Traumatized refugees: Morbidity, treatment and predictors of outcome

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Buhmann C., Mortensen EL, Ryberg J , Nordentoft M, Ekstroem M, Follow-up study of the treatment outcomes at a psychiatric trauma clinic for refugees, SUBMITTED

Buhmann C., Mortensen EL, Andersen I, Ryberg J , Nordentoft M, Ekstroem M, Cognitive Behavioral Psychotherapeutic treatment at a psychiatric trauma clinic for Refugees: description and evaluation, SUBMITTED

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1. Introduction

The treatment of traumatized refugees remains a challenge. It has been estimated that 30% of traumatized refugees suffer from PTSD (1). Therefore, identifying effective treatments of traumatized refugees in Western settings is of great importance. That is the topic of this PhD-thesis. In the following, the background of the two studies (FORLOB & PTF1) in the thesis will be explained and the existing knowledge of the psychopathology and treatment of traumatized refugees will be outlined. The introduction will start by looking at psychopathology and co-morbidity in traumatized refugees and the predictors of those, which corresponds to the topics covered in paper 1. This will be followed by a description of the published research evaluating the treatment of traumatized refugees, which is the topic covered in paper 2-4. Finally, the introduction will end with a brief explanation of the background of the studies and how they are related.

1.1 Traumatized refugees, PTSD and co-morbidity

Understanding the psychopathology of traumatized refugees is important because, previous trauma and current physical and mental health conditions have often been insufficiently characterized and addressed in most trials, and trials with traumatized patients tend to focus on PTSD. We also have limited knowledge of whether we can transfer results from other trauma populations to traumatized refugees because it is unclear whether trauma patients share the same psychopathology.

1.1.1 The traumas

Traumatized refugees experience accumulated and severe trauma, such as torture, imprisonment, living in refugee camps, loosing loved ones, witnessing others being killed and abused, sexual assault, losing their belongings and being in risk of losing their life. In civilian samples, the type of trauma is associated with the development of PTSD (2) and there is evidence that intentional trauma such as war or assault is associated with a higher prevalence of PTSD than unintentional trauma such as natural disasters and traffic accidents (3). Perceived life threat, type of trauma and peri-traumatic dissociation also predicts the PTSD severity in civilian populations (4).

Childhood trauma cannot be ruled out as a factor further complicating trauma reactions in traumatized refugees. Many have lived in war-like conditions most of their life in countries such as Iraq, Afghanistan or Palestinian refugee camps and they are no less prone to the kind of traumas observed in other civilian populations such as sexual abuse and accidents. Early childhood trauma has been found to increase risk of PTSD after trauma. In civilian populations, childhood accumulated trauma is associated with PTSD severity in adulthood (5). In military veterans, childhood trauma is associated with depression and suicidal ideation after controlling for PTSD (6) and a meta-analysis has shown that the co-occurrence of PTSD and depression is higher amongst patients who have experienced interpersonal trauma such as war and military action (7).

In addition, to the war-related trauma experienced by traumatized refugees, they also suffer from the trauma of leaving their country. They leave their friends and their family behind, travel to new countries on dangerous roads, spend time in asylum centers waiting in uncertainty for a residence permit and endure the stress of settling in a new culture, often living in isolation, poverty

and meeting intolerance and racism. A recent Australian multicenter study found that ongoing stress compound initial stress reactions and can lead to a delayed onset in severity of PTSD symptoms (8) and the trauma and stress of immigration is therefore likely to compound PTSD symptoms.

1.1.2 Psychiatric co-morbidity

It is well-established that PTSD and trauma are related (1) and PTSD is one of the only diagnoses in ICD-10 where the cause of the disorder is an integrated part of the diagnosis. The ability of the PTSD diagnosis to cover all typical trauma-related symptoms has been questioned and several other diagnoses have been suggested such as simple and complex PTSD / Disorder of Extreme Stress Not Otherwise Specified (DESNOS) and various PTSD subtypes. Whereas the PTSD diagnoses in ICD-10 and DSM-IV consist of a combination of avoidance, re-experiencing and hyperarousal, the DESNOS or complex PTSD diagnostic criteria consist of an alteration in regulation of affect and impulses, alterations in attention or consciousness, alterations in self-perception, somatization and alterations in systems of meaning (9-12). However, in the revision of the DSM-V the authors did not find enough evidence to support the DESNOS diagnosis. With the revision of the DSM-V, the trauma diagnoses have also been changed and a cluster of diagnoses relating to trauma have been collected in a separate chapter instead of classifying PTSD as an anxiety disorder. The PTSD diagnosis has largely remained the same albeit a few minor changes, but a new dissociative subtype with experiences of depersonalization or derealization has been added (13). In ICD-10, the diagnosis F62.0 Enduring Personality Change after Catastrophic Events, is the only diagnosis, which somehow catches the long-term and chronic personality changes that can be associated with trauma.

There are several other disorders, which are known to be related to trauma such as depression, anxiety disorders, somatization, dissociative disorders, borderline personality disorder and possibly other personality disorders (1, 14-18). Now evidence is also emerging that psychosis and bipolar disorder can be related to trauma (19-23). Most well-known is the relationship between trauma and depression. This has been observed in many samples of traumatized refugees (1, 7, 14, 18). It is also well documented, that traumatized refugees have a high co-morbidity of depression and PTSD (1, 14, 15, 18).

Psychosis has been argued to be related to trauma. In several case reports it has been described how traumatized refugees report psychotic symptoms without being diagnosed with a psychotic disorder. The understanding of the psychopathology is further complicated by the difficulties in distinguishing dissociative phenomena such as flashbacks from hallucinations and paranoid delusions from realistic fear, and in traumatized refugees the culturally bound expressions of distress ads to the complexity. Evidence exist for an association between childhood trauma and psychotic symptoms in first episode psychosis and in schizophrenia (20, 24). Reports also suggest that psychotic symptoms may be associated with PTSD in combat veterans without a psychotic disorder (21, 25), and in other traumatized populations (26, 27), which has led to the suggestion that a psychotic subtype of PTSD exists although the evidence so far is inconclusive. Braakman quotes a prevalence of psychotic symptoms of 15-64% amongst patients with PTSD and a study with U.S. combat veterans found a prevalence of 40% with psychotic symptoms in a sample with PTSD (25). In a more general review of auditory hallucinations Pierre argues that they are prevalent in populations who have suffered childhood abuse, in bereaved, after combat trauma and on a cultural basis although he points out that none of this has been solidly established (28). Reports of traumatized refugees who do not have psychotic or bipolar disorder (ICD-10 F2x & F30-F31.9), but have psychotic symptoms as a complication to their PTSD and depression have also been published, although they are scarce (29-31). Finally, Bhui has attempted to look at psychotic symptoms and trauma in a sample of Somali refugees with co-morbid depression and anxiety, however, he does not diagnose PTSD specifically and it is unclear whether the psychotic symptoms in this sample can be explained by psychotic depression or substance abuse (32).

1.1.3 Somatic disease, pain and somatization

Somatic complaints and pain are prevalent in traumatized refugees (33-38). This probably includes a combination of higher prevalence of somatic disease, chronic pain conditions caused by physical torture, a widespread vitamin D deficiency in transcultural populations (39), somatic components of psychiatric disorders such as anxiety, depression or PTSD and various somatization disorders. Studies have generally taken very different approaches to the identification and categorization of somatic complaints and few studies have examined patients for medical disorders. It has been suggested that somatic symptoms are an integral part of the PTSD diagnosis and the DESNOS diagnosis is trying to address this by including an item on somatic symptoms (9, 11). Evidence from other population groups is emerging for the links between trauma, PTSD and somatic disease and this is supported by biological models and corresponding biomarkers. Patients with PTSD have increased cardiovascular disease, rheumatoid arthritis, psoriasis, osteoporosis and thyroid disease and it has been suggested that this connection may be mediated by autoimmune activation. The autoimmune activation may be present before the development of PTSD or be caused by neuroendocrine and sympathetic nervous system activation (40, 41). The higher prevalence of hypertension and diabetes has also been observed in traumatized refugees, but it is not known whether this is due to the trauma or other risk factors present before the trauma (42). Another suggestion is that the association between somatic disease and PTSD is modified by depression (34, 43). Chronic pain is prevalent in patients with PTSD and depression and in particular in torture survivors and traumatized refugees (44-49).

New developments in the field of somatoform disorders and changes in the DSM-V can inform the study of somatic symptoms in traumatized refugees. Bodily Distress Syndrome (BDS) is a new diagnosis, which has so far only been used in a research context although it has served as an inspiration for the diagnosis “somatic symptom disorder” in DSM-V (13). It encompasses diagnoses from all organ systems covering various syndromes with somatic unexplained symptoms including somatoform disorders and somatization. The diagnosis itself requires three or more symptoms from at least three of the following categories: Musculoskeletal (muscle and joint pain, numbness and localized weakness), gastrointestinal (constipation, diarrhea, abdominal pain, regurgitations, nausea and vomiting), cardiovascular (palpitations, breathlessness, hot and cold sweats, dry mouth, flushing and trembling) or general symptoms (dizziness, headache, fatigue, memory impairment and concentration difficulties). The symptoms should not be explainable by other somatic disease (50). The causes of the syndrome is thought to be either dysfunction of the hypothalamic-pituitary-adrenal axis (HPA axis) or autonomic

regulation of physiological arousal (51, 52), which are both involved in the neurobiology of trauma as well.

1.1.4 Predictors of mental health condition in traumatized refugees

Understanding predictors of trauma-related disorders in traumatized refugees is important for the prevention of disease and understanding of psychopathology. There have been sporadic studies of predictors of the health condition of traumatized refugees, but they are mostly inconclusive. The inconclusiveness is further exacerbated by large heterogeneity amongst traumatized refugees and differences in study population and characterization of predictors so that comparability across studies becomes difficult. Some studies include patients who have stayed in their new country of residence for decades while others include patients still awaiting clarification of their legal status as refugees. Study samples have different trauma backgrounds, come from different cultures and live under different social circumstances.

The association between PTSD, depression and pre-migratory trauma is well-documented (1, 14, 15, 18), but any association depends on the pre-migratory context, which might also affect the association between mental health and demographics such as age and sex because each conflict has its own characteristics (15, 53). In a Latin American country with a military dictatorship, where torture is used systematically against dissidents of the regime, the trauma survivors will have a very different profile from the survivors of an African genocide where the civilian population was generally targeted in killings and human rights abuses. There seems to be a cumulative effect of trauma although the type of trauma might also influence mental health outcomes (14, 18, 54).

Numerous studies of the influence of post-migratory stressors and protective factors on PTSD and depression have been undertaken (15, 48, 55)**,** but they differ widely in study population, outcome measures and ways of assessing predictors. In most outcome studies, the social situation of patients (legal status, housing, income, employment etc.) is only summarily described. Most predictor studies have come from North America where social welfare and health services are organized differently than in Scandinavia and it is therefore questionable whether results can be transferred. However, there seem to be some evidence for the importance of employment (14, 15, 55-57) and economic strain (15, 58), language proficiency (14, 15, 56, 59) and social support (18, 55, 60, 61). In addition to this, the importance of legal status has been examined and there is evidence that the length of the asylum procedure and stay in asylum centers (62, 63) is of importance whereas the evidence on the importance of type of legal status is unclear (62, 64). Finally, there is indication that post-migratory predictors play an increasingly important role in relation to mental health, the longer the patients have been in their new country of residence (65-67).

Past psychiatric treatment and pre-trauma mental health have been less well described and studied in traumatized refugee populations. This may partly be explained by the fact that this kind of information is difficult to assess, as it is less factual, depends on self-report and patient recall as well as the patients' understanding of what mental health problems are and which treatment they have received in the past.

1.2 Treatment of traumatized refugees

The treatment of PTSD and other trauma-related disorders is currently under development. According to three Cochrane reviews on the pharmacological, psychotherapeutic and combined pharmacological and psychotherapeutic treatment of PTSD, the treatments with most evidence are Sertraline and Trauma-Focused Cognitive Behavioral Therapy (TFCBT) (68-71), but this mainly reflects the lack of good studies of treatment effect of many of the treatment modalities commonly used to treat trauma. The study populations in the reviews varies and few are comparable with traumatized refugees. Most studies are undertaken on survivors of traffic accidents, sexual assault victims and western war veterans, and there are reasons to believe that traumatized refugees differ significantly from war veterans and even more from persons who have experienced single traumas such as traffic accidents. Therefore, treatment cannot readily be transferred. Traumatized refugees often have several co-morbidities, they have suffered many consecutive traumas, they are in a foreign cultural and societal context, often have fewer social resources such as a job, secure housing and a social network than the background population, and their mental health problems are often chronic in nature.

The effect of treatment of traumatized refugees remains sporadically examined. Many studies have very limited methodology, working with small samples and without a control group. Treatments and study populations are very different and often not described in sufficient detail for results to be compared. Some studies focus on traumatized refugees in their country or region of origin and sometimes in refugee camp settings (72, 73), while others focus on the treatment of traumatized refugees in immigration countries and with different legal status ranging from asylum seekers to persons who have had long-term residence in the country where they are treated (74-78). A systematic review from 2010 (79), which specifically evaluated trials in refugee populations, found only 10 trials that used an acceptable methodology, and even these studies differed with regards to ethnic group, legal status of the patients, co-morbidities and outcome measures. Several studies of multi-disciplinary treatment for refugee populations in Denmark have been published, but they were based on small samples receiving ill-defined treatment and no significant change in patient condition was detected (44, 49, 65, 80).

1.2.1 Pharmacotherapy

In the Cochrane Review of pharmacotherapy for PTSD (69), the overall conclusion was that although evidence was limited it looked like there was some effect of medicine on PTSD. The majority of studies were made on SSRIs and only two studies included a NaSSA (Mirtazapine). One of these studies compared Sertraline and Mirtazapine. The authors found that there was no certain evidence of any pharmacological drug having more effect than others do on PTSD. Most of the trials were 12 weeks long. The current Danish and UK recommendations for pharmacotherapy of PTSD is SSRI treatment, preferably Sertraline (SSRI = Selective Serotonin-Reuptake Inhibitor) (81, 82). Since the publication of the Cochrane review, one RCT on Sertraline for PTSD in war veterans did not detect any effect of Sertraline on PTSD (83), whereas a more recent RCT comparing Sertraline and placebo in Iranian war veterans did find a positive effect of Sertraline treatment for PTSD (84). Mianserin is a noradrenergic and specific serotonergic antidepressant (NaSSA) and in addition to its antidepressant effect it also has a sedative effect and is therefore commonly used to improve sleep disturbances that are a part of

depression (85). Evidence for the treatment of PTSD with NaSSA remains scarce and most studies are made on Mirtazapine and not Mianserin, which is a similar drug, but not the same. One non-randomized trial of war-veterans in Australia found a positive effect of Mirtazapine on PTSD (86) and one study, which is also included in the Cochrane Review, compared Sertraline and Mirtazapine in war veterans from Korea and found a slightly higher effect of Mirtazapine on PTSD compared with Sertraline, but no differences in effect on depression (87). Finally, a pilot trial comparing Mirtazapine with placebo in the treatment of PTSD due to a variety of traumas found a positive effect of Mirtazapine on PTSD (88). Augmentation of SSRI treatment with Mianserin has been found effective in one trial (89).

