Trauma-affected refugees: Pharmacological treatment and psychosocial predictors of treatment outcome

PhD thesis by Charlotte K. Sonne

Competence Centre for Transcultural Psychiatry, Mental Health Centre Ballerup

and

University of Southern Denmark
**Principal Supervisor:** Professor Ask Elklit, Center for Psychotraumatology, University of Southern Denmark.

**Other project supervisors:**

Professor Erik Lykke Mortensen, Institute of Public Health and Center for Healthy Aging, University of Copenhagen

Professor Per Bech, University of Copenhagen, Mental Health Centre North Zealand.

Associate professor Jessica Carlsson, Competence Centre for Transcultural Psychiatry, Mental Health Centre Ballerup.

**Committee of Examiners:**

Professor Dan Stein, Department of Psychiatry and Mental Health, University of Cape Town, South Africa

Professor Poul Videbech, Center for Neuropsychiatric Depression Research, Copenhagen University Hospital, Mental Health Centre Glostrup, Denmark

Professor Morten Sodemann, Center for Global and Migrant Health, University of Southern Denmark, The Migrant Health Clinic, Odense University Hospital (Chairman)

**Charlotte Kærgaard Sonne, MD.**

Competence Centre for Transcultural Psychiatry (CTP)

Phone: + 45 3864 6180

E-mail: charlotte.sonne@regionh.dk

[www.ctp-net.dk](http://www.ctp-net.dk)
List of abbreviations

ACT: Acceptance and Commitment Therapy
CAPS: Clinician-Administered PTSD Scale
CBT: Cognitive Behavioural Therapy
CTP: Competence Centre for Transcultural Psychiatry
CSS: Crisis Support Scale
EMDR: Eye Movement and Desensitisation Therapy
GAS: Goal Attainment Scale
GAF: Global Assessment of Functioning
HAM-A: Hamilton Anxiety scale
HAM-D: Hamilton Depression scale
HTQ: Harvard Trauma Questionnaire
HSCL-25: Hopkins Symptom Checklist-25
MTV: Abbreviation for Medical Technology Assessments in Danish. Until 2012 this was the name of the Danish health authorities’ official assessments of evidence for interventions used within the health sector.
PTF: Abbreviation for Psychiatric Trauma research on Refugees in Danish. All randomised trials at CTP are named PTF followed by the number of the trial. Therefore, the trial described in the present thesis is called PTF3.
PTSD: Post-traumatic Stress Disorder
RCT: Randomised Controlled Trial
SAS-SR: Social Adjustment Scale - Self Report
SCL-90: Symptom Checklist-90
SDS: Sheehan Disability scale
SM: Stress Management
SNRI: Serotonin–norepinephrine reuptake inhibitors
SSRI: Selective Serotonin Reuptake Inhibitors
TF-CBT: Trauma-focused Cognitive Behavioural Therapy
VAS: Visual Analogue Scale
Preface

This PhD thesis represents the majority of the work I have conducted during my employment as a PhD fellow at the Competence Centre for Transcultural Psychiatry (CTP) and Institute of Psychology, University of Southern Denmark, from December 2011 to December 2015 (on maternity leave from June 2014 to March 2015). My primary focus during my employment has been the randomised trial called PTF3, (PTF is an abbreviation for Psychiatric Trauma research on Refugees in Danish, while 3 is the trial number), the third in a row of consecutive randomised trials described further below. While the basic data collecting and monitoring system of the clinics’ randomised trials and the majority of the outcome measures were settled before I commenced PTF3, I was the person primarily responsible for designing the study, including the determination of hypotheses, aims and objectives. Additionally, I was responsible for obtaining the permissions necessary for the study approval from the Danish health authorities, ethics committee and the data protection agency. During the study I was responsible for the treatment of some of the patients included in the trial as well as for continuous training of clinical staff, project monitoring and for communication with the relevant authorities. After completion of the study, I have been primarily responsible for the statistical analyses which have been conducted together with project supervisor Erik Lykke Mortensen, as well as for writing this thesis and the included papers. The papers in the thesis are all related to PTF3, although paper 1 does not directly concern the study, but is a review of the available literature on pharmacological treatment of trauma-affected refugees with PTSD. Paper 1 was submitted to the transcultural research contest Young Researcher Award 2013 and became the winning paper. Paper 2 is a protocol paper concerning the design of the trial while results from the trial are presented in papers 3 and 4.
Acknowledgements

