General introduction
This thesis focuses on new developments in the treatment of, and research looking at, personality disorders (PD) in adolescents and adults. There is a dearth of research on PDs in adolescents despite it being known that PDs in adolescents can be diagnosed reliably (GGZ Nederland, 2009), and that the prevalence in both the community and this treatment population is high and comparable with that in the adult population (Johnson, et al., 2000) (Feenstra, Busschbach, Verheul, & Hutsebaut, 2011; Grilo, et al., 1998; Westen, Shedler, Durrett, Glass, & Martens, 2003). Professionals in mental health care seem reluctant to diagnose PDs in adolescents, and so these disorders are probably underdiagnosed in this group. These adolescents may therefore only receive appropriate treatment at a later stage when a lot of damage already has been done. In addition, there is a scarcity of evidence-based and effective treatment models for adolescents with PDs. In this thesis we aim to remedy this knowledge gap and to raise awareness of PDs in adolescents. More specifically, we focus on the seeming reluctance of professionals in mental health care to diagnose PDs in adolescents and on the burden of disease for these patients, and we describe a pilot study for the treatment for adolescents with PDs.

A lot more research has been performed on PDs in adults, and particularly on borderline personality disorder (BPD) since the latter is one of the most common mental disorders in psychiatric populations (Leichsenring, Leibing, Kruse, New, & Leweke, 2011; Paris, 2010). For a long time, the focus of treatment for BPD was on very intensive treatments with the aim of losing a standardized diagnosis of BPD and on improving symptomatic outcomes such as self-harm and parasuicidal behaviour. However, interpersonal functioning and vocational adaptation remained impaired after intensive treatment (Bateman & Fonagy, 2008; Skodol, et al., 2005; Zanarini, Frankenburg, Reich, & Fitzmaurice, 2012), especially in patients with a severe PD such as BPD (Bateman, Gunderson, & Mulder, 2015). There is therefore some debate about whether very intensive treatment for BPD patients is the best approach for these severely disturbed patients since it is very hard for patients to improve their social skills outside the treatment room when they are in treatment wards for five days a week. This has resulted in a new theoretical development, salutogenesis, which means that patients have the opportunity to practise their new insights in the outside world (Fonagy, Luyten, & Allison, 2015). As a consequence, very intensive treatments for BPD now need to be compared with less intensive treatment forms. This thesis compares very
intensive treatment for BPD (Day Hospital Mentalization-Based Treatment; MBT-DH) with specialized treatment as usual (S-TAU). We also calculate the burden of disease in patients eligible for MBT as this is treatment for BPD patients at the most severe end of the continuum (Bales et al., 2012). This thesis is part of a broader research programme looking at PDs (including BPD) and MBT. The rationale underlying the thesis is explained in greater detail in the sections below.

Personality disorders
The DSM-IV-TR states that a PD can be defined as “an enduring pattern of inner experience and behaviour that deviates markedly from the expectations of the individual’s culture, is pervasive and inflexible, has an onset in adolescence or early adulthood, is stable over time, and leads to distress and impairment” (American Psychiatric Association, 2000). The general diagnostic criteria of the DSM-IV-TR (American Psychiatric Association, 2000) are shown in Table 1. Prevalence rates for PDs in adults are high: around 10-15% of adults in the community (Lenzenweger, Lane, Loranger, & Kessler, 2007; Torgersen, Kringlen, & Cramer, 2001) and up to 45% of psychiatric outpatients (Zimmerman, Chelminski, & Young, 2008; Zimmerman, Rothschild, & Chelminski, 2005) suffer from a PD. In adolescents, the prevalence rates of PD in both the general population (6-17%) (Johnson, et al., 2000) and clinical patient populations (41-64%) (Feenstra, et al., 2011; Grilo, et al., 1998; Westen, et al., 2003) are comparable with prevalence in adults. Moreover, there is evidence indicating that PDs in adults are associated with impaired quality of life (QoL) (Soeteman, Verheul, & Busschbach, 2008) and high societal costs (Soeteman, Hakkaart-van Roijen, Verheul, & Busschbach, 2008).