Very few studies of pharmacological effect of treatment of traumatized refugees exist (79, 90). The few studies that have been published covers various pharmacotherapies tested under circumstances, which are methodologically suboptimal and which leaves no possibility to compare the outcomes of studies. In a RCT, Smajkic (91) compared treatment with Sertraline, Venlafaxine and Paroxetine and found a positive effect of treatment with SSRIs and a number of follow-up studies have reported changes after treatment with a combination of psychopharmacological agents. However, no follow-up studies have looked specifically at one agent and study populations have been too small and not had control groups, why it is not possible to identify any treatment effect (92-96).

1.2.2 Psychotherapeutic treatment

A Cochrane review of evidence-based psychotherapy interventions for PTSD in the general population concludes that individual Trauma-Focused Cognitive Behavioral Therapy (TFCBT), Eye Movement Desensitization and Reprocessing (EMDR), Stress Management and group TFCBT are effective in the treatment of PTSD (68, 70). Overall, it highlights that trauma focused treatments are more effective than non-trauma focused treatments.

There are some promising results on psychotherapeutic treatment of traumatized refugees although this area suffers from the same methodological problems as the studies of pharmacotherapy. Although several different kinds of treatment have been studied, the main modalities are TFCBT (44, 78, 97), culturally adapted TFCBT (74-76, 98) and Narrative Exposure Therapy (NET) (72, 73, 77). However, the evidence suffers from each treatment modality mainly having been studied by the same groups of researchers and their generalizability is therefore unknown. In addition to these, group therapy using trauma exposure has also been evaluated (99). Two recent systematic reviews concludes that there is cautious evidence for TFCBT, including culturally adapted versions, and NET (79, 100). A number of follow-up studies have described changes associated with multidisciplinary treatment, but in none of those studies individual treatment elements have been characterized in sufficient detail for them to be reproduced. This is summarized in several systematic reviews on the topic (90, 100, 101).

1.2.3 Combination therapies

One of the three Cochrane Reviews analyzed the combined effect of pharmacological and psychotherapeutic treatment and only found three studies of adults that lived up to the inclusion criteria in the review. These included one study on traumatized refugees (76) and the rest were predominantly on victims of sexual assault. The conclusion was naturally that more research was needed although the included studies suggested a possible positive interaction of therapy and medicine (102). Since then a study of survivors of terrorist attacks has found a larger effect of treatment with Paroxetine and prolonged exposure therapy than with prolonged exposure therapy alone (103). The only trial investigating combination treatment of traumatized refugees (76) compared Sertraline and Sertraline in combination with CBT, and found an added effect of combination treatment. This trial is the one included in the Cochrane Review on combination treatment.

1.2.4 Treatment in a transcultural setting

There is limited experience with adaptation of standardized and evidence-based treatment to various cultural contexts. When working with transcultural populations such as traumatized refugees there is either the possibility to work predominantly with one ethnic and cultural group and develop treatment specifically to the given cultural context such as it has been done by Hinton (74, 75, 98). This creates an opportunity to recruit therapists from the same cultural and linguistic background or to train a few translators in how to translate language used in a psychotherapeutic context. Alternatively, treatment and outcome measures will have to be translated into a variety of languages, which has been the model used frequently in Scandinavia (44, 49, 65, 80). However, this means that it is more difficult to tailor-make treatments to a specific cultural context and that nuances in language in psychotherapeutic treatment can be lost in translation. It also decreases effective time of therapeutic sessions unless the duration of each session is increased correspondingly. In a research context, working with many cultures and languages makes the validation of outcome measures more difficult.

Transcultural traumatized patients are facing the challenges of acculturation, which is defined as the "changes that take place as a result of contact with culturally dissimilar people, groups, and social influences" (104), which results in numerous challenges for migrants and refugees. One result can be demoralization syndrome, which has been characterized as consisting of 1) symptoms of existential distress, meaninglessness, pointlessness, hopelessness; 2) sense of pessimism, 'stuckness', helplessness, loss of motivation to cope differently, and a desire to die; and 3) associated social isolation, alienation or lack of support (105). Furthermore, transcultural patients often experience social stressors in the form of job and housing insecurity, uncertainties about their legal status in the country and a limited social network.

Finally, there are specific challenges with regards to pharmacotherapy in multicultural patients. Research is indicating that there are transcultural differences in pharmaco-genetics such as the CYP450 system (106) and in pharmaco-dynamics (107). This will affect tolerability and responsiveness to pharmacological treatment, and recommendations from one culture to another is therefore not necessarily directly transferable.

1.3 The background for the studies

The Competence Center for Transcultural Psychiatry (CTP) admitted the first patient in April 2008 and from the beginning, systematic data collection was integrated in the daily clinical work and the patients' condition was evaluated with self-rating scales before and after treatment. This enabled the follow-up study (FORLOB) which is part of this PhD. Treatment at the clinic was manualized from the beginning and manuals were based on

treatment with Sertraline and TFCBT, which was the best practice treatment of PTSD at the time (68-71, 81, 82).

The patients referred to the clinic are all transcultural patients with immigrant of refugee background. They must have specifically war-related trauma in their past and symptoms of trauma-related disorders such as PTSD and/or depression. Most patients referred have previously been in treatment elsewhere in the health care system. To receive treatment in the public health care system a patient needs to have temporary or permanent resident status and therefore no asylum seekers are treated at the clinic.

To be able to offer the best possible treatment to the patients, there was a need to evaluate the specific effect of best practice treatment for trauma in relation to the traumatized refugee patients seen at the clinic as little evidence existed on this. It was furthermore necessary to characterize the patient population better with regards to psychiatric diagnoses, demographic information and socioeconomic factors.

1.4 Objectives

The overall purpose of the PhD is therefore to characterize traumatized refugees in Denmark needing psychiatric treatment with regards to psychopathology and predictors of mental health and to evaluate the effects of the treatment.

- The purpose of Paper 1 (FORLOB) was to characterize physical and mental health in trauma-exposed refugees by describing a sample of the first 127 patients referred to CTP.

- The purpose of Paper 2 (FORLOB) was to evaluate the change in the condition of the patients after a combination treatment of TFCBT and antidepressants with a follow-up study of the first 85 patients seen at the clinic before the PTF1 trial started.

- The purpose of Paper 3 (FORLOB) was to describe and evaluate the psychotherapeutic treatment offered at CTP including identification of predictors of changes on outcome measures.

- The purpose of Paper 4 (PTF1) was to evaluate the treatment of traumatized refugees with Sertraline, Mianserin, psycho-education and TFCBT.

The National Committee on Health Research Ethics, the Danish Data Protection Agency, has approved FORLOB and PTF1 and PTF1 is also approved by EUDRACT, the Danish Health and Medicines Authority and the Research Committee of the Danish Association of General Practitioners.

2. Methods

In this section the methods used in FORLOB (paper 1-3) and PTF1 (paper 4) will briefly be outlined. For more detail, the reader is referred to the papers. The section is organized so that the methodology of FORLOB is described first, followed by a description of PTF1. In the end of the section, the interventions and outcome measures are described in more detail as this information is common to both studies.

2.1 FORLOB (Paper 1-3)

2.1.1 Design

The study is a follow-up study with patients answering self-ratings before, during and after treatment.

2.1.2 Participants

Eligibility criteria were

- A diagnosis of either PTSD or depression according to ICD-10
- More than 18 years old
- A history of war-related trauma or persecution
- No substance abuse (cannabis, cocaine, hallucinogens or opioids) apart from the regular use of benzodiazepines according to ICD-10
- No diagnosis of psychosis (any F20-F29 or F30.0-F31.9 diagnosis according to ICD-10)
- No urgent need for psychiatric hospitalization due to suicide risk or a need for intensive care

The baseline sample (Paper 1) consisted of 127 patients whereas 85 patients were included in the evaluation of the treatment (Paper 2-3); see details in figure 1. All participants were screened at the CPT from April 2008 to June 2009. For the evaluation sample (Paper 2-3) included patients had received a minimum treatment of 4 months' duration including treatment with an antidepressant, had received at least 4 consultations with a therapist, and had at least two outcome ratings (out of 4 possible) from baseline assessment and follow-up. All included patients had PTSD and/or depression according to ICD-10 and DSM-IV.

2.1.3 Data collection

Data collected during the initial assessment of the patients at the beginning of treatment, included self-ratings, a clinical assessment of the current psychiatric status and a structured interview collecting information on predictors and diagnoses according to the ICD-10 research criteria. Diagnoses of depression and PTSD were made according to the ICD-10 research criteria by physicians with psychiatric experience. Information on predictors included trauma history, socioeconomic situation, previous mental health problems and treatment and current physical health problems. Information about psychotic symptoms was based on information from the patient records during treatment in addition to the assessment made by the physician at first interview in the clinic. Psychotic symptoms included hallucinations on all sensory modalities and delusions. Symptoms were only included if they were not trauma-related. Somatic symptoms reported at assessment were compared to self-reported pharmacological treatment. If a patient reported a symptom, but did not receive medical treatment for it, it was categorized as "untreated somatic complaint", whereas somatic symptoms with corresponding treatment was categorized as "treated somatic complaint". Information on trauma including torture was obtained by asking the patients directly about a number of pre- and post-migratory factors. Self-reported information about somatic complaints, current and previous mental health as well as psychiatric treatment was supplemented with information from the letter of referral to the clinic. At every consultation, the patient's current clinical condition was rated by the health-professional responsible for the consultation.

Outcome measures in FORLOB included Harvard Trauma Questionnaire (HTQ), Hopkin's Symptom Checklist-25 (HSCL-25), Sheehan Disability Scale (SDS) and WHO-5 (See the description of ratings later in this section).

2.1.4 Statistical analysis

In Paper 1, linear regression analysis was used to investigate associations between diagnoses, initial scores on WHO-5, HTQ, SDS and HSCL-25 before treatment and pre-migratory and post-migratory factors. First, associations between outcomes and predictors were tested individually in linear regression models. Afterwards, variables that were found to be significantly associated with outcome measures were all included in multivariate regression models. Associations between various co-morbid diagnoses and self-ratings were examined with Pearson's correlations and student's t-test. In all analyses, a significance level of 0.05 was used.

In Paper 2 & 3, the change in self-rating scores between the beginning and the end of the treatment was evaluated with a paired t-test. Cohen's d was calculated (mean change divided by the standard deviation at baseline) (108) to evaluate the effect size of change on each self-rating scale and Pearson correlations were used to calculate the correlation between outcome measures and correlation between baseline and follow-up. Finally, a measure of reliable change was calculated (109) for each outcome rating scale. In addition to descriptive statistics, linear univariate and multivariate regression models were used to investigate possible associations between changes in the patient's state and potential predictors of change. Change was measured as the difference between ratings at baseline and at follow-up and all regression models were adjusted for baseline scores. The predictors included in the analysis were indicators of trauma history, previous psychiatric history, co-morbidity, socioeconomic indicators and treatment received. Variables, which in univariate regressions models were found to be significantly associated with change in the patient's state ($p \leq 0.05$), were all included in multivariate regression models. In Paper 3, Pearson's correlation coefficients were used to evaluate the correlations between therapist assessments and outcome. Paired t-tests were used to evaluate the change over time in Beck & Young Cognitive Therapy Rating Scale (CTRS) score and the therapists' evaluation of the patient.

2.2 PTF1 (Paper 4)

2.2.1 Trial design

The trial was a pragmatic randomized controlled 2x2-factor trial. The allocation ratio to the four groups was 1:1:1:1. An overview of included and excluded patients can be seen in Figure 1.

2.2.2 Participants

Eligibility criteria for participants were:

- Adults (18 years and older)
- Refugees and persons based in Denmark due to family reunification
- Persons with PTSD according to the ICD-10 diagnostic criteria.
- Persons with a history of war-related psychological trauma such as imprisonment, torture, gross human rights abuses, inhuman and degrading treatment or punishment, organized violence, prolonged political persecution and harassment or war.
- Persons motivated to receive treatment and who had given written informed consent

Patients were excluded if they:

- Had a severe psychotic disorder (ICD-10 diagnosis F2x and F30.1-F31.9). However, patients were not excluded solely based on psychotic symptoms, as these are prevalent in the study population.
- Had addiction to psychoactive substances (ICD-10 F1x.24-F1x.26). The use of benzodiazepines or morphine prescribed by a physician did not lead to exclusion as many patients take several different kinds of painkillers and tranquilizers.
- Had a need for somatic or psychiatric hospitalization
- Were pregnant or lactating

Patients were screened for psychoses using chapters 1, 10, 14, 16, 17, 18 & 19 of the Schedules for Clinical Assessment in Neuropsychiatry (SCAN), version 2.1 (110).

2.2.3 The interventions

The four intervention groups were as follows:

1) *Combination treatment:* TFCBT, psychopharmacological treatment and consultations with a physician for 6 months, starting with 2 months of treatment with antidepressants and psycho-education weekly, followed by 4 months of TFCBT sessions weekly and monthly consultations with a physician for adjustment of antidepressant treatment. In total, the aim was for the treatment to consist of 10 consultations with a physician and 16 sessions with a psychologist.
2) *Medicine:* Psychopharmacological treatment, psycho-education and consultations with a physician on a weekly basis for 2 months followed by a monthly consultation for a period of 4 months. The aim was for the treatment to consist of a total of 10 consultations with a physician.
3) *Therapy:* TFCBT sessions including psycho-education with a psychologist over 6 months. The aim was for the treatment to consist of a total of 16 sessions with a psychologist. Any psychopharmacological treatment was administered by the referring physician and was ideally continued as it was at baseline.
4) *Waiting list:* The control group was on a waiting list for six months. Any psychopharmacological treatment was administered by the referring physician and ideally continued as it was at baseline.

2.2.4 Outcome measures

The primary outcome measure was PTSD measured with

- Harvard Trauma Questionnaire (HTQ).

Secondary outcome measures included

- Hopkin's Symptom Checklist-25 (HSCL-25)
- Hamilton ratings on depression and anxiety (Ham-D, Ham-A)
- SCL-90 (somatization section)
- VAS scales for back pain, pain in the upper and lower extremities and headache
- Sheehan Disability Scale (SDS)
- Global Assessment of Functioning, Function and Symptom section (GAF-F/GAF-S)
- WHO-5 on Quality of Life (See the description of rating scales below for more details).