This thesis is primarily based on data collected by psychiatrists, medical doctors, psychologists and social counsellors working at CTP during my study. A total number of 207 patients have given their consent to participate in the randomised trial PTF3 and generously shared their stories and treatment experiences with us. Moreover, no treatment sessions or research would have been possible without our team of secretaries, interpreters and students. I wish to express my warmest gratitude to all of you who, in different ways, have made this thesis possible and especially the following:

My main supervisor, Ask Elklit, for his support and inspiration throughout the study.

Project supervisor, Erik Lykke Mortensen, for endless hours of support and guidance and for his patience in teaching me statistical methods.

Co-supervisor Jessica Carlsson for sharing her great knowledge and experience in the field with me and for her continuous support during the process of designing, completing and evaluating PTF3.

Co-supervisor, Per Bech, for sharing his enormous breadth of knowledge on psychometrics and for valuable scientific discussions.

Fellow PhD student, Erik Vindbjerg, for patiently teaching me the basics of STATA 14 and for his contribution to paper 4 of this thesis.

Senior Consultant, Morten Ekstrøm, head of CTP, for always believing in me and for his invaluable support throughout the design and implementation of this – and many other - studies.

The research coordinator team: Laura Lindberg, Henriette Laugesen and Klement Dymi for their invaluable work in making data ready for analyses.

Sarah Højdrup, Susan Søndergaard and AMNielsen Aps for English proofreading.
My husband, Mikkel Duckert, for technical support, assistance with design, proofreading and loving care.

My baby daughter Sofia, for keeping my spirits high during intensive periods of work.

**Financial support**

I furthermore wish to thank the following funding bodies from which the study received grants: The Health Foundation (Helsefonden), The Tryg Foundation (TrygFonden), The Research foundation of the Capital Region of Denmark and the Research foundation for the Mental Health Services - Capital Region of Denmark.

These funding bodies of the trial had no influence on the design, analysis, interpretation, drafting of the manuscript, the decision to publish, or any areas other than funding.
**English summary**

**Introduction and aim:** There is a lack of evidence for evaluating which types of treatment approaches are the most efficient for trauma-affected refugees, especially when it comes to pharmacological treatment. Additionally, only a very few studies have been published on predictors of treatment outcomes for this patient group. This omission in evidence constitutes a problem for patients and clinicians as well as for society. Accordingly, this PhD thesis aims to generate new knowledge on pharmacological treatment and predictors of treatment outcome for trauma-affected refugees in order to optimise treatment outcome for this patient group.

**Methods:** This thesis includes four papers based on two studies – a literature review and a randomised trial called PTF3:

The aim of the literature review was to provide an overview of the existing literature on the pharmacological treatment of refugees with PTSD and/or depression. Searches were performed in PubMed, psycINFO, EMBASE and the Cochrane library using MeSH/Thesaurus terms as well as free text words. Abstracts (and if necessary full papers) were reviewed and all types of studies (except reviews) describing specified pharmacological interventions were included.

The aim of PTF3 was to examine differences in the effects of venlafaxine and sertraline on Post-traumatic Stress Disorder (PTSD), depression and functional impairments in trauma-affected refugees as well as research predictors for treatment outcome. The patients included were 207 adult refugees diagnosed with PTSD and/or depression who had their first appointment at Competence Centre for Transcultural Psychiatry (CTP) between April 1st 2012 and September 16th 2013. Patients were randomised into one of the two treatment groups: a sertraline group (n=109) or a venlafaxine group (n=98). Patients in both groups received the same manual-based Cognitive Behavioural Therapy (CBT) as well as social counselling. The mean length of the treatment course was 6.3 months. The primary outcome measure was self-reported PTSD symptoms assessed on the Harvard Trauma Questionnaire (HTQ). Other outcome measures were self-reported depression and anxiety symptoms measured on Hopkins Symptom Check List-25 (HSCL-25), self-reported social functioning measured on the Social Adjustment Scale Self Report, short version (SAS-SR), and observer-rated depression and anxiety symptoms assessed on the Hamilton Depression and Anxiety Ratings Scales (HAM D+A). Social support was
assessed on the Crisis Support Scale (CSS), level of functioning assessed on the Sheehan Disability Scale (SDS), quality of life was assessed on the WHO-5, the somatisation items of the Symptom Checklist-90 (SCL-90), pain in four different body areas measured on Visual Analogue Scales (VAS) and levels of symptoms and functioning assessed on the Global Assessment of Functioning (GAF). These measures are all self-report ratings except the GAF-scores which were completed by the medical doctor in charge of the treatment and the HAM D+A, which were performed by blinded assessors.

