijden van een ouder of broer/zus op de psychische gezondheid van de adolescent. We vonden dat de verpletterende ervaring van het overlijden van een ouder gedurende de jeugd niet geassocieerd was met een groter aantal psychiatrische diagnoses tijdens de volwassenheid. Ook bleek dat kinderen in staat waren om het overlijden van een ouder of zus/broer te verwerken zonder psychische problemen te ontwikkelen zoals internaliserende problemen. Een klein aantal adolescenten bleek wel een verhoogd risico voor ernstige internaliserende problemen te laten zien. In een volgende studie bleek dat een verhoogd niveau van internaliserende problemen voorafgaand aan het overlijden, een risicofactor was voor internaliserende problemen na een overlijden binnen een gezin. Een andere belangrijke risicofactor voor het ontwikkelen van een depressie werd gevormd door stressvolle relationele gebeurtenissen, zoals conflicten tussen de adolescent en zijn/haar ouders of vrienden. Daarbij bleek dat binnen de klinische groep, depressieve adolescenten die rapporteerden dat de gezondheid

van ouders, zus/broer of zichzelf bedreigd werd, meer depressieve symptomen hadden dan degenen die niet zo'n bedreiging rapporteerden.

Een andere focus van dit proefschrift betrof de processen die bij kunnen dragen aan het daadwerkelijk ontwikkelen van depressieve symptomen na het ervaren van stressvolle levensgebeurtenissen, namelijk cognitieve emotieregulatiestrategieën. Mal-adaptieve strategieën, zoals ruminatie (het steeds weer blijven denken aan negatieve ervaringen/het eindeloos blijven nadenken over negatieve gebeurtenissen en de daarbij behorende gevoelens en gedachtes), maar ook adaptieve strategieën, zoals positieve herwaardering (in gedachten een positieve betekenis aan een gebeurtenis toekennen), bleken samen te hangen met een verhoogd niveau van depressieve symptomen. Mal-adaptieve strategieën konden geïdentificeerd worden als mediatoren van depressieve symptomen na stressvolle relationele gebeurtenissen, maar adaptieve strategieën niet. Deze resultaten suggereren dat stressvolle relationele levensgebeurtenissen het risico op het ontstaan van depressies in adolescenten vergroten en dat dat nog sterker het geval is als jongeren gebruik maken van mal-adaptieve cognitieve emotieregulatiestrategieën.

Betreffende de behandeling van adolescenten met een depressieve stoornis die aangemeld waren bij een GGZ-instelling, werd geconstateerd dat beide groepen die behandeld waren met CGT of andere reguliere behandelingen, duidelijk verbeterden. CGT bleek niet betere resultaten te behalen dan andere reguliere behandelingen. Echter, de helft van de behandelde adolescenten rapporteerde na afloop van de behandeling nog steeds een verhoogd niveau van depressieve symptomen in vergelijking met de norm. Alhoewel het toepassen van geprotocolleerde CGT binnen de geestelijke gezondheidszorg haalbaar was, bleek toch dat het afbreken van de behandeling in de CGT-groep vaker voorkwam dan in de groep die andere reguliere behandelingen ontving. Dit leverde nieuwe ideeën op over de manier waarop CGT voor depressieve adolescenten verbeterd kan worden.

De drie thema's uit dit proefschrift en de resultaten van de onderzoeken die gericht waren op deze thema's, worden hieronder in detail besproken (zie ook Tabel 7.1). Het model dat de drie thema's bevat is weergegeven in Figuur 7.1.

Focus op risicofactoren: levensgebeurtenissen

Het eerste thema van dit proefschrift was gericht op levensgebeurtenissen. In Hoofdstuk 2 en 3 worden twee studies beschreven die de invloed van levensgebeurtenissen onderzochten, in het bijzonder het overlijden van een gezinslid (ouder of broer/zus), op het ontstaan van psychische problemen tijdens de adolescentie en op lange termijn tijdens de

volwassenheid. De resultaten van de eerste studie (Hoofdstuk 2) lieten zien dat het overgrote deel van de inmiddels volwassen getroffenen het verlies van een ouder tijdens hun jeugd kunnen verwerken zonder sterke toename van psychiatrische stoornissen (inclusief depressieve stoornissen) tijdens de volwassenheid, en zonder toename van beperkingen in het functioneren of gebruik van geestelijke gezondheidszorg. De levenslange prevalentie van middelen en alcoholmisbruik was zelfs iets lager in deze groep.

Niettemin toonde ons tweede onderzoek (Hoofdstuk 3) aan dat rouw om verlies binnen het gezin tijdens de kindertijd en adolescentie geassocieerd was met een toename van internaliserende en externaliserende problemen op 19-jarige leeftijd, in vergelijking met adolescenten die niet met rouw te maken hadden gehad.