2.2.5 Sample size and power calculations

The power for the analysis of the quantitative outcome variables (scale scores) was calculated to be 32%, 70%, 93% if the differences between two groups corresponded to 0.3, 0.5 and 0.7 standard deviation respectively. Thus, power would be low if treatment effects were much smaller than 0.5 standard deviation, but if there was no significant interaction between the TFCBT and the pharmacological treatment, it would be possible to compare groups with 100 individuals in each group. This provides substantially greater statistical power with the calculation for comparison of an average difference of 0.3, 0.5 and 0.7 SD showing power of 56%, 94% and close to a 100%. All the power calculations were performed with a significance level of 5%. These power calculations are valid for the HTQ scores and other quantitative outcome measures. Based on the power calculations we aimed at 50 patients completing the treatment in each group. With a drop-out rate of 25% it would require 270 patients to be included. Due to slightly higher drop-out in the waiting list group the trial was continued until 280 patients had been included.

2.2.6 Randomization

Randomization took place after a pre-trial assessment performed by a physician at the clinic. The randomization sequence was computer generated by the Department of Biostatistics at the University of Copenhagen, which was not involved in the research project. Randomization was stratified by sex and score on HTQ (above and below 3.2), so that patients with equal illness severity were allocated to the groups. Allocation was concealed by using sequentially numbered sealed envelopes. The envelopes were kept in an office physically separate from the clinic and were administered by a secretary, who was not associated with the research project. When a patient had been included in the trial, the physician telephoned the office administering the randomization envelopes and was immediately informed which group the patient was allocated to.

2.2.7 Blinding

It was not deemed possible to blind the patients, the physicians or the psychologists to the treatment group because of the large difference between the treatment modalities. A blinded outcome measure was obtained by rating all patients at baseline and follow-up with Ham-D and Ham-A. No similar observer rating existed for PTSD. A group of medical students not otherwise involved in the treatment, undertook the blinded ratings and met regularly to practice to increase rater reliability.

2.2.8 Statistical methods

Dropout analyses were conducted comparing included and excluded patients screened at the initial assessment and completers and non-completers with the chi2 test and the Kruskal-Wallis equality-of-populations rank test for categorical and ordinal variables. A series of analyses of the primary and secondary quantitative outcome variables were conducted: 1) Linear regression analyses of differences between pre-treatment and post-treatment scores 2) Linear regression was also used to analyze post-treatment scores in models including pre-treatment scores as predictor 3) Mixed models using Stata's xtmixed procedure were used to conduct intention-to-treat analyses. The basic model included the two treatment effects and an interaction term. Since there were no significant interaction between medicine and psychotherapy, results are reported for models only including the two main effects. Significantly, different distributions in the four treatment groups were found for country of origin and language, and these potentially confounding variables were included in models, which also included the two treatment effects. To characterize the effect size Cohen's d was used. We calculated Cohen's d for differences between groups (difference between pre-treatment and post-treatment score in each group divided by the standard deviation of the whole sample at pre-treatment) and for within group changes from pre-treatment to post-treatment (difference between pre- and post-treatment rating within group divided by SD at pre-treatment in group). A Cohen's d of 0.2 equals a small effect, 0.5 equals a moderate effect and 0.8 equals a large effect. Trials are often designed to compare a new treatment with Treatment As Usual (TAU). In this trial, we did not have a TAU given the limited evidence on treatment. In principle patients, were compared to a waiting list, but the participants on the waiting list continued treatment as usual, which in PTF1 meant that of waiting list patients 32% received antidepressants including trial medicine and 13% received antipsychotics. In all analyses $p<0.05$ was considered significant.

2.3 Outcome measures

All self-report questionnaires were available in the six most common languages at the clinic (Arabic, Farsi, Bosnian / Serbo-Croatian, Russian, Danish and English), which included the language of 92% of patients. If no translation was available, a translator gave a verbal translation from the official version in the language he/she felt most comfortable using.

2.3.1 Rating of PTSD and depression

HTQ is used to evaluate PTSD. We used the first 16 questions of the symptom part (Part IV) of HTQ, which are used to evaluate the PTSD-diagnosis according to ICD-10 and DSM-IV. HSCL-25 is a shorter version of the Symptom Checklist-90 (SCL-90) with a focus on anxiety and depression symptoms (111-114). Both HSCL-25 and HTQ have been used on refugees and torture victims in several previous studies. In HSCL-25 and HTQ, individual questions have a 1-4 Likert format with 4 being the highest symptom level. The cut-off value for PTSD on HTQ is 2.5 and for depression and anxiety on HSCL-25 it is 1.75. Depression and anxiety was further assessed with the Hamilton depression and anxiety scales (Ham-D and Ham-A), which are observer scales measuring the progression of depression based on a semi-structured interview. The items on the scales are scored in a 0-4 /0-2 Likert format with 4 being the highest symptom level. Ham-D has 17 items and Ham-A has 14 items. Ham-D and Ham-A have been used extensively in psychiatric research (115, 116).

2.3.2 Pain and somatization

Somatization was rated with the somatization section of the SCL-90, which is a 1-5 Likert format with 5 being the highest symptom level (117). The level of pain was estimated with four Visual Analogue Scales (VAS) one for back pain, one for pain in the upper extremities, one for pain in the lower extremities and one for headache. The VAS scale is widely used to assess intensity of symptoms (118) and has been used with traumatized patients before (45). The patients marks the symptom intensity on a 10 cm long scale with 10 being the highest symptom intensity.

2.3.3 Quality of Life and level of functioning

To assess quality of life we used the WHO-5 scale, which is a widely used self-administered questionnaire with five questions (0-5 6 point Likert scale with 0 being the lowest score and 5 the highest). The theoretical raw score ranges from 0 to 25 and is transformed into a scale from 0 (worst thinkable well-being) to

100 (best thinkable well-being). Thus, higher scores mean better well-being (119). The scale has been used to assess the quality of life in a series of psychiatric diagnostic groups (120-123).

The Sheehan Disability Scale (SDS) is a self-report rating scale, which assesses the level of functioning in terms of family, work and social network by using three visual analogue scales from 0-10 with 10 being the lowest possible level of functioning. The scale has been used in a variety of psychiatric patient groups (124, 125). Global Assessment of functioning, function (GAF-F) and symptom (GAF-S) scores are numerical observer scales used to assess the degree of social functionality and the overall severity of symptoms among adults. Each of the two measures consists of a number between 0 and 100 with 100 representing the highest level of functioning. The scale are used widely in psychiatry. It has been validated in a variety of languages and it is used frequently in clinical trials in psychiatry (126, 127). GAF-F and GAF-S were estimated by a physician at pre-assessment and at follow-up. Unfortunately, due to implementation error, no post-treatment GAF was assigned to patients in the group receiving only psychotherapy and the analyses have therefore been adjusted accordingly.

2.3.4 Therapist's self-evaluation and evaluation of patient suitability for treatment

At the beginning and at the end of the psychotherapeutic treatment (session 4 and 12) the psychologist responsible for the treatment of the patient evaluated his/her own performance in therapy by using the Beck & Young Cognitive Therapy Rating Scale (CTRS) (128). CTRS is used to evaluate the therapist's competences and consists of 11 items scored on a 6 point Likert type scale. It covers general therapy skills (feedback, understanding, interpersonal effectiveness, and collaboration), CBT skills (guided discovery, focus on key cognitions and behavior, strategy for change, application of CBT techniques) and structure in therapy (agenda, pacing and efficient use of time, and use of homework assignments) (129). The scale has been used in previous CBT research (129, 130) and its psychometric properties are well-described (128). If pacing, use of homework and use of behavioral strategies were excluded, the internal consistency of the scale was acceptable (coefficient alpha = 0.87). We therefore made an aggregated score of the remaining eight items, which was used in the analysis of predictors of change in patient condition in FORLOB.

The therapist evaluated the patient's suitability for therapy at session 4 and session 12 using a Likert type scale of 1-5, where 5 is the best score. The scale comprises six items: motivation, mental flexibility, participation in therapy, empathy, introspection and treatment alliance. The scale has been adapted to various clinical settings (131, 132). The items on the scale are highly correlated and consequently we calculated a total score for the 6 items and this was used in the further analysis (alpha = 0.92).

2.4 The interventions

The TFCBT treatment was manualized and consisted of sessions with a psychologist with training in CBT. The manual included core CBT methods, methods from Acceptance & Commitment Therapy (ACT), mindfulness exercises and in vivo, interoceptive and visualized exposure. Psychologists, who were trained in this method and received supervision by specialists in CBT, conducted the psychotherapeutic treatment. The manual was developed in co-operation with experts in cognitive behavioral therapy.

Medical treatment consisted of treatment with Sertraline gradually increased by 25-50 mgs to a maximum dose of 200 mgs. If patients had trouble sleeping Sertraline treatment was supplemented by treatment with Mianserin in doses of 10-30 mgs at night, increased weekly by 10 mgs. Patients who had too many side effects from Sertraline were switched to Mianserin only. Any other psychopharmacological treatment at baseline was ideally discontinued following the Maudsley Guidelines (133). If patients were psychotic during treatment any antipsychotic treatment was continued and if the patient wasn't in antipsychotic treatment at baseline small doses of Perphenazine was administered. The patients received Sertraline and Mianserin free of charge. The cheapest generic products were used, which at the time of the studies was Sertraline Ranbaxy and Mianserin Merck. Psycho-education was manualized and covered the illness, the treatment, sleep, life-style incl. relaxation-exercises, physical and social relations, pain, cognitive functions, and the influence of the illness on the family.

All patients attended one session with a social worker at the beginning of the treatment to clarify their social situation. If needed during the treatment period there was a limited opportunity to have additional appointments with the social worker. Each treatment ended with an evaluation session where the patient, the physician, the psychologist and the social worker (if need be) were present.
If necessary, translation was provided during assessment and treatment consultations, which was the case for 54% of patients. All the interpreters were associated with the clinic and had experience in interpreting the ratings, the psychotherapy and the psycho-educational sessions. In order to determine the program compliance psycho-education topics covered, psychotherapeutic methods used and compliance with medical treatment were registered at each session

Patients in FORLOB (Paper 1-3) only received combination treatment, whereas patients in PTF1 (Paper 4) received either combination treatment, only medicine, only psychotherapy or were on a waiting list.

3. Results

The sizes of samples in PTF1 (paper 4) and FORLOB (papers 1-3) are shown in the flow diagram in figure 1. The study population in PTF1 and FORLOB are very similar with regards to baseline characteristics (see table 1). When tested with Pearson's Chi2-test significantly ($p<0.05$) more patients in PTF1 had experienced war and had been in treatment with antidepressants before treatment at CTP. In addition to this, significantly more PTF1 patients had treated and untreated symptoms from the central nervous system and the cardiovascular system. With regards to all other factors the two study populations were alike.

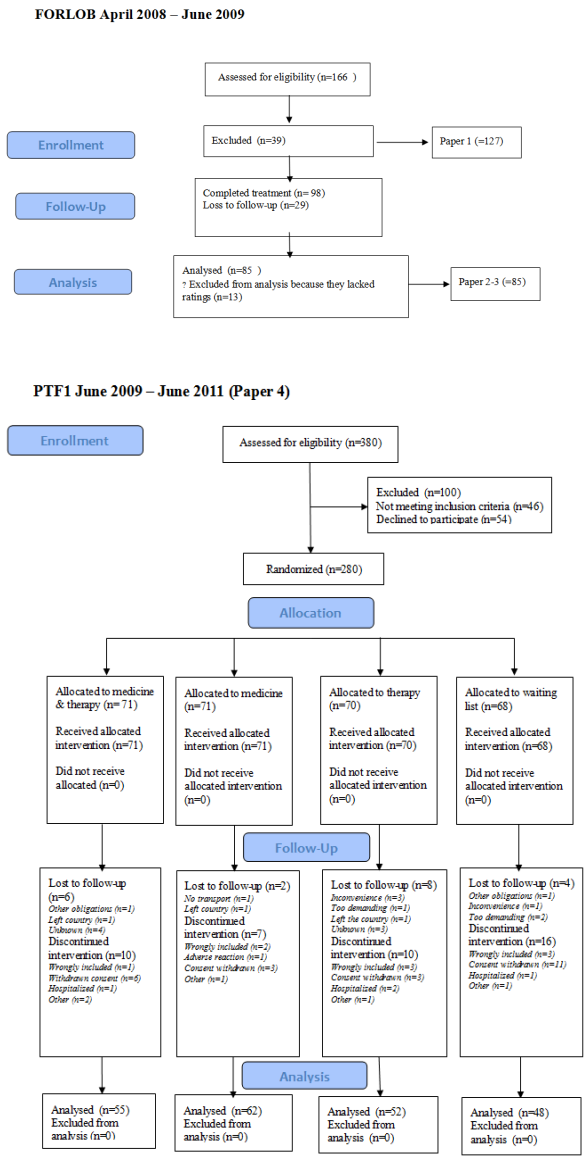
3.1 Psychopathology of traumatized refugees

3.1.1 Trauma-related disorders

Inclusion criteria in PTF1 required all patients to have PTSD whereas FORLOB only required patients to have either PTSD or depression. Generally, patients had high scores on self-ratings in both PTF1 and FORLOB. Scores on observer-ratings in PTF1 were slightly lower corresponding to moderate depression and anxiety on Ham-D and Ham-A, and moderate level of functioning on GAF-F/GAF-S. In both studies we found high co-morbidity between the

two disorders with 94% of patients in PTF1 having moderate and severe depression according to ICD-10 in addition to PTSD and 85% of patients in FORLOB having both PTSD and depression.

Figure 1: flow diagrams for the two studies



Both studies are thereby mainly studies of the treatment of patients with a combination of depression and PTSD. There was a significant ($p<0.05$) and high correlation between self-ratings (HSCL-25, HTQ, SDS, WHO-5) in FORLOB (lowest correlation = 0.35 between HSCL-Anxiety and SDS / highest correlation between HSCL-depression and HTQ = 0.69). The correlation between self-ratings and ICD-10 diagnosis was lower (HSCL-25 & ICD-10 depression and HTQ & ICD-10 PTSD both had a correlation coefficient of 0.28). In PTF1 we also systematically assessed enduring personality change after catastrophic events (ICD-10 F62) although pre-trauma personality could not be assessed validly. We found a prevalence of 27% in the sample, which, due to the lack of valid personality disorder diagnosis in transcultural populations, is the best possible estimate of personality disorder, although it is limited to personality change caused by the trauma. In addition to this, 46% of patients in PTF1 reported previous traumatic brain injury as part of their trauma. In multivariate regression models, HTQ arousal symptoms were significantly associated with social isolation, persecution, headache, pain in the arms and number of body parts with pain. Higher HSCL-25 depression score was associated with pain in the legs (paper 1).

3.1.2 Somatic disease

Patients in both studies had equally high levels of pain and many somatic complaints. When asked about pain at pre-treatment assessment 80-100% of patients reported pain depending on the site of the pain, on VAS scales, patients had mean scores of 6-8, and 49% of patients were taking pain medication. When comparing treated and untreated somatic complaints based on patient reporting of treatment and symptoms, there was a 48% prevalence of treated somatic complaints in FORLOB and 58% of treated somatic complaints in PTF1, but only 36% with actual somatic disease (epilepsy, Horton's headaches, arthritis, hypothyroidism, diabetes, colitis, asthma, Recklinghaus' disease, HIV and cardiovascular disease). In Paper 1, we found no correlation between treated and untreated somatic complaints and PTSD or depression. In multivariate linear regression models lower age, being an ex-combatant and social isolation was associated with higher self-reported pain score. Untreated somatic complaints was associated with back pain (paper 1). Although patients in FORLOB and PTF1 have not specifically been screened for BDS, we made a rough estimate by fitting information on pain, somatic complaints and somatic disease to the diagnostic algorithm for BDS (52). This results in 60% of patients in PTF1 having symptoms corresponding to a diagnosis of BDS, although lack of specific information and lack of controlling for other explanations of the symptoms will likely have resulted in over- or under-reporting.