Furthermore a rating index consisting of 15 potential psychosocial predictors was specifically developed for this study. Five of the items were rated by the medical doctor, five by the psychologist and five by the social counsellor. The items rated by the medical doctor concerned the patient’s upbringing, previous and current psychiatric condition and treatment as well as chronic pain. The items rated by the psychologist all related to the patient’s prerequisites for engaging in psychotherapy, while the items rated by social counsellor related to the patient’s social situation such as job situation and dwelling.

Results:

The literature review: Fifteen studies were included, of which the majority were primarily focused on antidepressants. The included studies differed widely in method and quality. Most of the available studies were observational/case studies. Few studies reported effect sizes, confidence intervals and statistical significance of findings.

PTF3: In the intention-to-treat sample, we found small but significant improvements in both the sertraline and the venlafaxine group on the primary outcome measure HTQ, as well as on a number of other ratings: We found no statistically significant group differences between the venlafaxine and sertraline groups on the primary outcome measure, the HTQ, but found a small but statistically significant group difference on the SDS and a borderline significant group difference on WHO-5 and VAS-leg, all in favour of sertraline.

For the CTP predictor index we found a statistically significant correlation to the change in score between baseline and follow-up on most of the ratings, with the exception of two of the VAS scales for pain and the GAF-functioning score. For the primary outcome measure HTQ the correlation was borderline significant (P=0.06). The only item from the rating scale that was
significantly correlated to outcome on HTQ was job status, while a number of other items were significantly related to changes in depression and anxiety symptoms. The size of correlation coefficients was, however, modest. In addition, we found that the following baseline variables were significantly associated with improvements on HTQ in univariate analyses: female gender, younger age, being family reunified (versus being a refugee), shorter duration of stay in Denmark and a lower level of depression and anxiety at baseline. In adjusted analyses only gender was significantly correlated to outcome on HTQ, while the correlation was borderline significant for duration of stay in Denmark.

**Conclusion:** Existing evidence for pharmacological treatment of trauma-affected refugees was generally scarce. In our trial, PTF3, we aimed to overcome some of the methodological shortcomings found in other studies by conducting a relatively large randomised trial. We found small differences in the effects of two antidepressants on a number of secondary outcome measures, all in favour of sertraline. We therefore continue to recommend SSRIs as the first line of pharmacological treatment for trauma-affected refugees. Moreover, we found that the CTP predictor index total score correlates significantly with treatment outcome on most of the rating scales used, but that the sizes of the correlation coefficients were not large. There is a need for further studies on other pharmacological agents as well as studies focusing on identifying predictors of treatment outcome for trauma-affected refugees.
Dansk resumé


Metode: Denne afhandling omfatter fire artikler baseret på to studier - et litteraturstudie og et randomiseret forsøg kaldet PTF3.