Een van onze vragen was of psychische problemen na het overlijden van een gezinslid voorspeld werden door psychische problemen die voor het overlijden al aanwezig waren (Hoofdstuk 3). Het antwoord was bevestigend voor internaliserende problemen, maar niet voor externaliserende problemen. Bovendien was overlijden binnen het gezin geassocieerd met een toename van 22% nieuwe casussen met een klinisch significante verhoging van internaliserende problemen, in vergelijking met 5,5% toename gedurende een overeenkomstige periode in de groep adolescenten die niet met verlies en rouw geconfronteerd waren. Deze bevindingen bevestigden de associatie tussen overlijden van een ouder en psychische problemen tijdens de adolescentie. Bovendien bleek het gezinsfunctioneren vaak al vrij slecht te zijn *voordat* het overlijden plaats had, in vergelijking met adolescenten die geen overlijden meegemaakt hadden in dezelfde periode. Daarnaast bleek uit onze studie dat internaliserende of externaliserende problemen niet voorspeld konden worden door slecht functioneren van het gezin *na* het overlijden van een gezinslid.

Focus op mechanismen: cognitieve emotieregulatie

Het tweede thema van dit proefschrift was cognitieve emotieregulatie als een potentieel mediërend mechanisme tussen stressvolle levensgebeurtenissen en depressieve symptomen bij zowel klinisch depressieve als niet depressieve adolescenten (Hoofdstuk 4).

We vonden ondersteuning voor de algemene hypothese dat specifieke stressvolle levensgebeurtenissen samenhingen met het niveau van depressieve symptomen en dat deze relatie gemedieerd werd door mal-adaptieve cognitieve emotieregulatiestrategieën. De associatie tussen relationeel uitdagende stressvolle levensgebeurtenissen (zoals ouders die scheiden, verhuizen, falen op school of gepest worden) en depressieve symptomen werd gemedieerd door mal-adaptieve cognitieve emotieregulatiestrategieën (zelfbeschuldigen,

catastroferen en rumineren). Adaptieve cognitieve emotieregulatiestrategieën bleken geen mediërende rol te spelen. Zoals wij verwachtten bleek dat vaker gebruik van mal-adaptieve cognitieve emotieregulatiestrategieën gerelateerd was aan meer depressieve symptomen. Frequenter gebruik van adaptieve cognitieve emotieregulatiestrategieën was gerelateerd aan minder depressieve symptomen. Wij hebben echter geen significant verschil in gebruik van mal-adaptieve of adaptieve cognitieve emotieregulatiestrategieën tussen depressieve en niet depressieve adolescenten gevonden. Relationeel uitdagende stressvolle levensgebeurtenissen waren geassocieerd met depressieve symptomen.

Stressvol verlies (zoals het overlijden van een gezinslid of huisdier) was niet geassocieerd met meer depressieve symptomen in de gehele steekproef, bestaande uit de klinisch depressieve en niet depressieve groep. Dit resultaat stelt de relatie tussen verlies en depressieve symptomen opnieuw ter discussie: "Wie lopen een risico en waarom?".

Focus op behandeling: CGT versus andere reguliere behandelingen

Het derde thema van dit proefschrift was gericht op het reduceren van depressieve stoornissen in adolescenten door psychologische behandeling, in het bijzonder Cognitieve Gedrags Therapie (CGT). In Hoofdstuk 5 en 6 zijn de onderzoeksopzet en resultaten van de RCT die de effectiviteit van CGT in vergelijking met andere reguliere behandelingen onderzocht beschreven.

Onze RCT werd uitgevoerd binnen de reguliere zorg en de deelnemers waren aangemeld voor een behandeling. Uit het onderzoek bleek dat CGT evenals de andere reguliere behandelingen leidde tot een significante reductie van affectieve diagnoses en zelfgerapporteerde depressieve symptomen in een steekproef van adolescenten met een klinische depressieve diagnose, een hoge mate van depressieve symptomen en forse beperkingen in het dagelijks functioneren. Het verschil tussen beide condities in symptoomreductie na afloop van de behandeling en na 6 maanden follow-up was niet significant, met effectgroottes van respectievelijk 0,20 en 0,09. De bevinding dat depressieve symptomen significant gereduceerd zijn na behandeling in beide condities kan beschouwd worden als vertrouwenwekkend. Desondanks is het verbeteren van de behandeluitkomsten noodzakelijk omdat er nog steeds een verhoogd depressiesymptoomniveau werd gevonden aan het eind van de behandeling en na 6 maanden follow-up, respectievelijk bij 58.4% en 68.2% van de behandelde adolescenten. Daarnaast is de behandeling binnen CGT (n = 25) vaker

voortijdig gestopt in vergelijking met de controleconditie (n = 18). Het is mogelijk dat een meer flexibele behandeling meer geschikt is voor deze complexe klinische steekproef. Behandeleffecten werden niet voorspeld of gemodereerd door leeftijd, etniciteit, geslacht, suïcidale gedachten of plannen, comorbiditeit en de ernst van de depressie.