3.1.3 Psychotic symptoms

In FORLOB, we looked through all patient records and identified patients where psychotic symptoms like hallucination and delusions had been described. In addition to this, we had information from the pre-treatment assessment on self-reported psychotic experiences and information on whether the patients had been hallucinating during treatment sessions. In PTF1, in addition to the above information, all caregivers had noted whether the patient reported psychotic experiences since last session and whether these were estimated to be trauma-related (7%) or not (1%). In FORLOB (paper 1), we found 16% of patients to have been assessed psychotic during treatment and in PTF1 (paper 4) the corresponding number was 9%. In correlation analysis in FORLOB, we found a significant correlation between psychotic symptoms and depression/PTSD/level of functioning measured with HTQ, HSCL-25 and SDS (correlation coefficient of 0.22). Analyzed with t-test, there was a higher symptom score on all three symptom clusters of PTSD (re-experiencing, avoidance and arousal) in patients with psychotic symptoms and the difference between psychotic and non-psychotic groups was significant for avoidance symptoms (diff=1.03, p=0.02). In multivariate linear regression models, higher age was associated with psychotic symptoms (paper 1).

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3.2 Description of treatment

The treatment in FORLOB (paper 2-3) and PTF1 (paper 4) are compared in Table 2. In FORLOB, the sample was selected for being in both treatment with antidepressants (Sertraline and Mianserin) and psychotherapy, which means that overall FORLOB corresponds to the group receiving combination treatment in PTF1. Fewer details on medical treatment is available in FORLOB than PTF1, but generally FORLOB patients were treated with higher mean dose Sertraline and more patients were treated with core cognitive methods in FORLOB than in PTF1. All patients in active treatment in both studies received psycho-education from either the physician or the psychologist. Treatment in FORLOB may also have been slightly longer although the six months' treatment in PTF1 is counted from first to last treatment session and the eight-month treatment in FORLOB is counted from pre-treatment assessment to last treatment session. In FORLOB 36% of patients received TFCBT whereas only 19% of patients received exposure treatment in PTF1. When tested with Pearson's Chi2-test, significantly fewer patients in PTF1 had been treated with ACT and CBT methods ten times or more and there was a significant difference in duration of treatment.

3.2.1 Predictors of treatment outcome

In Paper 3, psychotherapeutic predictors of treatment outcome were examined with univariate and multivariate regression models. Only few predictors had a significant ($p<0.05$) association with treatment outcome in multivariate analysis. Mindfulness was associated with negative changes in WHO-5 score ($\beta = -17.1$, $p = 0.05$) and breathing exercises were negatively associated with change in SDS score ($\beta = 1.06$, $p = 0.01$). There was a significant improvement in HSCL-25 ($\beta = -0.40$, $p = 0.02$) with the use of thought records and homework compliance was significantly associated with a marginal positive change on HTQ score ($\beta = -0.004$, $p = 0.03$). The 42% who had received therapy involving the use of restructuring of thoughts generally had a larger positive change on all four treatment outcomes than the remaining patients. When t-tests were performed, the change was significantly larger on HTQ (difference=0.2, p=0.05) and on WHO-5 (difference=10.6, p=0.03). There was no significant difference in baseline score on any of the outcome measurements between the group who had received cognitive therapy using the core CBT

Table 1: Description of study population in FORLOB and PTF1

Description of patient population	FORLOB (N=85)	PTF1 (N=217)
	Mean (s)	
Mean no. Of years in DK	14.5 (6.4)	14.7 (6.1)
Age	43.4 (8.0)	45 (9)
Mean no. Of years since first trauma	22.6 (8.9)	14.7 (9.6)
	All N (%)	
Sex (man)	40 (47)	128 (59)
Trauma		
Experienced war*	72 (86)	209 (96)
Been a soldier	19 (24)	51 (24)
Been persecuted	64 (81)	190 (89)
Lived in a refugee camp abroad	18 (26)	60 (28)
Been in prison	51 (61)	124 (57)
Been subjected to torture	46 (54)	92 (43)
Been politically active	19 (41)	56 (26)
Lived in asylum centre in Denmark	45 (71)	130 (63)
Mental Health		
PTSD	74 (87)	217 (100)
Depression (moderate or severe)	83 (98)	204 (94)
Both PTSD and depression	72 (85)	204 (94)
Assessed psychotic during treatment	13 (15)	19 (9)
Pain	83 (99)	214 (99)
Headache	80 (95)	201 (93)
Back pain	73 (90)	198 (91)
Pain in arms	67 (81)	172 (79)
Pain in legs	70 (83)	183 (84)
Previous mental health		
Previous addiction	12 (14)	25 (12)
Previous psychiatric treatment	75 (88)	173 (80)
Previous psychopharmacological treatment	68 (80)	186 (86)
Antidepressants*	51 (60)	157 (73)
Antipsychotics	15 (18)	41 (19)
Benzodiazepines	29 (34)	80 (37)
Mood stabilizers	2 (2)	4 (2)
Physical health		
Treated somatic complaints	41 (49)	125 (58)
CNS (incl. headache)*	16 (19)	20 (9)
Heart & lungs*	10 (12)	62 (29)
Gastrointestinal	18 (22)	55 (25)
Untreated somatic complaints (excl. Pain)	78 (94)	206 (95)
CNS (incl. Headache)*	65 (78)	182 (86)
Heart & lungs*	23 (28)	93 (43)
Gastrointestinal	36 (44)	82 (38)
Psychosocial resources		
Social relations		
Living with a partner	51 (65)	133 (64)
Children	68 (85)	182 (87)
Have no friends/familiy in Denmark/ live alone	10 (12)	20 (10)
Income		
Working	6 (8)	13 (6)
Retired	7 (9)	18 (9)
Public support	63 (82)	172 (85)
Any education	58 (76)	193 (96)
Employment Status*		
Currently	8 (12)	17 (13)
Never	13 (20)	39 (20)
Previously	44 (67)	137 (67)
Country of origin		
Iraq	31 (36)	79 (36)
Afghanistan	9 (11)	21 (10)
Iran	9 (11)	27 (12)
Permanent leave to stay	65 (90)	175 (86)
Translator needed	42 (49)	118 (54)

*Significant difference between FORLOB and PTF1 with Chi2-test (p<0.05)

methods several times and the group where the core methods had only been used sporadically.

3.2.2 Patient suitability ratings and the therapist's self-evaluation

Patient suitability for therapy was evaluated for 46 patients in paper 3. Patient suitability for therapy was positively associated with change on SDS (β = -1.1, p = 0.003) and HSCL-25 (β = -0.27, p = 0.03) scores in multivariate analysis. There was a high correlation between the therapist's self-evaluation and the therapist's evaluation of the patient's suitability for therapy (Pearson correlations 0.6 – 0.9) and there was a significant correlation between scores on patient suitability and bad baseline scores on SDS (cor=-0.26, p<0.02) and WHO-5 (cor=0.22, p<0.04) when evaluated with Pearson's correlations. There was a significant correlation between high score on patient suitability for therapy and change in outcome with regards to HSCL-25 (cor=-0.27, p<0.02) and HTQ (cor=-0.24, p<0.03). For SDS and WHO-5 the trend was the same although these results were not significant. On the therapist's self-evaluation, the total score was 3.3 of 6 possible. There was a significant association between score on the therapist's self-evaluation and change in SDS (-0.48, p<0.009). Likewise there was a significant correlation between self-evaluation score and SDS at baseline (cor -0.53, p<0.002). We also found a significant correlation between WHO-5 baseline score and self-evaluation score (cor=0.46, p<0.009).

3.3 Change in condition

At pre-treatment assessment, most patients had high scores on the self-report rating scales (See table 3 paper 2 and table 3 paper 4). The overall changes on the scales in FORLOB (paper 2) had a mean Cohen's d at about 0.6 (ranging from 0.44 on the HSCL-25 anxiety scale to 0.67 on HTQ), and thus moderate effects of the treatment was observed by Cohen's standards at the group level. The Reliable Change Index (RCI) is a measure of the minimum individual change in pre–to post-treatment ratings, which can be called statistically significant. On HTQ 30% of patients showed reliable change from baseline to follow-up, whereas the proportion of patients with a statistically significant individual change for the other rating scales was 35% for HSCL-25 28% for WHO-5 and 16% for SDS. In multivariate regression models improvement in HTQ score was negatively associated with being on public financial support ((β = 0.42, p = 0.01, CI = 0.11-0.74) and improvement in HSCL-25 scores was negatively associated with pain in the arms (β = 0.37, p = 0.03, CI= 0.05-0.68). We found no correlation between the baseline values and the changes in outcomes when calculating the correlation coefficients. They were very close to zero for all four scales ranging from 0.1 on SDS to 0.2 on HSCL-25 and WHO-5.

In PTF1 (paper 4) there was no significant differences among the groups in pre-treatment outcome measures when tested with linear regression. Analyses of the differences between pre- and post-treatment outcome scores showed no significant main effects or interactions between the two treatments for the primary outcome measure HTQ or any of the secondary outcomes. None of the secondary outcome measures showed a significant effect of psychotherapy, whereas treatment with antidepressants in combination with psycho-education was associated with significant improvement (p<0.05) on Ham-D, VAS headache, SDS, GAF-F and GAF-S when tested with linear regression models and Ham-A was borderline significant with p=0.056. The effect associated with the two treatments as estimated by the difference between pre-treatment and post-treatment ratings remained significant when adjusted for the potential confounders, country and language and they were also significant in models including pre-

treatment scores as predictor and analyzing post-treatment scores as outcome. The effect sizes calculated as Cohen's d for differences between groups receiving medicine and not receiving medicine were generally small except for on GAF-F and GAF-S. The Ham-D reg. coefficient was 2.35 and Cohen's d was 0.41, the Ham-A reg. coefficient was 2.35 and Cohen's d was 0.33, the GAF-F reg. coefficient was 6.3 and Cohen's d was 0.91, the GAF-S reg. coefficient was 6.5 and Cohen's d was 1.01, the SDS reg. coefficient was 0.8 and Cohen's d was 0.40 and the VAS reg. coefficient was 0.9 and Cohen's d was 0.31. To be able to compare effect sizes in PTF1 with the results in FORLOB we also calculated Cohen's d for the differences between pre-treatment and post-treatment ratings within groups for HSCL-25, HTQ, WHO-5 and SDS, which were used in both studies (see table 3). This resulted in a lower Cohen's d in PTF1 than in FORLOB on all self-ratings.

Table 2: Comparison of treatment in the two studies

	FORLOB	PTF1
	N=85	*N=217*
	N (%)	
Psychopharmacology		
Other antidepressant treatment during trial (excl. trial medicine)	-	30 (14)
Benzodiazepines during trial	8 (9)	14 (7)
Antipsychotics during trial	5 (6)	14 (7)
Trial medicine	85 (100)	115 (98)
Sertraline	82 (96)	109 (93)
Mianserin	65 (76)	101 (86)
Stops Sertraline	9 (8)	-
Stops Mianserin	15 (13)	-
Stops Sertraline and Mianserin	4 (3)	-
Psychotherapy		
Core CBT methods used at least 5 times	69 (81)	62 (58)
No CBT core methods have been used	1 (1)	11 (10)
ACT methods used	88 (75)	74 (70)
Mindfulness methods used	92 (78)	88 (83)
Cognitive methods used	99 (84)	95 (90)
Trauma-focused exposure used	31 (36)	20 (19)
CBT >= 10 times*	48 (56)	30 (28)
Exposure >=3 times	9 (11)	8 (7)
ACT >= 10 times*	24 (28)	10 (9)
Mindfulness >=10 times	11 (13)	8 (7)
TFCBT (CBT >=10 & exposure >=3)	6 (7)	5 (5)
Any of the above >=10 times	59 (69)	41 (38)
	Mean (sd)	
No. of sessions with doctor	8.7 (2)	8.8 (2)
No. of sessions with psychologist	13 (4)	11.9 (3)
Duration of treatment (mo)**/*	8.2 (1)	6.0 (1.3)
Sessions with doctor where social problems do not limit the flow of the session (%)	-	3 (7)
Mianserin at end of trial (mgs)	-	15.4 (12)
Sertraline at end of trial (mgs)	-	110.9 (68)
Max dose Sertraline (mgs)	131.8 (60)	123.6 (58)
Max dose Mianserin (mgs)	14.1 (11)	19.9 (11)
Mean dose of Sertraline during trial (mgs)	-	91.5 (47)
Mean dose of Mianserin during trial (mgs)	-	14.2 (7)

*Significant difference between FORLOB and PTF1 with Chi2-test ($p<0.05$)
**FORLOB is from pre-treatment assessment till last treatment session, whereas PTF1 is from first to last treatment session

The GAF-F and GAF-S measures were not blinded and were only available for the waiting list group and the two groups receiving medicine. Two sets of analyses were conducted. In the first analysis, effects of medicine were evaluated in a subsample comparing the group receiving medicine with the waiting list group and effects of psychotherapy were evaluated in a subsample comparing the group receiving medicine and psychotherapy with the group receiving medicine only. The second set of analyses was conducted based on all the three groups with GAF ratings (medicine alone, medicine and psychotherapy and the waiting list group). This analysis showed essentially the same results as the subsample analysis showing significant effect of medicine and no effect of psychotherapy.

3.3.1 Adverse reactions

Both Sertraline and Mianserin have been thoroughly tested for their safety in other settings. In PTF1, we only registered adverse reactions and reactions not listed in the product summary. Furthermore, planned hospitalization was not considered a serious adverse event. Overall 75% of patients treated with Sertraline and 70% of patients treated with Mianserin reported known or unknown adverse reactions. Only 13% had unknown adverse reactions. During the trial 13% had to stop Mianserin treatment, 8% had to stop Sertraline treatment and 4% stopped both Sertraline and Mianserin treatment during the trial. In the groups receiving psychotherapy, 10% of patients reported discomfort due to TFCBT.

4. Discussion

The discussion will follow the structure of the objectives of the thesis. I will start by discussing the characteristics of traumatized refugees in Denmark needing psychiatric treatment with regards to psychopathology and predictors of their mental health. This will be followed by a discussion of the treatment offered at CTP and the evaluation of its effect comparing results from FORLOB and PTF1 with other studies in the field. The section will end by a discussion of the perspectives for clinical practice and future research that can be drawn from the results of the thesis.