Part I: PERSONALITY DISORDERS IN ADOLESCENTS
The DSM-IV-TR (American Psychiatric Association, 2000) states that a PD is present in a child or adolescent when “the individual’s particular maladaptive personality traits appear to be pervasive, persistent, and unlikely to be limited to a particular developmental stage or an episode of an Axis I disorder” (APA, 2000, p. 687). In addition, treatment guidelines state that PDs can be diagnosed in adolescents starting at age 13 (National Institute for Health and Clinical Excellence (NICE), 2009). Furthermore, there are high levels of co-morbidity of both Axis I and Axis II disorders in adolescents with PDs (Coid, Yang, Tyrer,
General introduction

Table 1: General diagnostic criteria for a DSM-IV-TR Axis-II personality disorder
(American Psychiatric Association, 2000)

A. An enduring pattern of inner experience and behavior that deviates from the expectations of the individual’s culture. This pattern is manifested in two (or more) of the following areas:
   1. cognition (i.e., ways of perceiving an interpreting self, other people, and events)
   2. affectivity (i.e., the range, intensity, lability and appropriateness of emotional response)
   3. interpersonal functioning
   4. impulse control

B. The enduring pattern is inflexible and pervasive across a broad range of personal and social situations.

C. The enduring pattern leads to clinically significant distress or impairment in social, occupational, or other important areas of functioning.

D. The pattern is stable and of long duration, and its onset can be traced back at least to adolescence or early adulthood

E. The enduring pattern is not better explained as a manifestation or consequence of another mental disorder.

F. The enduring pattern is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition (e.g., head trauma).

Roberts, & Ullrich, 2006; Feenstra, et al., 2011; Loas, et al., 2013) that lead to current problems and predict future difficulties such as an elevated risk of suicide (or suicide attempts) (Johnson, et al., 1999; Yalch, Hopwood, Fehon, & Grilo, 2014), interpersonal problems, and problems at work (Crawford, et al., 2008; Winograd, Cohen, & Chen, 2008). It also seems that, by comparison with healthy controls, adolescents with a BPD make significantly more use of mental health services (Cailhol, et al., 2013). Given these difficulties faced by adolescents with PDs, one might suppose that there has been extensive research looking at adolescents with PDs, as is the case in adults. However, the opposite is true. For a long time, professionals in mental health care have been reluctant to diagnose PDs in adolescents, and the current and future pervasive effects of PDs in adolescents seem to be underestimated in clinical practice (Newton-Howes, Clark, & Chanen, 2015). Furthermore, there is not a great deal of research looking at treatments for adolescents with PDs. To raise awareness of PDs in adolescents, some questions need to be answered. First, we need to know to what extent scientific evidence and practice guidelines relating to PDs in adolescence have found their way into actual clinical practice. Second, we need to establish a picture of the burden of disease in these young people. Third, we need to know whether adolescents with
PDs are amenable to treatment. These questions are discussed in greater detail below.

Turning to the first of these points: despite the support that guidelines provide for diagnosing PDs in adolescents, it remains unclear to what extent scientific evidence and practice guidelines relating to PDs in adolescence have found their way into actual clinical practice since professionals in mental health care still seem reluctant to diagnose PDs in adolescents. This could be linked to the supposed transient nature of adolescent personality problems (Johnson, et al., 2000), stigmatizing effects (Griffiths, 2011; Miller, Muehlenkamp, & Jacobson, 2008) and the lack of effective treatments for this group. However, personality development is a lifelong process without sudden changes at the age of 18, and personality stability and change co-exist throughout life (Newton-Howes, et al., 2015). Furthermore, the consequences of not receiving appropriate treatments may be more far-reaching than the possible stigmatization associated with a PD diagnosis (Kongerslev & Chanen, 2015). In addition, the acceptance of a PD diagnosis in adolescents is usually hindered by the concern that the diagnosis is stigmatizing. Not diagnosing PDs in adolescents in order to avoid stigma or discrimination may therefore reinforce this stigma rather than diminishing it, and could do the patient more harm than good (Chanen & McCutcheon, 2013). The finding that adolescents with PDs are more likely to have a wide range of problems and to develop problems in adulthood than adolescents without PDs (Chen, Cohen, Kasen, & Johnson, 2006; Johnson, et al., 2005; Kasen, et al., 2007) is another reason that makes this reluctance to diagnose PDs in adolescents a source of concern. In addition, this reluctance may result in the underdiagnosis of personality pathology in adolescence and may, in turn, prevent referral to specialized treatment so that these adolescents do not receive appropriate care. Furthermore, even if they finally receive treatment at a later stage, it is possible that the effectiveness of treatment will be impaired because the patient will already be faced with a large number of functional difficulties (Bateman, et al., 2015; Gunderson, Stout, McGlashan, & et al., 2011).