Klinische implicaties en overwegingen vanuit een scientist-practitioner perspectief

De bevindingen uit de verschillende studies in dit proefschrift zijn belangrijk voor de klinische praktijk. Met betrekking tot het overlijden van een gezinslid komt naar voren dat kinderen en hun ouder(s) het tragische verlies van een gezinslid moeten dragen maar daar bovenop ook de dreiging van het ontstaan van psychische problemen als een mogelijk resultaat van het rouwproces. Rouwconsulenten waarschuwen ouders voor het ontstaan van psychische problemen in het latere leven van het kind als het rouwproces niet goed verloopt. Zelfs als het op een bepaald moment goed gaat met het kind kunnen ouders dat gedrag verdacht vinden. Ouders kunnen denken dat het kind de gevoelens van rouw ontkent. De bevinding dat het overlijden van een ouder niet automatisch lijdt tot psychische problemen op de korte of lange termijn kan geruststellend zijn voor adolescenten, ouders en volwassenen. Onze studie toonde aan dat het niet nodig is om de consequenties van een overlijden te verergeren door het kind te stigmatiseren als een potentiële toekomstige psychiatrische patiënt.

De bevinding dat psychische problemen na het overlijden voorspeld worden door psychische problemen voorafgaand aan het overlijden is zeer relevant voor de professionals rondom het kind, zoals docenten of de huisarts. Als de adolescent al internaliserende problemen ervoer voor het overlijden dan zou de professional beducht moeten zijn op een toename van internaliserende problemen na een overlijden in het gezin en zou deze moeten voorzien in voldoende ondersteuning.

Als er toch psychische problemen ontstaan na het overlijden van een gezinslid en de adolescent verwezen wordt voor hulp, zou actieve screening op depressie en gecompliceerde rouw plaats moeten vinden. De reden dat op beide problemen gescreend moet worden is dat de behandeling verschilt. Zo kan een ernstige depressieve stoornis aangepakt worden met antidepressiva, maar dit geldt niet als een geschikte behandeling voor gecompliceerde rouw.

Selectie van type behandeling en klinisch oordeel

De gevonden resultaten uit het onderzoek naar de behandeling van depressies gaf geen antwoord op de vraag "Welk type behandeling is de beste keus als behandeling van depressies?" Toch zal de therapeut een behandeling moeten kiezen. Op basis van de resultaten die beschreven zijn in dit proefschrift kunnen wel enkele overwegingen geformuleerd worden die van belang zijn voor het selectieproces van een type behandeling.

De bevindingen met betrekking tot relationele stressvolle levensgebeurtenissen zijn van klinisch belang voor het selecteren van het type behandeling voor depressieve adolescenten.

De behandeling die het meest gericht is op het hanteren van relationele stressvolle levensgebeurtenissen zou wel eens de beste keus kunnen zijn. Een voorbeeld van zo'n therapie is Interpersoonlijke Therapie (IPT; Mufson, Pollack Dorta, Moreau, & Weissman, 2004) die specifiek gericht is op interpersoonlijk functioneren. CGT bevat ook enkele componenten die zich richten op het verbeteren van sociale vaardigheden maar niet exclusief.

Cognitieve emotieregulatie bleek een mediator te zijn van de relatie tussen levensgebeurtenissen en depressieve symptomen, waaruit duidelijk werd dat in het bijzonder mal-adaptieve strategieën deze relatie medieerden.

We hebben niet onderzocht of adaptieve strategieën verandering in depressieve symptomen mediëren. Toch kunnen de bevindingen bijdragen aan een beter begrip van het uitvoeren van een CGT-behandeling voor depressies. CGT bevat cognitieve herstructurering. Cognitieve herstructurering is gericht op mal-adaptieve strategieën en probeert patiënten hun gedachten uit te laten dagen zodat ze veranderd kunnen worden en meer adaptieve strategieën geïnduceerd kunnen worden. Toch komt het voor dat na het toepassen van cognitieve herstructurering patiënten zeggen "Ik weet dat mijn gedachte niet juist is, maar het voelt nog steeds wel zo.". Een uitdagende situatie voor zowel de therapeut als de patiënt omdat de hopeloosheid nogmaals bevestigd wordt en dit indirect de depressie versterkt. De therapeut zou een andere strategie kunnen overwegen, zoals activatie, om eerst de stemming te verbeteren en cognitieve herstructurering pas opnieuw toe te passen nadat de stemming verbeterd is.

Het onderzoek naar effectiviteit van 'Doepressie' liet zien dat een grote diversiteit aan comorbide stoornissen eerder regel dan de uitzondering was. De CGT-behandeling moest vaak afgebroken worden. In die gevallen kan behandeling een ontmoedigende ervaring zijn geweest die de hopeloosheid versterkt en de verwachtingen ten aanzien van een volgende behandeling verminderen. Bovendien is hopeloosheid het meest lastig te behandelen kenmerk van een depressie (Kennard et al., 2005).

In het geval van comorbiditeit lijkt een meer flexibele behandeling dan de D(o)epressiecursus beter toepasbaar.

De kans dat de behandeling niet resulteert in voldoende reductie in problemen en symptomen is aanzienlijk. Het vertrouwen van de therapeut in de behandeling kan daardoor verminderen en het selectieproces voor deze behandeling wordt negatief beïnvloed.