4.1 Psychopathology of traumatized refugees and predictors of their mental health

In paper 1, it was demonstrated that patients have several co-morbidities and not just PTSD. Almost all patients had depression, pain and untreated somatic complaints in addition to PTSD. Furthermore, 36-58% had physical problems they were in treatment for, 9-16% of patients had psychotic symptoms mainly related to their trauma, 27% had enduring personality change due to catastrophic events according to ICD-10 and 46% reported traumatic brain injury. Patients reporting chronic pain had higher symptom scores on HSCL-25 and HTQ and patients with psychotic symptoms scored higher on all symptom clusters on HTQ. At pre-treatment assessment, the patients' level of functioning and quality of life were very low, the majority of patients lived on public subsidies, education levels were low and most patients had a limited social network. In the following, the psychopathology of traumatized refugees will be discussed focusing first on trauma-related psychiatric disorders and then discussing psychotic and somatic symptoms.

The understanding of psychopathology of traumatized refugees emerging from this study can have been affected by the validity of information. Only inclusion and exclusion diagnoses in FORLOB and PTF1 were based on a semi-structured interview and therefore we might have missed some co-morbidity diagnoses. For instance, it was deemed impossible to distinguish the combination of PTSD and depressive symptoms from anxiety symptoms, and consequently additional anxiety-diagnoses were not used. The self-ratings might over- or under-estimate the patients' symptoms and the analysis is further complicated by the fact that the study was made with a convenience sample of patients.

4.1.1 PTSD and depression

The majority of patients in FORLOB and PTF1 suffered from a combination of PTSD, depression and pain with HTQ and HSCL-25 scores even higher than scores for similar patient populations in Denmark (44, 49, 65). This may reflect very high levels of PTSD and depression symptoms, but it may also reflect the validity of self-ratings. The high levels of co-morbidity means that FORLOB and PTF1 are studies of patients with both depression and PTSD and not just PTSD. This should be considered in the interpretation of results and when comparing them to results from other studies, in particular the results of studies of trauma patients only with PTSD such as those summarized in the Cochrane Reviews on PTSD (68-71, 102).

It remains unclear whether there are different types of PTSD. The diagnosis complex PTSD has been suggested by Judith Herman (134) and others have suggested that there is a psychotic subcategory of PTSD (21), while yet others operate with the diagnosis DESNOS (Disorders of Extreme Stress Not Otherwise Specified) (135). All of these try to capture variations of PTSD that have more complexity, more severity and in most case are more chronic in nature than PTSD. We found an increased intensity of PTSD symptoms associated with psychotic symptoms in FORLOB (paper 1) and 27% of the study population in PTF1 (paper 4) meets the criteria for enduring personality change after catastrophic events, which is the ICD-10 equivalent to DESNOS. This can indicate that more severe forms of PTSD does exist and getting a better understanding of it, would be of great importance in addressing the disorders of traumatized refugees.

4.1.2 Psychotic symptoms and PTSD

A significant proportion of patients were assessed psychotic during treatment in both FORLOB and PTF1, which is surprising as all patients with a psychosis had been excluded from the studies and PTSD does not include psychotic symptoms in the diagnosis according to ICD-10. The majority of psychotic symptoms in PTF1 were trauma-related. This confirms previous, although scarce, reports of PTSD with psychotic symptoms in traumatized refugees (29, 30). Braakmann quotes a prevalence of psychotic symptoms of 15-64% amongst patients with PTSD, which corresponds with the observations in FORLOB (paper 1), but it is higher than the 9% we observed in PTF1. The differences may be due to variance in the definition of psychotic symptoms, which is complex in any patient sample and even more complex in transcultural patients, where trauma-symptoms may be expressed in a variety of ways, which to the observer from a different cultural context may be misinterpreted as psychotic. In the categorization of cases in FORLOB we used criteria, which corresponded to those suggested by Braakman (26), whereas our estimation is likely to have been more conservative in PTF1. In FORLOB, we found that psychotic symptoms were related to higher self-rated symptoms of PTSD and depression and level of functioning. This can partly be explained by psychotic symptoms being difficult to distinguish from flashbacks, depressive psychotic reactions and culturally-bound ways of expressing distress, which is supported by depression and PTSD being the most common diagnoses for patients with psychotic symptoms in FORLOB (paper 1). The findings calls for further examination of psychotic symptoms in traumatized transcultural patients. The presence of psychotic symptoms may very well be testament to a more severe form of trauma-related disorder and therefore also be a contributing factor in treatment resistance. It remains to be seen whether the symptoms can be explained by depersonalization and derealization symptoms as suggested in the new DSM-V dissociative subtype of PTSD or whether they indicate a psychotic form of PTSD as it has been suggested in the past (21).

4.1.3 Somatic symptoms and pain

It has been well documented that refugees with PTSD suffer from a high prevalence of somatic complaints (33-36). It has been suggested that the association between pain and PTSD is modified by depression (136) and the same could be the case for somatic symptoms and PTSD (34). Another explanation can be that somatic complaints are an integrated part of the psychiatric syndrome resulting from trauma. Finally, there are indications that somatic disease and trauma have a high correlation and untreated somatic symptoms can be associated with that (137).

In both FORLOB and PTF1, information about somatic disease was based on patient reporting at pre-treatment assessment, although this was more systematically registered in PTF1. The prevalence of various somatic complaints corresponds to one another in the two studies. In PTF1, in which information on pharmacological treatment for somatic symptoms was most complete, 36% of patients were in treatment for specifically defined somatic disorders while the treated complaints were 58% and 95% of patients had untreated somatic complaints. The distribution between the two groups may be influenced by cognitive dysfunction such as memory and concentration problems in most patients, which may have resulted in underreporting of medicines for somatic disease in both studies. Considering that the mean age in the study population was 45, even the more conservative estimate of 36% somatic disease (epilepsy, Horton's headaches, arthritis, hypothyroidism, diabetes, colitis, asthma, Recklinghaus' disease, HIV and cardiovascular disease) is high, compared to other populations.

An unpublished register-based study comparing traumatized refugees with the general population of refugees in Denmark, in which the traumatized refugee population included 268 patients from FORLOB and PTF1 comprising 66% of the traumatized group (138) concluded that traumatized refugees diagnosed with PTSD and depression had significantly higher incidence rates of somatic disease than refugees with no diagnosis of PTSD or depression. Evidence for an association between trauma, PTSD and somatic disease is emerging from other studies as well and it is supported by biological models and corresponding biomarkers. In other studies it has been found that patients with PTSD have increased prevalence of cardiovascular disease, rheumatoid arthritis, psoriasis, osteoporosis and thyroid disease and it has been suggested that this association may be mediated by autoimmune activation, which may be present before the development of PTSD or be caused by neuroendocrine and sympathetic nervous system activation (40, 41). Higher prevalence of diabetes and hypertension has also been observed in a study of traumatized refugees (42).

Another hypothesis is that somatic complaints are an integrated part of trauma-related disorders. This is reflected in the DESNOS diagnosis that incorporates somatic complaints. This is also supported by the commonalities in suggested neurobiology of BDS and PTSD, that both affect the autonomic nervous system and the HPA-axis. The same arguments have been made regarding pain symptoms, which are also an important part of the BDS diagnosis. Chronic pain symptoms in torture survivors are well described

(45-47) and pain in PTSD populations has been examined although it is debated whether PTSD is directly associated with pain symptoms or whether this is mediated by depression (43, 139). In FORLOB (paper 1), HSCL-25 score and HTQ score were both associated with self-reported pain, but pain was so prevalent in the study population that it is difficult to conclude anything based on these findings. However, the fact that chronic pain and trauma-related diagnoses co-exist is evident from the findings in PTF1 as well as FORLOB. That somatic symptoms and pain may be an integrated part of psychiatric trauma-related diagnoses cannot be ruled out based on our results, but further studies are necessary.

Finally, the untreated somatic symptoms in FORLOB and PTF1 may reflect that patients suffer from somatoform disorders. Medicines prescribed for somatic symptoms in PTF1 mainly reflects unspecific symptoms such as gastritis, arthrosis, musculoskeletal pain, headaches and migraine, irritated bowel syndrome, constipation and nausea. These may very well reflect symptoms that are part of somatoform or functional disorders or problems caused by adverse reactions to pharmacological treatment. The BDS diagnosis covers untreated symptoms from several organ systems and the prevalence of 60% of patients in PTF1 with BDS could very well explain the pattern of symptoms observed in the study samples. Scores on the somatization section of SCL-90 used in PTF1 were generally lower than mean scores on other self-ratings, but we cannot conclude whether this is due to symptoms being less due to somatization or whether it is a question of the validity of the scale in the study population. It remains impossible to distinguish symptoms of anxiety, symptoms of actual somatic disease and side effects of pharmacotherapy in the results, as they are likely all to be included in the patients' reporting of somatic symptoms. It is therefore very difficult to distinguish any symptoms of somatization. This and the data quality can possibly explain that we found a low and not significant correlation between treated and untreated somatic symptoms in Paper 1.

Studies have generally taken very different approaches to the identification and categorization of somatic complaints and few studies have examined patients for medical disorders. Therefore, it would be highly relevant to examine somatic complaints in more detail in traumatized refugees with the purpose of finding a way of distinguishing symptoms and decide whether somatic complaints should be treated in the somatic health care system or in the psychiatric system and to understand the interaction between physical and mental health consequences of trauma. Register-based data can be helpful in this, especially as a means to validating pharmacological treatment information, but some caution should be shown concerning conclusions based on register-based diagnostic categories. Several of the diagnoses in register-based studies are likely to reflect somatic symptoms, which are part of psychiatric disorders or the results of pharmacological treatment (nausea, dizziness and constipation). A thorough somatic examination ruling out somatic disease is also an important part of identifying which somatic symptoms are caused by somatic disease and which are more likely part of a psychiatric diagnosis and should therefore be integrated in treatment of traumatized refugees. A systematic Review (140) concluded that there is some, but limited evidence for the effectiveness of treatment of somatoform disorders with CBT and antidepressants and one trial has been published that found evidence for the effectiveness of mindfulness-based therapies in the treatment of BDS (141). More specifically targeting psychotherapeutic treatment of traumatized refugees to address symptoms of bodily distress could therefore be useful no matter whether the symptoms are an integrated part of the trauma-related syndrome or an independent somatoform disorder.

4.2 Pre- and post-migratory predictors of mental health and level of functioning

In general, the relationship between pre-migratory traumas and trauma-related disorders is well established, but it is hard to study more specifically because pre-migratory trauma is context dependent. Numerous studies have looked at the relationship between pre-migratory trauma and PTSD and depression (1, 14, 15, 18). In FORLOB, most of the patients had experienced war and persecution, but only about half of the patients were torture survivors. In this respect, the population differs from other study populations who have predominantly been torture survivors and survivors of political violence (48, 78, 97). Our sample only included patients who had suffered torture or experienced war and had a trauma-related affective or post-traumatic disorder. The high prevalence of trauma in the sample is directly caused by the inclusion criteria of FORLOB and it therefore makes it difficult to analyze the effects of trauma. However, we did found that persecution was significantly associated with higher score on HTQ arousal symptoms and being an ex-combatant was significantly associated with higher self-reported pain in multivariate linear regression models.

There is some evidence for the association between PTSD and/or depression and all of the post-migratory predictors analyzed in this study. However, the results of various studies may be affected by the differences in political context and cultural background of the populations in the studies. Few comparable studies exist and few results have been replicated. There seem to be some evidence for the importance of employment (14, 15, 55) and economic strain (15), language proficiency (14, 15) and social support (18, 48, 55). There is evidence that the length of the asylum procedure and stay in asylum centers (62) is of importance whereas the evidence of the importance of type of legal status is unclear (62). The findings in these and other studies further indicate that the contribution of post-migratory predicators increase over time relative to pre-migratory traumatic experiences (66, 67). In FORLOB, social isolation was the only predictor significantly associated with outcomes in the multivariate predictor analysis. Lack of social support was also the only post-migratory predictor of mental health in another study of a similar refugee population in Denmark (48, 49), which indicates that this finding may be of some validity. This makes it important to make possibilities for networking and support available for traumatized refugees as an integrated part of the treatment intervention or as a separate initiative. FORLOB included a number of factors reflecting previous mental health and treatment received in the past. This is less studied in traumatized refugee populations, which can be due to this kind of information being difficult to assess, as it is less factual, depends on self-report and is therefore vulnerable to recall bias and patients' understanding of what mental health problems are and which treatment they have received in the past. In addition, the limited availability of health services in some countries will affect previous treatment experiences of immigrant patients. This has likely also influenced our study and may explain that we were unable to detect any clear associations between previous mental health and psychiatric treatment and current mental state.

Studies of refugees and immigrants show that the symptoms of depression and PTSD generally decrease over time (14, 142), which does not seem to be the case in FORLOB (paper 1), where patients have very high symptom scores and low scores on level of functioning and quality of life despite having spent on average 15 years in Denmark. In this respect, the study sample in FORLOB differs from those study populations, which have traditionally been included in studies of post-migratory predictors of mental health. This is likely to be due to FORLOB being a study of a clinical population and not a population sample. Generally, the study populations have been in their new country of residence shorter time and they tend to improve in health and level of functioning the longer they have been in exile. The limited results of the predictor analysis in FORLOB can have been caused by methodological problems. The study sample was small and very homogenous with regards to most potential predictors and outcome measures. The quality of available information in FORLOB can have influenced the results as the validity can have been limited by the prevalence of memory and concentration problems among the patients. If other studies have had as selected a patient sample as ours, this may also account for the variation in results from study to study.

4.3 Description of and evaluation of the treatment at CTP

In the follow-up study (Paper 2), we found a moderate significant change (Cohen's d 0.44-0.67) on all self-report outcome measures (HTQ, HSCL-25, SDS and WHO-5) after combination treatment. We found less improvement in PTSD when patients were receiving public subsidies and less improvement of depression when patients reported pain in the upper extremities. We found a positive association between systematic use of CBT methods and improvement in patient condition (paper 3). In the randomized clinical trial (paper 4), we found a significant effect of treatment with medicine on blinded observer-ratings of depression, anxiety and non-blinded ratings of level of functioning (Ham-D, Ham-A, GAF-F and GAF-S), and on self-reported level of functioning and headache (SDS and VAS). Cohen's d calculated as the differences between randomization groups ranged from 0.91-1.01 on GAF-F and GAF-S corresponding to a large effect of medicine compared to no medicine, whereas on the other ratings showing significant change Cohen's d was 0.31-0.41 corresponding to a small to moderate effect. We did not find any effect of psychotherapy on any outcomes and nor any effect of psychotherapy or medicine on the primary outcome measure, PTSD. In this discussion of the treatment of traumatized refugees offered at CTP and its effect, I will start by addressing various methodological issues that can have affected the results of the studies. This will be followed by a discussion of the treatments offered and a comparison with other studies of the treatment of traumatized refugees.