Secondly, little is known about the burden of disease in adolescents with PDs. We defined burden of disease as QoL and societal costs. As QoL and societal costs play an important role in decisions about the level of medical cover, it is important to establish an evidence base for the burden of disease in adolescents with PDs.
The main focus of QoL research looking at adolescents has, until now, been on physical disorders. One of the studies that looked at mental disorders found that adolescents with a mental disorder have poorer QoL than those without, and even poorer QoL than adolescents with physical disorders (Bastiaansen, Koot, Bongers, Varni, & Verhulst, 2004). Other studies found that the costs of child and adolescent mental health problems in general are substantial (Hilderink & Van ‘t Land, 2009; Lynch & Clarke, 2006). However, no studies have looked at the burden of disease in adolescents with personality pathology.

Thirdly, the reluctance of clinicians to diagnose PDs in adolescents may delay the development of treatment models for this group. There is relatively little research at present looking at effective treatments for these adolescents. Some adaptations of evidence-based treatment programmes for adults with a PD have been tested, but this field is relatively new. For example, Chanen and colleagues (Chanen, et al., 2008) compared cognitive analytic therapy (CAT) (Ryle, 2004) with manualized clinical care in a randomized controlled trial (RCT) with 86 adolescents aged 15-18 years who fulfilled two to nine of the DSM-IV criteria for BPD. Both groups improved significantly in terms of psychopathology, parasuicidal behaviour and global functioning. Although there were no significant differences in outcome between the treatment groups, results suggested that the CAT group improved more rapidly (Chanen, et al., 2008). Emotion regulation training (ERT) was investigated in two RCTs in the Netherlands in adolescents aged 14-19 years. ERT plus TAU was compared to TAU only. One RCT included patients with ≥2 DSM-IV BPD criteria (Schuppert, et al., 2009) and the other included patients with ≥3 DSM-IV BPD criteria (Schuppert, et al., 2012). BPD features improved significantly in both treatment groups but no significant differences between the levels of improvement were found between the treatment groups. Dialectical behaviour therapy for adolescents (DBT-A) was compared with non-manualized, enhanced usual care (EUC) in an RCT looking at adolescents aged 12-18 with a history of non-suicidal self-injury and ≥2 DSM-IV BPD criteria. DBT-A was better than EUC at reducing self-harm, suicidal ideation, and depressive symptoms, both at treatment and at follow-up (Mehlum, et al., 2016; Mehlum, et al., 2014). Rathus and Miller (Rathus & Miller, 2002) evaluated DBT-A in a quasi-experimental design that included 111 suicidal adolescents. At follow-up, DBT-A resulted in fewer psychiatric hospitalizations and less dropout than TAU. However, there were no differences between the numbers of suicide attempts in the two groups.
Rossouw and Fonagy performed an RCT comparing MBT to TAU in self-harming adolescents aged 12-17 (Rossouw & Fonagy, 2012), most of whom fulfilled criteria for BPD (73%). They found that MBT was more effective than TAU at reducing self-harm and depression. In addition to Rossouw & Fonagy’s approach, other adaptations of MBT for adolescents have been described. Bleiberg described an adapted version of MBT for adolescents based on developmental and attachment theories (Bleiberg, 2001). Bevington and colleagues, in turn, developed Adolescent Mentalization-Based Integrative Therapy (AMBIT), which focuses on seriously disturbed and ‘hard-to-reach’ adolescents (Asen & Bevington, 2007). Nevertheless, none of these treatments specifically targeted adolescents with BPD features in an inpatient setting. Therefore, we report on feasibility and preliminary results of inpatient MBT for adolescents with borderline symptoms (MBT-A).