Het introduceren van een open en systematisch debat tussen therapeuten over '*mislukte*' psychologische behandelingen kan het klinische oordeel verbeteren. Ook potentiële tekortkomingen in type behandelingen en protocollen kunnen dan geïdentificeerd worden. Daarbij moeten uiteraard ook geslaagde behandelingen onder de loep genomen worden.

Personaliseren van de behandeling

Het onderzoek toonde aan dat de groep depressieve adolescenten zeer heterogeen is in velerlei opzichten, zoals met betrekking tot type levensgebeurtenis, aantal comorbide diagnoses, gebruik van bepaalde cognitieve emotieregulatiestrategieën en de ernst van de depressie. Deze onderlinge verschillen kunnen en zouden consequenties moeten hebben voor de inrichting van de behandeling. Een grote stap vooruit in de behandeling van depressies is het personaliseren van de behandeling zodat er omgegaan kan worden met comorbiditeit en dat het afbreken van de behandeling beter voorkomen wordt. Een veelbelovende strategie om zowel comorbiditeit te behandelen en tegelijkertijd de disseminatie van evidence-based behandelingen op een gepersonaliseerde wijze in praktijk te brengen is de Modular Approach to Therapy for Children with Anxiety, Depression, trauma, or Conduct Problem (MATCH; Chorpita & Weisz, 2009). MATCH bevat componenten die vergelijkbaar zijn met evidence-based protocollen voor een specifiek psychisch probleem of psychische stoornis maar die flexibel geselecteerd kunnen worden op basis van een klinisch algoritme. Een grote RCT binnen de reguliere zorg stelde vast dat MATCH de reguliere behandelingen overtrof, zelfs na 2 jaar. De evidence-based protocollen voor een enkele diagnose waren niet beter dan de reguliere zorg (Chorpita et al., 2013). Ook bleek dat de therapeuten meer tevreden waren over de modulaire benadering dan de reguliere behandelingen of de behandelprotocollen voor slechts een diagnose (Chorpita et al., 2015). Een andere nieuwe benadering is de transdiagnostische benadering, die tot doel heeft om een breed scala aan emotionele stoornissen (i.e. angst en depressie) tegelijkertijd te behandelen door emotieregulatie te veranderen (Trosper, Buzzella, Bennett, & Ehrenreich, 2009). De resultaten van een pilotstudie suggereren dat transdiagnostische behandeling

met het "Unified Protocol-Youth" mogelijk effectief is voor adolescenten met meerdere emotionele problemen (Queen, Barlow, & Ehrenreich-May, 2014).

Gepersonaliseerde behandeling kan ook componenten voor ouders bevatten. Het risico op het krijgen van een depressie tijdens de adolescentie is geassocieerd met meerdere ouder- en gezinskenmerken, zoals weinig emotionele warmte, specifieke cognitieve stijl van de ouders, of weinig autonomie (Sander & McCarty, 2005; Yap, Pilkington, Ryan, & Jorm, 2014). In onze RCT kregen ouders enkel psycho-educatie en geen behandeling binnen de CGT-conditie en toch werd een significante reductie in depressieve symptomen behaald. Recentelijk is individuele CGT vergeleken met Behavioral Parent Training gericht op gedragsproblemen bij kinderen tussen de 7 en 13 jaar die verwezen waren naar een kliniek voor behandeling. Dit onderzoek toonde aan dat een significante reductie in diagnoses en depressieve symptomen werd behaald in beide behandelingen (Eckshtain, Kuppens, & Weisz, 2015). Dit veelbelovende resultaat laat zien dat verdere exploratie van de wijze waarop ouders kunnen bijdragen aan het verbeteren van de effectiviteit van de behandeling vruchtbaar en noodzakelijk is.

Disseminatie van behandelingen

Onze RCT onthulde ook een specifiek punt van zorg. Adolescenten zochten behandeling of werden verwezen op het moment dat de depressie ernstig was. Bovendien ontving de helft van de deelnemers geen professionele hulp op het moment van de verwijzing. Vanuit het stepped care model, zoals toegepast in de multidisciplinaire richtlijn voor depressie (Buitelaar et al., 2009), is juist het doel opgesteld om een depressie zo snel mogelijk te behandelen zodat ook zo snel mogelijk een positief resultaat kan optreden. De vraag is op welke wijze zorg geboden kan worden aan depressieve adolescenten en hun ouders in een vroeg stadium en op een niet stigmatiserende en acceptabele wijze om de aarzeling om professionele hulp te zoeken te verminderen. Nieuwe technologieën lijken de potentie te hebben om adolescenten te bereiken en zouden in interventies verwerkt kunnen worden (Ebert et al., 2015). Face-to-face behandeling kan bijvoorbeeld toegevoegd worden aan online behandeling zoals bij de behandeling D(o)epressie blended (Stikkelbroek & van Dijk, 2013). Op dit moment wordt een pilotonderzoek verricht naar de tevredenheid van patiënten over D(o)pressie blended en de reductie van diagnoses en depressieve symptomen. Blended behandelen kan de periode tot respons verminderen omdat de adolescenten online op een interactieve wijze door kunnen werken aan hun behandeling tussen de sessies door.