4.3.1 Methodological considerations regarding FORLOB and PTF1

Overall, PTF1 is a well-designed trial compared to other studies published about the treatment of traumatized refugees. PTF1 has a large study population, has systematically registered program adherence and patient compliance, examines treatment modalities separately and in combination and in contrast to FORLOB, PTF1 includes a control group. However, despite the fact that PTF1 is designed to meet as many of the CONSORT criteria for clinical trials (143) as possible there are some methodological challenges such as blinding, program compliance and validity of ratings. These are not only relevant to PTF1, but also to FORLOB and therefore both studies will be discussed in the following covering common methodological concerns as well as contrasting methodological issues that differed from one study to the other.

4.3.1.1 Change due to spontaneous recovery

The most important methodological limitation of FORLOB is that there is no control group, which is the largest problem with follow-up studies. This means that we cannot rule out that the results of FORLOB are due to spontaneous recovery over time. In contrast, PTF1 had a waiting list control group, which is generally rare in research on traumatized refugees. That makes it possible to account for any change due to spontaneous recovery over time. In PTF1, there was no change during the 6 months patients were monitored in the waiting list group. This point towards little spontaneous recovery in the group, the likelihood of which is further increased by the patients' symptoms persisting for 15-20 years since the arrival in Denmark. Another factor that supports this is that a previous study of a similar patient population in Denmark found no significant change in clinical condition of patients (49). Therefore, although, regression towards the mean due to patients seeking treatment when their condition is worst cannot be ruled out, this is less likely to have caused the observed changes in patient condition in FORLOB. The vast majority of studies published evaluating the treatment of traumatized refugees are follow-up studies without a control group and only follow-up studies have been published from Denmark (44, 49, 65), where the patient population is comparable to the one in FORLOB and PTF1 with regards to country of origin and current social context. As the differences between FORLOB (paper 2) and PTF1 (paper 4) clearly demonstrates, the results from follow-up studies must be interpreted with much caution and it is very likely that the treatment effects demonstrated in follow-up studies are overestimating the treatment effect.

4.3.1.2 The 2x2 factorial design of PTF1

Another strength of PTF1 is the fact that medicine alone is compared with psychotherapy alone. In the one trial with traumatized refugees comparing psychotherapy and medicine (76), psychotherapy is an add on and in most psychotherapy trials medicine is continued as usual, but is not accounted for in much detail in the published results. Economically, it is an advantage that two treatments are compared in the same trial. It cannot be ruled out that the small positive effect observed of treatment with Sertraline and Mianserin in PTF1 means that in some psychotherapy trials where patients have received medicine, this may in fact have accounted for parts of the observed effect. This is also a possible explanation of the findings in FORLOB where only combination treatment was studied, as we found no interaction between psychotherapy and medicine in PTF1.

4.3.1.3 Program compliance and adherence

FORLOB and PTF1 are two of the first published studies evaluating a standardized treatment described in detail in manuals and documented thoroughly during treatment. This has enabled us to ensure that the patients actually receive the same intervention, which has been one of the many methodological problems of other studies on refugee populations using multi-disciplinary treatment (44, 49, 65). The lack of well-described treatments may reflect variability in the administered treatments or reflect a situation where an otherwise standardized treatment has not been described in sufficient detail to be replicated. This is an important problem when comparing treatment outcomes. Thus, the statistically significant change observed in FORLOB may be

the result of an efficient and standardized intervention that was administered to patients in the study sample.

In FORLOB and especially in PTF1, the program compliance is well-described. In PTF1, we monitored medicine compliance by counting the number of tablets the patients returned at each appointment with a physician. In addition, all other medicines than trial medicine were monitored. In both studies, psycho-education was monitored by registering the topics covered and psychotherapy compliance was monitored by registering the methods used at each session, physical activity between sessions and homework compliance. This makes it more likely that any observed effect or lack thereof is due to the active treatment provided. An even better understanding of compliance and adherence could have been obtained by using videos of sessions, but it was deemed economically unfeasible to have all videos rated by expert CBT- therapists given the large number of patients in the trial.

Treatment adherence was a challenge. Although all treatment was manualized it was often difficult for psychologists and physicians to follow it. In PTF1, physicians registered if they had felt unable to give the patient a sufficient treatment intervention in the form of psycho-education because social problems had taken up most of the conversation and in only 7% of the sessions, this was not a problem. Likewise in psychotherapeutic treatment, when demanding that CBT-methods like restructuring of thoughts, the CBT diamond, working with schemata, in vivo exposure and working with avoidance behavior were used at least 10 times during treatment (which is even a low threshold compared to a standard 10-15 session treatment for depression), only 28% of patients in psychotherapy treatment met these criteria. This was partly due to an overall high frequency of absence from treatment on the patients' part with regards to psychotherapy and physician appointments, and partly due to the fact that patients in a majority of cases were unable to participate in psychotherapy according to the manual. Only 51% of patients completed homework assignments. However, it is not uncommon to have problems with treatment compliance in trials when demanding treatments are investigated and a 51% homework compliance is relatively good considering that the patient group have a very low level of functioning. TFCBT is based on visualized or interoceptive exposure to traumatic events and bodily sensations associated with traumatic experiences. In PTF1 only 19% of patients worked with trauma-focused exposure at least once during the treatment. When compared with FORLOB (paper 3) the proportion of patients with "effective treatment" is higher in FORLOB than PTF1 (see table 2). In FORLOB 56% of patients had CBT-methods used 10 or more times and 36% worked with trauma-focused exposure at least once. This could account for some of the differences observed in change in patient condition between FORLOB and PTF1. All in all, the CBT treatment offered in both studies was less than optimal, however, PTF1 and FORLOB probably gives a realistic idea of the psychotherapeutic treatment possibilities in this chronically ill group of patients.

Compliance with medical treatment was monitored in PTF1, however, patients often forgot to bring their medication at sessions and therefore compliance with Sertraline and Mianserin treatment may have been overestimated. Compared to other PTSD trials on Sertraline (83, 84), the mean maximum dose of 132 mgs (+/- 60 mgs) was comparable. The discontinuation rate was 19% with regards to Sertraline and 25% with regards to Mianserin in PTF1. This is low compared to a 30% discontinuation rate in the PTSD trial with American war veterans (83), which did not find any effect of Sertraline on PTSD, but higher than the 6% discontinuation rate in an Iranian trial with war veterans, which did find a positive effect of Sertraline treatment (84). The discontinuation rate is therefore likely to have influenced the results of the trial.

In PTF1, there was a higher drop-out in the waiting list group and ratings sometimes took place a while before treatment started and after treatment ended. However, the results are very consistent and clear, so the few extra patients that dropped out of treatment are unlikely to have influenced the outcome of the study and given that there was no change in the waiting list group, it is unlikely that delay in the beginning of treatment has affected the treatment results. There was also some cross-over between groups in PTF1. In the psychotherapy group, 27% received antidepressants of another type than the trial medicine and so did 21% in the waiting list group. In the psychotherapy and waiting list groups, 12% and 11% respectively received trial medicine. All patients received psychotherapy as planned. It cannot be ruled out that the cross over between groups somehow have affected the results of the trial under-estimating the effect of medicine.

4.3.1.4 Sample size

Another advantage of PTF1 compared to other published trials in the field is that the intervention groups are of a certain size with >50 patients in each arm except in completer-analysis where the waiting list group was reduced to 48. This increases power dramatically. Other published trials have had very small numbers. All but one trial (72) have had 20 patients or less in each arm and with drop out, most trials have had less than 10 patients in each arm (75, 76, 78, 98, 144). Only one trial had comparable numbers of patients at inclusion, and that particular trial did not find any difference between NET and trauma counselling (72). The trial took place in an African refugee settlement and the context of patients is not comparable to that of patients in PTF1 who are immigrants with chronic trauma-related disorders persisting more than 15 years after the trauma. The trial had very high drop-out rates resulting in <50 patients in each of the intervention groups and only 19 in the control group. The statistical analysis chosen to account for missing data is likely to have overestimated the effect size (79). This means that PTF1 to date is the largest published trial on the treatment effect in any traumatized refugee population.

4.3.1.5 Validity of ratings

The validity of the ratings used in the studies is an important question. An effort was made to identify translated versions of all self-ratings that had been validated by the translators and all self-ratings have been used extensively in psychiatric and some also specifically in traumatized refugee populations (HTQ and HSCL-25) (145). However, the ratings were not validated specifically in our study population. It is a general problem that scales used in refugee studies are poorly validated (145). This may have affected the outcome results. In FORLOB (paper 2) a moderate positive change was detected on all rating scales, whereas in PTF1 the significant changes were mainly small on all ratings scales (paper 4) and changes were predominantly detected on observer-ratings (Ham-D, Ham-A, GAF-F and GAF-S). This could reflect that the included self-ratings were unable to detect the small effect sizes in PTF1. The low correlation between self-ratings and observer-ratings may be a general problem. This was also the case in a

study of psychotic symptoms in depressed patients, where self-ratings and clinician-rated psychotic symptoms correlated poorly (146). It is therefore problematic that we did not have an observer rating of PTSD that could have been the primary outcome measure instead of HTQ, which is a self-rating. It is also problematic that due to errors in monitoring and the management of ratings, GAF-F and GAF-S were not assigned to patients after treatment in the group receiving only psychotherapy. Furthermore, it is a clear methodological challenge in FORLOB that we did not have any blinded outcome measures and we only had self-ratings, which in the light of the discussion of their validity and ability to detect changes may have affected the results. On the other hand, in PTF1 the improvements observed were on observer-ratings and not on the self-ratings used in FORLOB. The inability of self-ratings to detect small effects is therefore a less likely explanation for the differences observed between the two studies.

We made a deliberate choice not to blind patients and caregivers to the treatment in PTF1. It was found unfeasible that intervention arms not receiving medicine should have received placebo as this would likely have meant the discontinuation of any antidepressant treatment, which in itself could have created a negative treatment response. It was also deemed unfeasible to create a placebo psychotherapeutic intervention, as it would have been too difficult to distinguish psychotherapy from no psychotherapy. The GAF-F and GAF-S ratings were not blinded, which is likely to have affected the results and may account for the large changes seen on these two ratings compared to all other ratings. Ham-D and Ham-A were blinded and undertaken by medical students trained in Hamilton ratings. To our best knowledge, the blinding has remained intact, but of course, it cannot be ruled out that the results are biased if patients have accidentally revealed their treatment group or whether they were being rated before or after treatment. It has been suggested that standard rating scales for symptoms (HTQ and HSCL-25) in this patient group are less well-suited to measure treatment outcomes (147). A study found no changes in symptoms, but only changes in level of functioning and quality of life at an initial follow-up while only changes in symptoms were identified at a long-term follow-up (49, 65, 80). This could also be part of the explanation of the difference between the effect on GAF and the effect on other ratings.

4.3.2 Generalizability of results

When working with transcultural patients with trauma it is very difficult to ascertain whether results are generalizable to other contexts. The published literature on psychotherapeutic treatment of traumatized refugees is generally not generalizable, as it is based on specialized delivery by the founders of the various treatment modalities. PTF1 is one of the only trials where individual caregivers are not the persons who originally invented the treatment offered. The group led by Neuner, who invented the NET treatment, has mainly published the NET trials (72, 73, 77, 144, 148), and the group led by Hinton specializing in CBT adapted to Indochinese patients carries out most other trials (74-76, 98). Their generalizability is therefore questionable. Only a small trial (N=16) by Paunovic is not connected to any of the two large research groups, but this study did not include patients with other disorders (excluded a patient with OCD and a patient with severe depression) and it is difficult to distinguish the two interventions (78). Therefore, although the Paunovic trial found a positive effect of TFCBT it cannot be compared to the results of PTF1 where the patients are generally more ill and have multiple co-morbidities.

Traumatized refugees in new countries of origin are a challenging group to treat. As FORLOB and PTF1 have demonstrated patients have very high levels of co-morbidity and the psychopathology of trauma remains insufficiently understood. There is indication that the patients treated in FORLOB and PTF1 have chronically and treatment resistant psychiatric disorders. The vast majority of patients have been in treatment before, it is 15-20 years since patients experienced their significant traumas, a significant proportion has enduring personality change according to ICD-10, may have suffered traumatic brain injury with potential exacerbation of cognitive deficits and intensity of trauma-related symptoms and they generally live under difficult socioeconomic circumstances in Denmark. They have low levels of functioning, low quality of life, few patients are in current employment, many live in social isolation and patients generally find it difficult and stressing to navigate the Danish welfare and social security system. In this respect they can be compared to patients from some outcome studies, particularly studies published from Denmark (44, 49, 65) and with regards to chronicity there is some similarities with studies undertaken by Hinton on Indochinese patients living in the U.S. although cultural background and current social context are less comparable (74, 75, 98). Generally, however, patients in published studies on traumatized refugees have different levels of co-morbidity and come from diverse cultural and social backgrounds and therefore also with potentially different past and present traumas and stressors.

In many of the follow-up studies that have been published, treatment is not sufficiently characterized for it to be applicable in another context (90, 100, 101). It is a clear strength of FORLOB and PTF1 that the treatment is manualized and described in detail. Another strength of PTF1 that makes the results more generalizable is that it is a pragmatic trial. It includes typical patients treated at a Scandinavian trauma clinic for refugees without strict inclusion criteria. It allows for many co-morbidities and for a multicultural sample, which of course reflects the immigration patterns to Denmark. The difficulties of working with this patient group (cancellation, translation etc.) have affected the number of patients in the trial that received “effective treatment” with for instance only 18 of 107 completers in the two treatment arms receiving psychotherapy having worked with CBT methods at least 10 times. However, this is probably a realistic picture of what is possible with this patients group and in a context where individual caregivers are not highly specialized, as will be the case in most settings where traumatized refugees are treated for trauma-related disorders. The socioeconomic, psychiatric and cultural background of the patients were comparable to that of traumatized refugees in other Danish studies (44, 49, 65).

4.3.3 The effect of treatment

In this section the treatment in FORLOB and PTF1 with medicine, psycho-education and psychotherapy will be discussed and results of the two studies will be compared to each other and to other published studies. The discussion will start by looking at the treatment with Mianserin and Sertraline and will then be followed by a discussion of the psychotherapeutic treatment.

4.3.3.1 The effect of medicine

Sertraline and Mianserin are well-described for their antidepressant effect, whereas their effect on PTSD and anxiety is less sup-

ported in the literature. Despite Sertraline being the drug of choice for PTSD in the UK NICE guidelines and the Danish national guidelines (81, 82) the evidence for its effect is contradictory and in 2007 a study that did not find an effect of Sertraline in the treatment of PTSD in American war veterans was published (83). Considering this, it is less surprising that the effects observed in PTF1 are predominately on depression and partially on anxiety (Ham-D and Ham-A). That the effect size is small is not surprising either, as SSRI treatment is generally not recommended in the treatment of treatment-resistant depression, which is the prevalent problem in the PTF1 sample of traumatized refugees. In FORLOB, the symptoms which improved most during treatment were sleep, general symptoms of depression and general feelings of anxiety, which can also be explained by the combined treatment with Sertraline and Mianserin. That the largest change on all symptom scales in FORLOB was sleep improvement, can also reflect augmentation of Sertraline treatment with Mianserin, which is known for its positive effect on sleep disturbances (85). We did not find a correlation between change in sleep items on HSCL-25 and HTQ and Mianserin in FORLOB, but this is expected given the small sample size.