Research questions and hypotheses

These background considerations led to the following research questions (Q) and hypotheses (H):

Q1. To what extent have scientific evidence and practice guidelines relating to PDs in adolescence found their way into actual clinical practice?

H1. Scientific evidence and current guidelines have had little impact on actual clinical practice (Chapter 2).

Q2. What is the burden of disease in adolescents with personality pathology and is it comparable with the burden of disease in adults with PDs?

H2. Adolescents with personality pathology, like adults with PDs, suffer from a high burden of disease (Chapter 3).

Q3. Is MBT-A a feasible treatment for adolescents with borderline symptoms?

H3. We expect MBT-A to be a feasible treatment for adolescents with borderline symptoms (Chapter 4).
Part II: BORDERLINE PERSONALITY DISORDERS IN ADULTS

One of the key problems in BPD is thought to be the inability to mentalize, particularly in emotional interactions (Bateman & Fonagy, 2004). Mentalizing refers to “the mental process by which an individual implicitly and explicitly interprets the actions of himself and others as meaningful on the basis of intentional mental states such as personal desires, needs, feelings, beliefs, and reasons” (Bateman & Fonagy, 2004). These severe impairments in mentalizing often result in emotional instability, impulsive behaviour, and vulnerability in interpersonal and social interactions. Improving this capacity is therefore thought to be associated with a reduced need to rely on maladaptive coping strategies to deal with feelings of inner emptiness, impulsivity and conflicts in interpersonal relationships, and therefore to lead to the mitigation of symptoms and the enhancement of interpersonal functioning (Bateman & Fonagy, 2004). MBT is a promising approach for restoring this mentalizing ability in BPD patients. MBT was developed by Fonagy and Bateman in the United Kingdom (Bateman, Bales, & Hutsebaut, 2012; Bateman & Fonagy, 2004, 2006; Bateman & Fonagy, 2012). Two MBT approaches for adults with BPD have been developed in the meantime: MBT in a day hospital setting (MBT-DH) (Bateman & Fonagy, 1999) and intensive outpatient MBT (MBT-IOP) (Bateman & Fonagy, 2009). Both MBT-IOP and MBT-DH consist of a treatment phase and a maintenance phase, each lasting a maximum of 18 months.

Bateman and Fonagy were the only researchers to investigate the effectiveness of MBT-DH, comparing it with TAU (standard psychiatric care). After eighteen months of treatment, all the major outcome variables indicated that MBT-DH out-performed TAU in the following areas: depressive symptoms, suicide attempts and self-harm, number of inpatient days, and social and interpersonal functioning (Bateman & Fonagy, 1999). These results were maintained during the eighteen-month follow-up period (Bateman & Fonagy, 2001) and up to five years after discharge (Bateman & Fonagy, 2008). Two other studies, which were not conducted by the developers of MBT-DH, provided further support for the effectiveness of this treatment. Bales and colleagues (Bales, et al., 2012) investigated the effectiveness of MBT-DH in a naturalistic study in the Netherlands. They found significant improvements after eighteen months of treatment for all outcome variables, including a reduction in care consumption.
such as additional treatments and admissions during the last year before entry into MBT and during MBT treatment itself. In another study, Bales and colleagues (Bales, et al., 2015) matched 29 BPD patients receiving MBT-DH with 29 BPD patients receiving other evidence-based psychotherapeutic treatments (OPT) in a non-randomized design. Patients in both MBT-DH and OPT improved in terms of all outcome measures, psychiatric symptoms and personality functioning at 36 months of follow-up. Furthermore, at 36 months of follow-up, the effect sizes in the MBT-DH condition were significantly higher than in OPT, except for relational functioning (Bales, et al., 2015). Existing research looking at the effectiveness of MBT-DH indicates that there are other limitations in addition to the scarcity of that research. These include potential researcher allegiance (Bateman & Fonagy, 1999), problems with the generalizability of results to other countries given the large differences in health care systems between countries (Bateman & Fonagy, 1999), the lack of a control group (Bales, et al., 2012) and the use of a non-randomized design (Bales, et al., 2015). Given these limitations, we decided to further investigate the effectiveness of MBT-DH by comparison with manualized specialized TAU (S-TAU) in BPD patients.