Behandeluitkomsten

Een algemeen punt van bezorgdheid over effectonderzoek naar psychologische behandelingen van depressies onder adolescenten is dat de gerapporteerde effectgroottes in meta-analyses in werkelijkheid nog lager zijn door publicatiebias. Een recente meta-analyse liet zien dat de effectiviteit van psychologische behandelingen voor volwassenen overschat werd in de gepubliceerde studies door publicatiebias, op een vergelijkbare wijze als in farmacotherapie (Driessen, Hollon, Bockting, Cuijpers, & Turner, 2015). De effectgrootte van psychologische behandelingen verminderde met 25% als de resultaten van niet gepubliceerde artikelen wel meegenomen werden in de berekeningen (Driessen et al., 2015). Het vertrouwen van therapeuten in wetenschappelijk onderzoek naar effectiviteit kan daarmee worden ondergraven. Deze resultaten kunnen therapeuten aanmoedigen om vooral op hun eigen indruk af te gaan.

Hoe dan ook, de noodzaak om de effectiviteit van psychologische behandelingen van depressieve adolescenten te vergroten door grensverleggend wetenschappelijk onderzoek blijkt eens te meer dringender en noodzakelijker dan het al was.

Uitvoeren van een RCT

Kennis verwerven door het verrichten van een RCT binnen de reguliere zorg is ingewikkeld, tijdintensief, kostbaar en zeer moeilijk tot een goed einde te brengen. Om een methodologisch juiste onderzoeksopzet uit te voeren is het belangrijk om veel bedreigingen af te wenden. De symptomen van een depressie, zoals vermoeidheid of hopeloosheid, interfereren met de motivatie om aan het onderzoek deel te nemen en de metingen te voltooien. Therapeuten waren bereid om aan het onderzoek mee te werken maar vonden het moeilijk om depressieve adolescenten te belasten met deelname aan het onderzoek. We hebben zeer veel moeite gedaan om op allerlei manieren depressieve adolescenten met verschillende etnische achtergronden in de studie te betrekken. We hebben therapeuten met verschillende etnische achtergronden die werkzaam zijn binnen de zorg voor etnische minderheden speciaal getraind. We hielden regelmatig contact en boden ondersteuning waar mogelijk, maar zonder succes. Slechts twee participanten hadden een andere etnische achtergrond. Een ander punt dat aandacht verdient is hoe de blindering van de onderzoeksassistenten voor het type behandeling voldoende gewaarborgd kan worden. Een opmerking van de adolescent of ouder over de behandeling kan al bias induceren.

Onderzoek, kosten en uitvoeren van een RCT

Fondsen voor wetenschappelijk onderzoek naar psychologische behandelingen zijn slechts zeer beperkt beschikbaar. Over het geheel genomen is het budget voor de evaluatie van psychologische behandeling onbeduidend in vergelijking met budgetten voor evaluatie van farmacotherapie. Vanuit een klinisch maar ook volksgezondheidsperspectief is er geen rechtvaardiging voor dit verschil (Falissard, 2015). Onderzoeken naar de kosten van een depressieve stoornis bij adolescenten zijn noodzakelijk en kunnen argumenten bieden om fondsen en overheden over te halen om in te grijpen. Kosteneffectiviteit van CGT versus andere reguliere zorg zou onderzocht moeten worden om het budget voor behandelingen effectief in te zetten. De resultaten uit ons onderzoek naar de ziektekosten en kosteneffectiviteit zullen meer licht werpen op deze onderwerpen.

Algemene conclusie van de scientist-practitioner

De bevindingen uit de onderzoeken die in dit proefschrift besproken werden wijzen in de richting van de noodzaak van meer gepersonaliseerde interventies om de gevolgen van specifieke stressvolle levensgebeurtenissen en het gebruik van mal-adaptieve cognitieve emotieregulatiestrategieën aan te pakken, en de effectiviteit van behandelingen te vergroten. Modulaire behandeling kan een manier zijn om een lappendeken van psychische problemen en symptomen te behandelen en om cognitieve emotieregulatie op een flexibele maar consistente wijze te behandelen. Er is geen reden voor scientist-practitioners om depressief te raken, we weten wat de volgende stap is!

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Dankwoord

Dit proefschrift was nooit tot stand gekomen als niet vele mensen op een of andere wijze een bijdrage geleverd hadden. Als eerste wil ik de promotor, **Prof. Anneloes van Baar**, bedanken voor de enthousiaste en inspirerende houding waarmee ze het onderzoeksproject en het proefschrift begeleid heeft. Als ik met 'out of the box' ideeën op de loop ging dan temperde Anneloes niet mijn enthousiasme maar bewaakte wel de haalbaarheid. Dank ook voor de niet aflatende energie waarmee je de artikelen becommentarieerde en vragen aan de orde stelde. **Dr. Denise Bodden**, de copromotor, is van groot belang geweest bij het verwerven van de subsidie en de realisatie van het onderzoek en het proefschrift. Denise bedankt dat je niet terugschrok om de uitdaging aan te gaan en een promotietraject te begeleiden van een collega die even oud is als je moeder. Als twee lotgenoten trokken we elkaar door het hele proces van dataverzameling. Zonder jou hadden we dit nooit kunnen realiseren.