4.3.3.1.1 Comparison with other studies

Generally, the effect sizes observed in PTF1 are small compared to other studies. In a Korean study of war veterans comparing treatment with Sertraline and Mirtazapine significant changes were observed in PTSD and depression after 6 weeks treatment. The changes on Ham-D were 11.7 after treatment with Sertraline and slightly larger after treatment with Mirtazapine. However, the patient population was highly selected and patients were not included if they had previously been in treatment with any of the trial drugs (87). In a study comparing the effects of Fluoxetine (and SSRI), Mianserin and a combination of Fluoxetine and Mianserin in patients with depression, but no trauma, a significantly larger treatment effect was found in the group receiving combination treatment than in the other groups and effect sizes were in the range of 11 to 16 on Ham-D (89). In studies with Mirtazapine, "responders" have been characterized as patients with >50% decrease in Ham-D scores (149). The mean changes in Ham-D and Ham-A of 2.35 in PTF1 are very small compared to this. A study comparing Sertraline treatment for patients with PTSD, depression and PTSD or depression, anxiety and PTSD found a significant effect of treatment with Sertraline in groups with co-morbidity (150). In general, the effects sizes of Sertraline treatment are difficult to compare because most studies use CAPS as the primary outcome measure of PTSD instead of HTQ. In PTF1 and FORLOB, CAPS was not used as the studies are based on ICD-10 diagnoses and not DSM-IV, which CAPS measures. In the Cochrane review of the effect of pharmacotherapy on PTSD the changes on self-ratings (other ratings than in our studies) was 0.3 standard deviations, which is larger than the changes on self-ratings observed in PTF1, whereas the changes in FORLOB were slightly higher than 0.3 SD (69, 71). The effects of Sertraline on PTSD calculated as standardized mean differences in the Cochrane review corresponded to the size of Cohen's d in FORLOB and changes on Ham-A in the review that were deemed clinically insignificant corresponded to the changes of Ham-A in PTF1. Overall, an effect of 2.35 on Ham-D and Ham-A cannot be said to have a clinical significance. Only the changes on GAF-F and GAF-S can be said to have clinical significance, but the raters not being blinded may have influenced these results.

4.3.3.1.2 The role of psycho-education

Finally, it cannot be ruled out that the effect of medicine found in PTF1 can be due to the psycho-education offered as part of sessions with physicians as the trial is pragmatic and the individual treatment components in each intervention arm cannot be distinguished. The psycho-education offered by physicians was more systematic than psycho-education offered as part of psychotherapy, but in principle, all intervention groups receiving active treatment received psycho-education. On the other hand, only in 7% of cases the physicians felt able to undertake psycho-education without social problems or acute crisis dominating the sessions. Therefore, the effect observed in the group receiving medicine, is most likely due to the effect of medicine and not only the psycho-education.

4.3.3.1.3 Adverse reactions

Of the patients who received trial medicine, 75% had adverse reactions. In addition to this, 13% had to stop Mianserin treatment during the trial, 8% had to stop Sertraline treatment during the trial and 4% stopped both Sertraline and Mianserin treatment during the trial. This number is comparable to other trials with Sertraline treatment for PTSD (83, 84). No trials are available for Mianserin treatment of PTSD. The responsiveness of patients to treatment and tolerability of medicines may also be affected by transcultural differences in pharmacodynamics and pharmacogenetics. This is a new area of research, which is currently under exploration (106).

4.3.3.2 The effect of psychotherapy

The psychotherapies which have been studied in populations of traumatized refugees have mainly been adapted versions of trauma-exposure (NET and Den Bosch model) (72, 73, 77, 93) or a culturally adapted version to Indochinese culture (74-76, 98). The psychotherapy manual in FORLOB and PTF1 is based on a combination of trauma-exposure, standard cognitive techniques, behavioral techniques and third generation CBT forms such as ACT. When discussing the effect that can be expected from the psychotherapy treatment in FORLOB and PTF1 according to the literature, both the methods used and more general factors regarding the psychotherapy must be considered.

4.3.3.2.1 CBT and traumatized refugees

The results in FORLOB (paper 3) points towards CBT being a promising treatment with increasing effect, the more loyal it is to the CBT core methodology. In FORLOB, we found a positive association between the use of core cognitive methods such as restructuring of thoughts and the cognitive diamond and all outcome measures. When these methods were used more than once or twice, the patients showed larger improvement and this seemed to be unrelated to the baseline conditions of the patients. However, "reverse causality" cannot be ruled out where spontaneously improving patients are those who are able to cooperate with the cognitive methods. FORLOB indicates that a large proportion of patients are able to participate actively and make homework from session to session despite their serious condition at baseline. Otherwise, in other publications, it has been questioned whether traumatized refugees are able to do homework or if the use of homework is only useful in a Western cultural context (151, 152). However, we found 51% compliance with homework, which is a fairly high rate and it seems to be associated with a small positive change in mental health symptoms and social functioning. In clinical settings, it has also been suggested that focus on restructuring of thoughts and more advanced CBT methods might not be appropriate for traumatized

refugees because of the severity of the patients' condition and because of their few psychosocial resources, including limited education and language barriers. However, we have no indication that some of the patients will benefit more from a supportive and less structured therapy than CBT.

4.3.3.2.2 The use of trauma-exposure

The therapy was originally planned to be trauma-focused relying on trauma exposure. However, exposure was used much less than anticipated with only 36% of the patients working with visualized or interoceptive exposure at least once during FORLOB and only 19% in PTF1. In standard prolonged exposure therapy, it is recommended to use exposure 7-12 times in the case of trauma exposure with PTSD patients (153). In FORLOB, 9 % of patients worked with trauma-focused exposure three times or more and none more than six times, whereas in PTF1 only two patients worked with exposure 7 times or more and 8 patients (7%) worked with it at least three times. The lack of a positive effect might reflect too little use of exposure. Many therapists explained that exposure was used less than planned in the manual because patients refused to participate due to high levels of distress. Other researchers have, however, applied exposure with the same patient group (99), and thus other factors may be involved, such as a hesitation on the part of the therapist to use exposure.

4.3.3.2.3 The use of mindfulness-based methods

Mindfulness research is generally on more intensive treatments than ours is, and it is believed that the amount of daily practice by the patient is important for clinical effects (154, 155). For instance, the commonly used Mindfulness-Based Stress Reduction program is 12 weeks long with daily practice for 10-60 minutes (156). It is therefore questionable whether the use of breathing exercises a few times during therapy can be expected to have any effect. This might explain why breathing exercises and mindfulness in FORLOB were not associated with a positive effect. One explanation for the negative change in quality of life and level of functioning observed, is that when the patient was too upset for the therapist to use other methods, then mindfulness was the fall back position. Another explanation is that mindfulness is harmful to some traumatized patients suffering from PTSD as it may increase dissociation. On the other hand, overall, patients did not seem to find the psychotherapy harmful as only 7% of patients mentioned discomfort in talking about their traumas, when asked at the evaluation after treatment and no one mentioned the use of mindfulness as an unpleasant experience.

4.3.3.2.4 Duration of psychotherapy

The psychotherapy in FORLOB and PTF1 is of fairly short duration, but it is comparable to treatment given in other psychotherapy trials in transcultural populations (44, 73-75, 78). However, in other trials the length of sessions have been 60-120 minutes whereas sessions in PTF1 and FORLOB are only 45 minutes. Given that about 50% of sessions were undertaken with translation, the limited length of sessions may very well have influenced the results of the studies. The patients in the trial have very severe PTSD. That their condition is chronic and treatment resistant is evident from the low level of functioning and quality of life at baseline, the long time the patients have been settled in Denmark and the fact that the majority of patients had been unsuccessfully treated with antidepressants or other psychiatric treatment before. Therefore, the duration of treatment can possibly have been too short as CBT treatment for personality disorder, for instance, typically is of 12-18 months duration at least. This should be investigated further.

4.3.3.2.5 The therapists' competence

The importance of the therapists' competence in CBT is debated (130), but is likely to be relevant in this context since studies of depressed patients have demonstrated that the more complicated and chronic the problems of the patients are and the more anxious patients are, the greater is the importance of the therapists' skills. The therapists in FORLOB and PTF1 were all psychologists with a short post-graduate training in TFCBT. They had limited clinical experience, but experienced CBT psychologists supervised them regularly. In FORLOB, the therapists' self-evaluations were not associated with treatment results, but this may be due to the small sample. Therapists on average rated themselves 3 out of 5 and this may reflect limited experience with this patient group and CBT. Although very preliminary, the results in FORLOB suggests that the therapist's evaluation of patient suitability for therapy might be a useful tool in a clinical contexts, but this must be examined in more detail.

4.3.3.2.6 Adaptation to patient culture and psychopathology

The psychotherapy was not culturally adapted and patients from diverse cultural backgrounds were included in the trial. This may have influenced results as culturally adapted therapy has shown positive results in Indochinese patients (74, 75, 92, 98). Furthermore, the psychotherapy was targeted at treating PTSD, but the patients suffered from several other disorders including depression, somatization, enduring personality change, psychotic symptoms, pain, traumatic brain injury and somatic disease. In FORLOB, the improvement in rating scores were largest on HTQ and this can be explained by the psychotherapy manual having been made with a focus on PTSD.

4.3.3.3 The effect on treatment of psychopathology and social context

Apart from the content of treatment, factors related to the patients' condition and their socioeconomic context can affect treatment outcome, which is of importance when considering the large differences in patient population in evaluation studies with traumatized refugees. In FORLOB, we analyzed the influence of various predictors of treatment and found that living on public subsidies and having complaints of pain influences the changes in patient condition negatively. The association between pain in the arms and depression could be due to the larger variation in pain in the arms than in the other pain variables. However, another study has also found pain in the arms to predict patient condition in a similar patient sample (48). We found that more torture survivors had pain (66%) than those who had not endured torture (33%), which might partially explain the finding. With regards to the association between productive psychotic symptoms and improvement in the level of functioning, this could be due to these patients in previous treatments only having received treatment for psychotic disorder and not their trauma-related disease. If the psychotic symptoms are an integral part of the trauma-related mental distress, they could improve together with other trauma-related symptoms. However, it could also be due to insufficient classification of psychotic symptoms based on the crude way this information was obtained in FORLOB. All in all, in FORLOB we found fewer predictors of treatment outcome than expected, but this can be explained by the small sample size and the homogeneity in the sample with regards to co-morbidity, previ-

Table 3: Comparison of within-group Cohen's d in the two studies

Rating	N	Pre-treatment mean (SD)	Post-treatment mean (SD)	Difference mean (SD)	CI-95%	Cohen's d	P-value
WHO-5							
FORLOB	80	14.8 (15.7)	24.3 (23.6)	+9.5 (21.4)	+4.8 to +14.3	0.60	<0.01
PTF1 medicine & therapy	52	12.6 (10.4)	16.6 (21.0)	+4.0 (20.4)	-9.7 to + 1.7	0.38	0.16
PTF1 medicine	59	13.2 (14.1)	17.4 (20.6)	+4.1 (20.0)	-9.3 to +1.1	0.25	0.12
PTF1 therapy	50	10.6 (12.0)	15.0 (17.1)	+4.4 (16.4)	-9.0 to +0.3	0.37	0.06
PTF1 Waiting List	36	14.9 (15.2)	11.8 (10.5)	-3.1 (13.5)	-1.4 to +7.7	-0.23	0.17
SDS							
FORLOB	81	8.0 (1.4)	7.2 (2.3)	+0.8 (1.9)	+0.4 to +1.3	0.55	<0.01
PTF1 medicine & therapy	53	8.5 (1.5)	8.2 (2.3)	+0.3 (2.2)	-0.3 to +0.9	0.20	0.38
PTF1 medicine	59	8.0 (2.2)	7.7 (2.6)	+0.2 (2.5)	-0.4 to +0.9	0.09	0.50
PTF1 therapy	49	7.8 (2.0)	8.1 (1.8)	-0.3 (2.1)	-0.9 to +0.3	-5.0	0.30
PTF1 Waiting List	36	7.8 (2.0)	8.6 (1.2)	-0.9 (1.7)	-1.5 to -0.3	-0.05	0.01
HTQ							
FORLOB	80	3.3 (0.4)	3.0 (0.6)	+0.3 (0.4)	+0.2 to +0.4	0.68	<0.01
PTF1 medicine & therapy	52	3.3 (0.5)	3.2 (0.6)	+0.1 (0.7)	-0.1 to +0.3	0.20	0.32
PTF1 medicine	61	3.2 (0.5)	3.2 (0.7)	+0.1 (0.6)	-0.1 to +0.2	0.20	0.42
PTF1 therapy	50	3.3 (0.5)	3.2 (0.5)	+0.2 (0.6)	0.0 to +0.3	0.40	0.06
PTF1 Waiting List	41	3.3 (0.6)	3.3 (0.6)	0.0 (0.6)	-0.2 to +0.2	0.00	1.00
HSCL-25							
FORLOB	75	3.2 (0.4)	3.0 (0.6)	+0.3 (0.6)	+0.1 to +0.4	0.59	<0.01
PTF1 medicine & therapy	52	3.1 (0.5)	3.1 (0.7)	+0.1 (0.6)	-0.1 to +0.27	0.20	0.28
PTF1 medicine	61	3.1 (0.5)	3.0 (0.7)	+0.1 (0.7)	0.0 to +0.3	0.20	0.10
PTF1 therapy	50	3.1 (0.6)	3.1 (0.6)	+0.1 (0.7)	-0.14 to + 0.26	0.17	0.55
PTF1 Waiting List	41	3.2 (0.6)	3.1 (0.6)	+0.1 (0.6)	-0.1 to +0.3	0.20	0.17

ous treatment and socioeconomic factors (94% depression, 99% pain, 92% untreated somatic complaints, 76% previous psychiatric treatment). In FORLOB, the study sample selection means that the treatment was similar with regard to duration, number of

consultations, psychopharmacological treatment, psycho-education and psychotherapy and it was therefore not possible to investigate the association between these individual treatment elements and change on outcome measures.