Formålet med PTF3 var at undersøge forskelle i effekten af de to antidepressiva, venlafaxin og sertralin, på posttraumatisk belastningsreaktion (PTSD), depression og funktionsnedsættelse hos traumatiserede flygtninge samt at undersøge prædiktorer for behandlingsudbytte. Studiet inkluderede 207 voksne flygtninge diagnosticeret med PTSD og/eller depression, som var til førtevisitationssamtale på Kompetencecenter for Transkulturel Psykiatri (CTP) mellem 1. april 2012 og 16. september 2013. Patienterne blev randomiseret til en af to behandlingsgrupper: en sertralin gruppe (n = 109) eller en venlafaxin gruppe (n = 98). Patienterne i begge grupper blev desuden tilbudt manualbaseret kognitiv adfærdsterapi samt socialrådgiver samtaler. Den gennemsnitlige længde af behandlingsforløb var 6,3 måneder. Det primære effektmål var selvpårapporterede PTSD symptomer målt med Harvard Trauma Questionnaire (HTQ). De øvrige effektmål var selvpårapporterede depression og angst symptomer målt med Hopkins Symptom Check List-25 (HSCL-25), selvpårapporteret social funktion målt med Social Adjustment Scale-Self

**Resultater:**

*Litteraturstudiet:* Femten studier blev inkluderet, hvoraf størstedelen primært omhandlede antidepressiva. De inkluderede studier varierede meget i metode og kvalitet og de fleste af var observationelle studier eller case studier. Få studier rapporterede effektstørrelser, konfidensintervaller og statistisk signifikans af resultaterne.

**PTF3:** I intention-to-treat gruppen, fandt vi små, men statistisk signifikante forbedringer i både sertralin- og venlafaxingruppen på det primære effektmål HTQ, samt på en række andre effektmål. Vi fandt ingen statistisk signifikante gruppeforskelle mellem venlafaxin- og sertralingruppen på det primære effektmål, HTQ, men fandt en lille, men statistisk signifikant gruppeforskel på SDS og en borderline signifikant gruppeforskel på WHO-5 og VAS for bensmerter, alle til fordel for sertralin. For CTP prædiktor indeks fandt vi en statistisk signifikant korrelation med ændringer på de fleste effektmål, undtagen to af VAS skalaerne for smerter og GAF-funktions score. For det
primære effektmål HTQ var korrelationen borderline signifikant (p = 0,06). Den eneste enkeltvariabel fra CTP prædiktor indeks, der var signifikant korreleret med ændring af HTQ score var jobstatus, mens en række andre variable var signifikant korrelerede med ændringer i depression og angst symptomer på både selvvurderede og observatør vurderede rating-skalaer. Størrelsen af korrelations-koefficienterne var dog generelt beskedne. Endvidere fandt vi, at følgende baseline variable var signifikant associerede til forbedringer på HTQ i univariate analyser: kvindeligt køn, yngre alder, at være familiesammenført (kontra at være flygtning), kortere ophold i Danmark og lavere niveau af depressions- og angstsymptomer ved baseline. I multivariate regressions-analyser var kun køn signifikant korreleret med forbedring på HTQ mens korrelationen var borderline signifikant for opholdstid i Danmark.

**Konklusion:** Den eksisterende evidens for farmakologisk behandling af traumatiserede flygtninge er samlet set meget sparsom. I vores studie, PTF3 forsøgte vi at undgå nogle af de metodiske svagheder, som tidligere studier lider under, ved at gennemføre et relativt stort randomiseret studie. Vi fandt små men signifikante/borderline signifikante forskelle i effekten mellem to antidepressiva på en række sekundære effektmål, alle til fordel for sertralin. Vi anbefaler derfor fortsat SSRI som førstevalg ved farmakologisk behandling af traumatiserede flygtninge. Vi fandt desuden, at den samlede score for CTP prædiktor indeks korrelerer signifikant med behandlingsudbytte på de fleste af de anvendte rating-skalaer, men at størrelsen af korrelations-koefficienterne var beskedne. Der er således behov for flere farmakologiske effektstudier og for studier der fokuserer på at identificere prædiktorer for behandlingsudbytte hos traumatiserede flygtninge.
# Table of contents

1. **Introduction** ................................................................................................................................. 5  
   Pharmacotherapy for trauma-affected refugees ................................................................................. 5  
   Pharmacological treatment and psychotherapy for trauma-affected populations in general .......... 6  
   Pharmacotherapy ................................................................................................................................. 6  
   The combination of pharmacotherapy and psychotherapy ............................................................... 8  
   Manualised psychotherapy for trauma-affected refugees ................................................................. 9  
   Differences between refugees and other trauma-affected populations ........................................... 9  
   Predictors for treatment outcome ...................................................................................................... 10  