Vanaf de start van het onderzoeksproject tot nu toe hebben wij drieën ook de nodige levensgebeurtenissen te verwerken gekregen. Soms erg confronterend omdat er veel overlap was met het onderwerp van het proefschrift. Ondanks de druk hebben we elkaar de ruimte kunnen gegeven en zijn we elkaar altijd blijven steunen om het beste ervan te maken. Dat is gelukt.

Ik wil mijn dank uitspreken voor de constructieve wijze waarop de leden van de beoordelingscommissie, de hoogleraren **Claudi Bockting**, **Paul Boelen**, **Jan Buitelaar**, **Rutger Engels**, **Caroline Braet** het proefschrift gewogen hebben. **Prof. Rutger Engels** en **Prof. Caroline Braet** in het bijzonder voor hun bijdrage aan het symposium. **Prof. Caroline Braet** ook voor haar medewerking aan de CDI2 en de stimulerende woorden in het begin van het project die ons aanmoedigden om door te gaan. **Prof. Paul Boelen** voor het begeleiden van de eerste stappen in het doen van onderzoek. **Prof. Maaike Nauta** wil ik in het bijzonder danken om velerlei redenen. Door haar proefschrift over de interventie Dappere Kat kwam ik voor het eerst in aanraking met wetenschappelijk onderzoek dat leidde tot concrete veranderingen in mijn dagelijkse werk. Zo kon het dus ook. Misschien naïef van mij, maar tijdens mijn opleiding tot psychotherapeut was wetenschappelijke onderbouwing nagenoeg afwezig. En het is nog steeds problematisch. Later gingen we samenwerken en je gaf mij keer op keer het gevoel dat ik vanuit mijn praktijkervaring een zinnige bijdrage leverde. Altijd open om nieuwe gezichtspunten serieus te onderzoeken en te wegen en te switchen tussen therapeutische en wetenschappelijke argumenten. Daar genoot ik erg van en bovendien was het ook nog gezellig. Je was een belangrijke stimulator van de RCT en hebt actief bijgedragen. Ik verheug me op onze samenwerking binnen het Consortium Angst en Depressie.

Prof. John Weisz dank ik voor zijn toegankelijkheid en zijn concrete adviezen om de dreigende stagnatie van de RCT af te wenden en de bemoedigende woorden om vooral door te gaan.

Het **Bestuur van de faculteit**, met name **Prof. Marcel van Aken** en het departementsbestuur in de persoon van **Jacqueline Neefjes** wil ik bedanken voor de financiële bijdrage aan het tot stand komen van deze promotie toen dat na een aanvankelijk moeizame start wel mogelijk was. **Ruth Cramer** voor de flexibele opstelling en de niet aflatende pogingen om de beste oplossing te vinden voor de vele praktische problemen.

Zonder de steun van **ZonMw** was dit project niet mogelijk geweest. Met name de programma-secretarissen, eerst **Marjolein-Scholten** en later **Valesca Kuling** wil ik bedanken voor hun flexibele opstelling waardoor dit project tot een goed einde gebracht kon worden. **Utrecht Centre of Child and Adolescent Studies (CAS)**, bedankt voor de financiële bijdrage aan het symposium zodat de onderzoeksresultaten onder professionals verspreid konden worden. **Dr. Gerko Vink** die ondanks alle restricties van de statistische analyses naar oplossingen bleef zoeken om op een verantwoorde wijze de kennis uit de met 'bloed, zweet en tranen' verzamelde informatie te halen. Ook het geduld en helderheid waarmee Gerko mij deelgenoot maakte van zijn aanpak heb ik zeer gewaardeerd. **Prof. Wilma Volleberg** voor de medewerking aan een voor mij heel belangrijk artikel en het beschikbaar stellen van de TRAILS data.

Oneindig veel dank gaat uit naar de **ouders** en **adolescenten** die in een moeilijke periode van hun leven toch bereid waren om herhaaldelijk mee te werken aan interviews en het invullen van vragenlijsten. Ook wil ik het grote aantal **therapeuten** en **onderzoekscoördinatoren** van **Accare**, **Altrecht**, **Bascule**, **Curium**, **GGZ-centraal**, **Herlaarhof**, **Lentis**, **Orbis**, **Perspectief**, **Praktijk Appelboom**, **Traverse**, en **Triversum** bedanken voor hun medewerking aan het verzamelen van data en het uitvoeren van de behandelingen. Helaas teveel personen om hier iedereen te noemen. De onderzoeksassistenten, **Mirjam**, **Carlijn**, **Vera**, **Steffi** die met hun jeugdige enthousiasme, dadendrang en verbazing het onderzoek ook voortstuwden en ons terzijde stonden. De vele **studenten** die hand- en spandiensten hebben verricht bij het verzamelen van de data ben ik dank verschuldigd.