4.3.3.4 Discrepancies in results in FORLOB and PTF1

It is puzzling that we in FORLOB observed an overall significant change on HSCL-25, HTQ, WHO-5 and SDS and a moderate effect size measured with Cohen's d comparing ratings before and after combination treatment, and that this trend was not reproduced in PTF1. Several potential explanations have been covered in the previous sections, including the lack of a control group in FORLOB, validity of self-ratings and the selection of patients. However, this does not seem to offer clear explanations of the discrepancies in the results. As discussed above spontaneous recovery and regression towards the mean is unlikely given the lack of spontaneous recovery in the waiting list group in PTF1. The differences in the treatment given in FORLOB and PTF1 may explain some of the discrepancies. In FORLOB, patients were selected for having received at least 4 months' treatment including treatment with an antidepressant, had received at least 4 consultations with a therapist, and had at least two outcome ratings (out of 4 possible) from baseline assessment and follow-up. This selection of the study sample for FORLOB can have caused the differences in treatment offered where more patients in FORLOB received treatment with CBT and TFCBT. The differences in duration of treatment may also explain the lack of effect of psychotherapy observed in PTF1 and this can possibly have contributed to the differences in results. Another explanation can be the validity of self-ratings. In PTF1, patients generally rated their condition worse than observers did. On the other hand, only observer ratings changed in PTF1 whereas all self-ratings changed in FORLOB. In table 3, it can be seen that when Cohen's d is calculated as within-group differences between pre- and post-treatment so that it is comparable to the Cohen's d calculated in FORLOB, it is lower for all rating scales in PTF1 than in FORLOB. These small effect sizes were also reflected in Cohen's d when calculated on differences between groups. The only exception is the non-blinded measures of GAF, where the lack of blinding and the fact that no GAF was available for the psychotherapy group may have resulted in an over-estimation of effect size on this scale. The lack of significant p-values can maybe be explained by the differences in sample size, as the number of ratings in the waiting list group for instances are 36 in several ratings compared to 75-81 in FORLOB). However, this does not explain the differences in Cohen's d. Further study will therefore be necessary to fully rule out an effect of TFCBT and combination treatment.

4.4 Clinical and research perspectives

4.4.1 Clinical perspectives

There are a number of clinical implications of PTF1 and FORLOB. The studies indicate that it is better to treat patients with medicine than no medicine. Sertraline and Mianserin are good suggestions for such treatment. Treatment effect would likely increase with higher compliance rates and higher doses, which can be supported by psycho-education. All patients should be offered psycho-education, and given the importance of social problems, this element can be incorporated in psycho-education. Patients can benefit from systematic use of CBT methods in psychotherapy and homework should be encouraged whenever possible. Psychotherapy should address not only PTSD, but also other problems with high prevalence in the patient population such as somatic symptoms and pain, psychotic experiences and depression as well as the challenges of living in a new country and facing the social

problems prevalent in the study sample. Given the high co-morbidity in the patients, clear goals for treatment outcome should be established and depending on these, there could be an effect of increasing the duration of treatment. To accommodate the need for translation, session length could be increased as it has been the case in other trials with traumatized refugees. Training clinicians properly in working with traumatized refugees is of importance and the recruitment of experienced clinical staff and adaptation of therapy to the cultural background of patients is likely to improve treatment effect as indicated by trials by Hinton (74, 75, 98).

4.4.2 Research perspectives

As has been demonstrated above very little research has been published on the treatment of traumatized refugees and therefore the most important priority in this field is to carry out more RCTs, where a thorough methodology is applied to the study of well-defined treatment modalities based on their generalizability and adaptation to the specific needs of traumatized refugees.

4.4.2.1 The psychopathology of trauma

Identifying effective treatments will strongly benefit from a better understanding of the psychopathology of trauma. It will be helpful to understand whether the many co-morbidities are an example of this group being particularly disadvantaged or they are a result of an overall trauma-related syndrome incorporating anxiety symptoms, re-experiencing, mood symptoms, somatic symptoms and in some severe cases psychotic symptoms. Apart from understanding the underlying psychopathology in more detail, it is also of great importance to screen the patients thoroughly for other psychiatric disorders before trials, so that it is clear who the study addresses. The fact that several patients referred for their trauma-related disorder were found to be suffering from a psychosis at the systematic pre-trial screening in PTF1 suggests that it cannot be ruled out that numerous patients with either bipolar disorder or psychotic disorder receive treatment for only trauma-related disorders in some studies, which will bias treatment results. A systematic screening for all psychiatric disorders should therefore be used at inclusion of patients in future trials. Another challenge relating to psychopathology is the need for a better qualification of personality disorder in transcultural populations. It is known that affective disorders and anxiety are much more treatment resistant in patients with personality disorder and therefore it could potentially improve treatment results if this was directly addressed and treatment duration and content was adjusted accordingly. To date we have very little information about our patients' pre-trauma health condition. It is likely that many patients suffered developmental trauma that increased vulnerability to consecutive traumas. Other patients may suffer from other psychiatric disorders in which case the trauma is compounding existing disease as in the cases of psychosis discussed by Bendall (20), which makes the clinical representation of symptoms more complex and potentially requires different approaches to treatment.

4.4.2.2 Study design

It is problematic that so few studies have used a waiting list control group. That way it is hard to tell whether results of treatment can be attributed to spontaneous recovery. It also means that to date we do not have a generally accepted TAU to which new treatments can be compared. This must be established for future studies. One such treatment could be treatment with Sertraline and CBT as in FORLOB and PTF1 as these treatment modalities are the ones studied most frequently in refugee populations. Interpretation of study results are also complicated by the many add-ons in multidisciplinary treatment. The influence of these can be better understood if a proper TAU can be established that add-ons can be compared to in trials.

4.4.2.3 Ratings

Research methodology in this particular group of patients can be improved with a better understanding of the use of ratings. The validity of self-ratings should be studied, ratings used should be validated to the cultural context of each trial and it would be helpful if standard ratings could be identified, so that outcomes can be compared across studies and preferably also across study populations. That way the results from trials with other groups of traumatized patients can be compared to the results of trials with traumatized refugees.

4.4.2.4 Medicine trials

FORLOB and PTF1 indicates that Sertraline and Mianserin can be helpful in the treatment of traumatized refugees, but treatment effects are limited and probably of no clinical consequence and their effect on PTSD is still unclear. No other medicines have been studied in enough detail to give promising results and in future medicine trials for traumatized refugees it can be worth considering the co-morbidity between PTSD, depression and anxiety and the treatment resistance evident from the current literature on the subject when choosing the pharmacological treatment. A better understanding of transcultural differences in pharmacogenetics and pharmacodynamics will add to the identification and adaptation of potentially effective treatments.

4.4.2.5 The psychotherapy

One of the specific challenges identified in this thesis is to adapt psychotherapy to the special needs of traumatized refugees including language barriers, differences in culture, a difficult social context and many co-morbid problems. Psychotherapy treatment should address the broad spectrum of problems the patients are dealing with and therefore trauma-focused treatment should be integrated with treatment for chronic pain, untreated somatic symptoms and in some cases psychotic symptoms. The treatment delivered should be in a format that is possible even when translation is needed and that can be delivered by psychologists with a realistic level of specialization.

To date we have no clear indicators of what a standard treatment could consist of. Trauma-focused exposure remains insufficiently studied as most studies published on traumatized refugees use this in various adapted forms and therefore consensus has yet to emerge on its usefulness. Another challenge is to identify a psychotherapeutic treatment that may increase the patient compliance with treatment. Any treatment, which under pragmatic circumstances as in PTF1 will suffer from cancellations and the predominance of social problems, will be less effective than in studies where the treatment context is controlled. Treatment modalities should preferably be adapted to these circumstances instead of trying to adapt the patients to the treatment.

Finally, it would improve psychotherapy treatment if more treatments were manualized and manuals were published or made available in the public domain. Reporting on treatment compliance is a standard feature in psychotherapy research, but this is rarely done in studies with traumatized refugees. Given the high

level of non-compliance suggested in PTF1, this becomes even more important and is encouraged in future publications.

4.4.2.6 A meaningful clinical change

Another crucial challenge for the future of treatment evaluation in traumatized refugees is to establish a generally accepted meaningful clinical change. Many studies find improvements of symptom levels and in some cases level of functioning on various rating scales, but in very few studies patients recover from their trauma-related disorder. We must ask ourselves what clinical change is needed for the many resources being used in the treatment of traumatized refugees to be an acceptable choice. Should the patients recover? Should their symptoms change to a certain maximum level? Should symptoms remain stable or should level of functioning be improved and how much? Is it enough for patients to subjectively feel their level of functioning is better or should they be able to work or engage in other meaningful activities outside their home? In PTF1, the majority of patients felt their condition had improved due to the treatment, but this is not reflected in the results. In discussion on treatment of traumatized refugees the clinicians' or the patients' subjective sense that improvement is taking place is often used as an argument for resource demanding treatments. It may very well be so, that patients' condition would deteriorate even further without treatment intervention, but the field must be critical about its own reasons for continuing treatment as PTF1 clearly demonstrates that there is little correlation between patients' subjective sense of improvement and changes on ratings. In addition to this, the acceptability of treatment should be evaluated to include patients more in the decisions about future treatment approaches.

5. Conclusion

Traumatized refugees suffer from numerous co-morbidities including PTSD, depression, psychotic symptoms, somatic disease, untreated somatic complaints, chronic pain, traumatic brain injury and enduring personality change. They have very limited social resources and live under stressful social conditions. In FORLOB where we evaluated treatment with a combination of medicine and TFCBT we found moderate changes in symptoms of PTSD, anxiety and depression, level of functioning and quality of life on self-rating scales measured with Cohen's d. We found no effect of TFCBT as it was implemented in PTF1 and neither did we find an interaction between treatment with antidepressants and psychotherapy and therefore no added effect of psychotherapy. This stands in contrast to the otherwise scarce evidence of the treatment of traumatized refugees and other PTSD patients, which indicates that an added effect can exist when combining psychotherapy and medicine in the treatment of PTSD. In PTF1, we found a very limited effect of Sertraline and Mianserin treatment on level of functioning, depression and anxiety, but no effect of treatment on PTSD in contrast to other studies of traumatized refugees. These findings may be the results of the trial having been undertaken under more pragmatic circumstances and with a comparably better research methodology than most other published studies in the field. Because of the very limited published research, evaluating the treatment of traumatized refugees, many challenges lies ahead, and this thesis has contributed to the identification of these. FORLOB and PTF1 have added to the existing knowledge by reporting on the implementation of a well-described and systematic treatment of a representative sample of chronically traumatized refugee patients in a Western setting. PTF1 is the first study with sufficient power (>50 in each arm), one of the first studies with a waiting list comparison and one of the first studies separating pharmacotherapy and psychotherapy in traumatized refugees. The need for identifying effective treatments for traumatized refugees is urgent as human and societal consequences of costly and ineffective treatments are great. For effective treatment to be offered to traumatized refugees there remains a great need for randomized trials evaluating treatment under circumstances, which are comparable from trial to trial. PTF1 is a step in the right direction.

Summary

Introduction: Despite large numbers of traumatized refugees, little is known about effective treatment of war trauma in refugees and immigrants. Few studies evaluating treatment have been published and most studies are follow-up studies with methodological limitations and little comparability across studies.

Purpose: The purpose of the PhD is to characterize transcultural trauma patients in Denmark needing psychiatric treatment with regards to psychopathology and predictors of mental health and to evaluate the effects of the treatment.

Methods: Two studies reported in 4 papers form the basis of the thesis.

FORLOB (Paper 1-3) was a follow-up study that included all patients receiving treatment at the Competence Center for Transcultural Psychiatry in Copenhagen from April 2008 - February 2010. Patients completed self-ratings of symptoms of PTSD, depression and anxiety as well as level of functioning and quality of life (HTQ, HSCL-25, SDS & WHO-5) before treatment and after treatment. Associations of co-morbid diagnoses and predictors of the patients' health condition were examined with linear and logistic regression and Pearson's correlation coefficients. Treatment in FORLOB consisted of a combination of Sertraline, Mianserin, psycho-education and Trauma-Focused Cognitive Behavioral Therapy (TFCBT). The treatment administered to each patient was monitored in detail and changes in outcome and predictors of change were analyzed.

PTF1 (Paper 4) was a randomized controlled clinical trial with 2x2 factorial design (antidepressants, TFCBT, antidepressants & TFCBT, waiting list). Potential participants were screened amongst adult patients referred to the Competence Center for Transcultural Psychiatry in the period June 2009-2011. Patients with PTSD, war trauma and without a psychotic disorder were included. The manualized treatment consisted of weekly sessions with a physician and/or psychologist over a period of 6 months. The treatment effect was evaluated with a combination of self-ratings and blinded and non-blinded observer ratings. Outcome measures included symptoms of PTSD, depression, anxiety, pain and somatization, quality of life and level of functioning (HTQ, HSCL-25, SCL-90, WHO-5, SDS, VAS, Hamilton, GAF). Treatment was offered with translation and screening instruments were translated to the six most common languages in the patient group covering the needs of 92% of patients.

Results: In FORLOB, patients had several co-morbidities and not just PTSD. Almost all patients had depression, pain and untreated somatic complaints in addition to PTSD. Furthermore, 36-58% had physical problems they were in treatment for, 9-16% of patients had psychotic symptoms mainly related to their trauma, 27% had

enduring personality change due to catastrophic events according to ICD-10 and 46% reported traumatic brain injury. Patients reporting chronic pain had higher symptom scores on HSCL-25 and HTQ and patients with psychotic symptoms scored higher on all symptom clusters on HTQ. At pre-treatment assessment, the patients' level of functioning and quality of life were very low, the majority of patients lived on public subsidies, education levels were low and most patients had a limited social network. In FORLOB, we found a moderate significant change (Cohen's d 0.44-0.67) on all self-report outcome measures (HTQ, HSCL-25, SDS and WHO-5) after combination treatment. We found less improvement in PTSD when patients were receiving public subsidies and less improvement of depression when patients reported pain in the upper extremities. We found a positive association between systematic use of CBT methods and improvement in patient condition.

In PTF1, the randomized clinical trial, we found a small, but significant effect of treatment with medicine on blinded observer-ratings of depression and anxiety (Ham-D and Ham-A) and a large effect on non-blinded ratings of level of functioning (GAF-F and GAF-S), in addition to a small effect on self-reported level of functioning and headache (SDS and VAS). Cohen's d calculated as the differences between randomization groups receiving medicine and not receiving medicine ranged from 0.91-1.01 on GAF-F and GAF-S, whereas on the other ratings showing significant change Cohen's d was 0.31-0.41. We did not find any effect of psychotherapy on any outcomes and nor any effect of psychotherapy or medicine on the primary outcome measure, PTSD.

Conclusion: Traditionally, treatment of traumatized refugees have focused on PTSD, but this study demonstrates that patients suffer from numerous psychiatric and somatic co-morbidities and the comprehensiveness of PTSD in explaining symptoms of traumatized refugees is questionable. This has implications for the type and implementation of treatment. PTF1 is the largest randomized clinical trial published on the treatment of traumatized refugees. It is a strength of PTF1 that it includes a waiting list control group thereby accounting for any effects due to spontaneous recovery and that treatment modalities are examined separately and in combination. In both FORLOB and PTF1, treatment adherence and patient compliance with treatment was thoroughly documented. Effect sizes were moderate in FORLOB and small in PTF1. There were discrepancies between the results in FORLOB and PTF1 with regards to the effect measured on self-ratings that can only partially be explained by methodological limitations of the follow-up study. Both studies are undertaken under pragmatic and realistic circumstances and the results are therefore relevant to other contexts. Patients are representative of patients in other North-European studies of traumatized refugees but differ from patients in trials published on culturally adapted CBT and Narrative Exposure Therapy.

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