In addition, MBT is a very intensive and therefore expensive treatment and the current climate of cuts in medical cover threatens access to this intensive, but promising, treatment for BPD. In addition to cost, an important factor in reimbursement is QoL. There is some evidence about QoL in BPD patients and the societal costs (McMain, Guimond, Streiner, Cardish, & Links, 2012; Soeteman, Hakkaart-van Roijen, et al., 2008; Soeteman, Verheul, et al., 2008; Van Asselt, Dirksen, Arntz, & Severens, 2007), but not specifically about BPD patients eligible for MBT. More research on this topic is warranted since BPD patients who are eligible for MBT tend to be the patients situated at the more severe end of the continuum (Bales, et al., 2012).

Research questions and hypotheses

Q4. What is the burden of disease in adults with BPD who are eligible for MBT?

H4. As these patients tend to be situated at the severe end of the continuum, we expect them to have a high burden of disease, which will be even higher than in other PD/BPD patients (Chapter 5).
Q5. Is MBT-DH more effective than S-TAU in the treatment of BPD after 18 months of follow-up?

H5. The primary hypothesis is that MBT-DH and S-TAU are both associated with significant improvements in primary and secondary outcomes. The secondary hypothesis is that MBT-DH will be associated with at least 20% more improvement than S-TAU in the primary outcome measure, the Borderline Personality Disorder Severity Index (BPDSI), at 18 months after the start of the intervention (Chapter 6 and 7).

CONTENTS OF THIS THESIS

Chapter 2 reports on the extent to which psychologists’ opinions about, and practice for, the diagnosis and treatment of PD in adolescents in the Netherlands and Belgium have been influenced by extant research on PD in adolescence. Specifically, psychologists were asked whether they thought PDs existed in adolescents and they were also asked about their actual practice for the diagnosis and treatment of PDs in adolescence. Chapter 3 describes the assessment of QoL and the economic burden in adolescents with personality pathology, and compares the results with the burden of disease in adults with a PD. Chapter 4 reports on feasibility and the preliminary results of inpatient MBT for adolescents with borderline symptoms (MBT-A). Chapter 5 discusses the burden of disease in BPD patients eligible for MBT in terms of QoL and societal cost by combining the baseline data of two RCTs in the Netherlands. We expected the burden of disease for the target population to be high. Chapter 6 describes the study protocol for an RCT comparing MBT-DH with a S-TAU in the Netherlands. S-TAU was delivered by a well-established treatment service. We expected both MBT-DH and S-TAU to be effective in terms of both primary and secondary outcomes. Nevertheless, we expected MBT-DH to outperform S-TAU at 18 months of follow-up. These results are presented in Chapter 7. The thesis concludes with a general discussion of the main findings, their limitations and implications (Chapter 8).
TRIALS INCLUDED IN THIS THESIS

In this thesis we used data from two trials:

TRAP study
TRAP is an abbreviation for Treatment Refractory Adolescents with Personality disorders. The TRAP study was implemented at the adolescent department of De Viersprong, the Netherlands, to investigate the prevalence, burden, structure and treatability of adolescent PDs. At the time of this study, the adolescent department of de Viersprong offered outpatient, day hospital and inpatient treatment programs for adolescents aged 14 to 19 years. Two hundred and fifty-seven adolescents were included in this study between March 2006 and March 2008. One hundred and thirty-three of these adolescents (51.8%) were admitted to Inpatient Psychotherapy for Adolescents (IPA) and were followed for two years. Chapters 3 and 4 look at this study.

MBT-DH versus S-TAU
This trial was an RCT conducted with the purpose of generating further data about the effectiveness and cost-effectiveness of MBT-DH by comparison with specialist treatment as usual (S-TAU) in the Netherlands. The 95 patients who entered this study were recruited from March 2009 to July 2012 from two mental health care centres in the Netherlands (De Viersprong and Arkin), both of which specialize in the treatment of BPD. Patients with a DSM-IV-TR diagnosis of BPD and a score of $\geq 20$ on the Borderline Personality Disorder Severity Index were included.
REFERENCES


Chapter 1


General introduction


Chapter 1