Velen zijn belangrijk geweest voor het tot stand komen van het proefschrift, ook al betrof het geen directe bijdrage. **Prof. Paul Goudena** die mijn eerste stappen in het doen van onderzoek begeleid en gestimuleerd heeft. Maar ook als docent heeft hij ervoor gezorgd dat ik oorspronkelijke teksten zoals "Kleine Hans" van Sigmund Freud te lezen kreeg. Daardoor wist ik dat deze toen nog main-stream therapeutische oriëntatie in het geheel niet bij mij paste. Dat is zeer bepalend geweest voor de route die ik uiteindelijk

gegaan ben. **Dr. Hans Bleeker** die vanuit het Ambulatorium middelen ter beschikking stelde om een brug te slaan tussen wetenschap en praktijk. **Dr. Mariken Spuij** met wie ik samen de eerste stappen op het gebied van wetenschappelijk onderzoek gezet heb en daardoor wist dat het mogelijk was. **Dr. Saskia Wijsbroek** die in de afgelopen periode op een vanzelfsprekende wijze taken overnam zonder dat ik erom hoefde te vragen. Ook alle andere collega's die bij tijd en wijle interesse toonden, tips hadden of voor noodzakelijke afleiding zorgden tijdens de lunch. **Dr. Marjolein Vermande** die zeer attent en geduldig was als ik een deadline voor onderwijs niet haalde. De dagelijkse omgang met mijn collega's zorgde voor de nodige afleiding maar ook voor de constructieve feedback op het onderzoek. In het bijzonder de drijvende krachten achter Write Way, **Dr. Ellen Reitz**, **Dr. Marjolein Verhoeven** en **Dr. Kirsten Buist** die stimuleerden om ondanks de gekte van alledag toch de prioriteit bij het schrijven van artikelen te leggen.

Dr. Daan Creemers die tijdens de laatste loodjes 's ochtends vroeg belde met aanmoedigingen. Een goed begin van de dag.

Na dit proefschrift zie ik er naar uit om onderzoek te blijven doen naar de behandeling van depressieve adolescenten. Dat is mede mogelijk door de voortvarende wijze waarop **Prof. Rutger Engels** het Consortium Angst en Depressie gerealiseerd heeft. Samen met **Prof. Maaike Nauta**, **Dr. Rowella Kuijpers**, **Dr. Denise Bodden**, **Dr. Lisanne Stone**, **Dr. Irene de Graaf** en **Dr. Evelyn Vermeulen** gaan we onderzoek doen naar de preventie en behandeling van angt en depressie. **GGZ Oost Brabant** maakt het mogelijk dat ik direct onderzoek kan gaan doen naar de behandeling van depressie binnen de reguliere GGZ.

Renate (Proefschrift.nu) en **Jet (Jetswerk.nl)** wil ik bedanken voor de soepele samenwerking en de aantrekkelijke vormgeving van zo'n zwaar onderwerp.

Vele oud-collega's hebben bijgedragen aan het realiseren van de interventie die onderzocht is in dit proefschrift. **Henk Brans** die met veel enthousiasme op mijn uitnodiging in ging om een groepstherapie voor depressieve jongeren te starten toen iedereen nog vond dat dat onmogelijk was. Ergens moet je beginnen. **Ad van der Sijde** die vanuit de Kreek te Dordrecht een financiële bijdrage gaf aan het ontwikkelen van de D(o)epressie cursus hetgeen oneindig veel meer voor mij betekende dan geld. **Henk Bouman** waarmee ik samen de D(o)epressie cursus met veel plezier verbeterde, uitgevoerd en uitgedragen heb. Bedankt voor de prettige manier van samenwerking en je kordate opstelling waardoor het vele werk snel gedaan was. **Peter Mostert** die met oprechte belangstelling en prikkelende uitspraken mij uitdaagde en ervoor zorgde dat ik de juiste prioriteiten stelde. Mijn collega-pedagogen **José van Oene**, **Marijke van de Pol**, **Maureen Postma**, **Bart Groeneweg** en **Ellen Biersteker** wil ik bedanken voor hun jarenlange vriendschap, medeleven, vertrouwen,

open blik en kritische vragen in tijden van voor- en tegenspoed. In discussies met jullie was niets vanzelfsprekend en zo kwam ik op het idee voor het onderzoek dat in Hoofdstuk 3 beschreven is. **Yolanda** en **Annemarie** die in het begin van het traject letterlijk met me opgelopen zijn en voor ontspanning zorgden.