2. **Aim and objectives** ......................................................................................................................... 11  

3. **Methods** ........................................................................................................................................ 12  
   The literature review .......................................................................................................................... 12  
   PTF3 .................................................................................................................................................. 12  
   Setting .............................................................................................................................................. 12  
   The Treatment and Research Integrated Model (TRIM) ................................................................. 13  
   Ethics ................................................................................................................................................ 14  
   Study approval and monitoring .......................................................................................................... 15  
   Randomisation .................................................................................................................................. 15  
   Participants ....................................................................................................................................... 15  
   The treatment programme ................................................................................................................. 17  
   Pharmacological treatment and psycho-education ........................................................................... 17  
   The manualised psychotherapy .......................................................................................................... 19  
   Social counselling ............................................................................................................................... 20
Blinding ................................................................................................................................. 21
Outcome measures ............................................................................................................. 21
  Primary outcome measure ............................................................................................... 22
  Secondary outcome measures .......................................................................................... 22
  Translations of self-report ratings .................................................................................. 24
The CTP Predictor index .................................................................................................... 25
Other possible predictors of treatment outcome ............................................................. 25
Data analyses ...................................................................................................................... 26
4. Results ............................................................................................................................... 27
  The literature review ......................................................................................................... 27
  Studies on antidepressants ............................................................................................... 27
  Studies of prazosin ........................................................................................................... 28
  Studies on clonidine .......................................................................................................... 29
PTF3 ..................................................................................................................................... 29
Characteristics of the study population ........................................................................... 29
  Psychiatric comorbidity .................................................................................................... 30
  Trauma history and flight .................................................................................................. 30
  Social status ........................................................................................................................ 30
The treatment programme ................................................................................................. 31
Attrition and pharmacological side-effects ........................................................................ 31
Changes from baseline to follow-up .................................................................................. 32
  PTSD, depression and anxiety .......................................................................................... 32
  Somatic symptoms ........................................................................................................... 32
  Quality of life, social functioning, functional impairments and overall symptoms .......... 33
Differences in effect between the venlafaxine and the sertraline group ................................................................. 33
Differences between the intention-to-treat sample and the pharmacological completers .................. 33
Changes from baseline to follow-up ................................................................................................................ 33
Group differences ........................................................................................................................................ 34
The CTP predictor index .................................................................................................................................. 34
Other predictors of treatment outcome ........................................................................................................ 35
Patient satisfaction ........................................................................................................................................... 35
5. Discussion ................................................................................................................................................................. 36
The effect and tolerability of sertraline and venlafaxine .......................................................................................... 36
The overall effect of the treatment programme .................................................................................................. 38
Predictors of treatment outcome ...................................................................................................................... 39
Challenges in performing randomised trials with trauma-affected refugees ...................................................... 39
  Randomisation and control groups .................................................................................................................. 40
  Outcome measures ........................................................................................................................................ 41
  Blinding towards treatment allocation .......................................................................................................... 43
  Measures of compliance ............................................................................................................................... 43
  Generalisability of results ........................................................................................................................... 44
Comparability between trauma-affected refugees and other PTSD patients .................................................... 45
  Biological differences .................................................................................................................................. 45
  Differences in trauma history, culture and social context ............................................................................. 46
Methodological considerations ........................................................................................................................... 47
  The literature review .................................................................................................................................... 47
  PTF3 ................................................................................................................................................................. 47
6. Lessons learned from PTF3: Clinical implications and future research ....................................................... 48
Clinical implications........................................................................................................ 49

Recommendations for future studies ........................................................................ 50

7. Conclusion ................................................................................................................. 52

8. Tables and figures .................................................................................................... 54

9. References ................................................................................................................ 66

Papers

Paper 1: Pharmacological treatment of refugees with trauma-related disorder - What do we
know today? .................................................................................................................... 79

Paper 2: Treatment of traumatized refugees with Sertraline versus Venlafaxine in combination
with psychotherapy – study protocol for a randomized clinical trial..............................111

Paper 3: Treatment of trauma-affected refugees with venlafaxine versus sertraline combined
with psychotherapy – a randomised study ......................................................................119