Judith Knipscheer, **Roos Rispens** en **Sahila** hebben indirect bijgedragen aan dit proefschrift doordat ze zorgtaken van Pim en mij overgenomen hebben. Op een spontane wijze sprongen ze in als dat nodig was en zorgden dat mijn stressniveau beperkt bleef. **Sahila** wil ik in het bijzonder bedanken voor de jarenlange trouw, gezelligheid, goedheid en het delen van onze lotgevallen als moeders. We zouden samen een boek kunnen schrijven.

Marie Renée, de paranimf, wil ik in het bijzonder bedanken omdat ze mij door dik en dun gesteund heeft en met veel humor en originele reacties mij aan het wankelen kreeg om vervolgens steviger dan daarvoor te staan. De dank daarvoor kan ik niet in woorden vatten.

Josian, mijn oudere zus die er altijd al was en mij in vele dingen is voorgegaan en daardoor de weg vrij maakte op velerlei wijze. Twee zussen maar zo verbroederd. Dat te weten en te ervaren maakt dat ik bergen kon verzetten. **Joop**, jij kunt letterlijk bergen verzetten en dat heb je vaak voor mij gedaan zonder iets terug te verwachten. Met grote dankbaarheid gaan mijn gedachten uit naar mijn **moeder** voor wie tot op het allerlaatst niets teveel was als het om haar kinderen ging. Zonder haar was veel niet mogelijk geweest.

Arnout, **Vera** en **Eric** die ik mocht 'opvoeden'. Een experiment in vivo? Mijn illusies over het pedagogisch handelen werden al snel ontmaskerd door mijn ervaringen als ouder. Dat riep veel vragen in mij op en maakte dat ik bescheidener werd in mijn rol als hulpverlener. In de tijd dat het belangrijk was heb ik met veel aandacht en rust voor jullie kunnen zorgen. Ik heb veel van jullie geleerd terwijl ik met jullie mee opliep. Ik was blij dat ik aan het promoveren was toen jullie het ouderlijk gezin verlieten zodat ik veel afleiding had. Dank voor alle steun, relativering, uitdaging, aanmoediging, afleiding, begrip en gezelligheid.

Pim, een kunstenaar zou zeggen mijn muze. Ik wil je bedanken voor de stimulans om wetenschappelijk onderzoek te gaan doen. Na jouw bijdrage aan het eerste artikel heb je wijselijk afstand gehouden tot dit proefschrift. Je hebt mij m'n eigen gang laten gaan. Ik ben je daar dankbaar voor. Dat neemt niet weg dat je toch van grote invloed bent geweest. Alleen al door jouw publicaties.

Mijn **Opa** wil ik danken voor zijn wijsheid, "Als je aan het ploegen bent dan moet je niet vooruit kijken maar achterom, naar wat je al gedaan hebt". Nu weten we dat het

proefschrift tot een goed einde gekomen is. Toch was dat tijdens het proces niet evident. Op momenten dat de problemen rondom de dataverzameling onoverkomelijk leken en een dipje op de loer lag keek ik achterom. Ik was dan verbaasd over de hoeveelheid werk die we al met succes verzet hadden. Dan stelde wat voor ons lag niets meer voor.

About the author

Curriculum vitae

Yvonne Stikkelbroek (1958) was born in Heerlen, the Netherlands. She completed her secondary education at Grotius College in Heerlen in 1978 and received her master degree in Clinical Pedagocical Sciences in 1984. She decided to work as a practitioner within mental health care with children and their parents (Elmar, Heerlen until 1988; RIAGG de Grote Rivieren at Dordrecht until 1995; Yulius de Kreek at Dordrecht until 2002; Karakter at Tiel until 2004; Ambulatorium at Utrecht until January 2016; GGZ Oost Brabant until now). She also started post-graduate education and became a registered child and adolescent psychotherapist (Psychotherapeut BIG, 1995), health care psychologist (GZ psycholoog BIG, 1998), Clinical Psychologist (Klinisch Psycholoog BIG, 2011) and supervisor (VKJP, 2010; NVP, 2011).

As a psychotherapist she treated a broad range of problems, in different settings and during many years. She gradually specialised in the treatment of depression. Much of her work was aimed at constructing, implementing and disseminating interventions for youth depression in mental health care. She adapted and introduced the Coping with depression course for adolescents into the Netherlands. Later on she developed an E-mental health intervention for adolescent depression combining face-to-face sessions with interactive online components. Besides that, she developed a CGT intervention for dyslectic adolescents with psychosocial problems. She became a frequently asked speaker and trainer on treatment of adolescent depression. In order to reach out to parents and teachers, she wrote a book on childhood depression for parents in 2012.

She started lecturing as an Assistant Professor at the Utrecht University in courses on clinical topics, mainly on Master level. In 2006 the University Teaching Qualification (BKO) was granted. Also teaching in post-graduate courses for psychotherapist, health psychologists and others became part of her work. In 2011 she and Denise Bodden obtained funding to start a large RCT and started research on treatment of adolescent depression. She was involved in the development and implementation of guidelines for youth depression and was a chairman to the guideline for social work in the Netherlands. Her main focus is the integration of science, practice and education werever possible to speed up innovation in favour of the children with mental health problems and their parents.

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