Paper 4: Psychosocial predictors of treatment outcome for trauma-affected refugees ........150

Appendices

A: Psycho-education material used in PTF3 ................................................................ 175

B: Flowchart from the PTF3 psychotherapy manual...................................................... 189

C: The CTP Predictor Index - Score sheet and instructions for raters ............................ 190

D: Pharmacological completer analyses, PTF3............................................................. 195
1. Introduction

Posttraumatic stress disorder (PTSD) is a serious psychiatric condition that, in some individuals, causes severe disabilities. In Denmark, PTSD has been the most common cause of early retirement during the last seven years (1). It is estimated that PTSD affects approximately 30% of all refugees and that comorbidity with other trauma mental health disorders such as depression is commonly found in this patient group (2). Despite the recognition of the possible severe and multifaceted psychiatric consequences of trauma for many years, research on the efficacy of treatment has not been a priority within the field of refugee mental health. While there might be a range of historical, economical and contextual reasons for this, the existing gap in evidence is now being addressed by an increasing number of clinicians and researchers in the field (3–5). With the present thesis I seek to contribute to rectifying this omission.

Pharmacotherapy for trauma-affected refugees

While studies of the effect of psychotherapeutic interventions for PTSD for trauma-affected refugees have gradually emerged during the past ten years (6–8), little conclusive evidence exists regarding the pharmacological treatment (9) of this patient group. Paper 1 in this present thesis is a literature review from 2013 that presents an overview of available literature on the subject at the time. In the paper we included all types of studies, regardless of evidence level. We found 15 papers eligible for review, mainly observational studies and case reports and concluded that the body of evidence had severe limitations in both size and quality. Since then, one large randomised trial has been published, originating from the same treatment facility as the present thesis. The study included 280 patients randomised to either a combined medicine and therapy group receiving the selective serotonin reuptake inhibitor (SSRI) sertraline in combination with flexible cognitive behavioural therapy (CBT), a group receiving medicine only, a group receiving CBT only or a waiting list control group (10). The authors found no effect on the primary outcome measure Harvard Trauma Questionnaire, but found significant effects on some of the secondary outcome measures, the Hamilton depression scale (HAM-D), Sheehan
disability scale (SDS), Global assessment of Functioning (GAF) and a visual analogue scale (VAS) in favour of those receiving medicine when compared to waiting list controls.

**Pharmacological treatment and psychotherapy for trauma-affected populations in general**

In contrast to the field of trauma-affected refugees, treatment outcome research has burgeoned in the general field of PTSD. During recent years, accumulated evidence has supported the efficacy of both pharmacological treatments and psychotherapy for PTSD (11–14).

*Pharmacotherapy*

The Danish Medical Technology Assessment report (MTV) “The treatment and rehabilitation of PTSD inclusive traumatised refugees” is the Danish health authorities official clinical guidelines and assessment of the evidence for the treatment of PTSD, published in 2008 (15). It concluded that selective serotonin reuptake inhibitors (SSRIs) were currently the best documented pharmacological treatment of PTSD. However, it also stated that more trials were needed on patient with treatment refractory PTSD and complex PTSD in multi-traumatised patients such as refugees, as SSRI seemed to be inadequate for these groups (15).

During the last couple of years a number of reviews and meta-analyses have been conducted of the pharmacological treatment of PTSD in mixed patient groups. The only existing Cochrane review on pharmacotherapy as monotherapy for PTSD is from 2009 (16) although the three most recent meta-analyses are from 2012 (12), 2013 (13) and 2015 (11).

The Cochrane review included 35 short-term RCTs, with placebo-arms in all but four trials (16). At the time of the review being conducted, the authors found that the largest body of evidence existed for the use of SSRIs. For single SSRI agents the authors found significant effects for paroxetine and, to a lesser extent, sertraline, but none for citalopram or fluoxetine on PTSD symptoms measured by the Clinician-Administered PTSD Scale (CAPS).

Ipser and Stein reviewed the existent evidence for pharmacological treatment of PTSD in 2012 (12). They found the largest body of evidence to be for SSRI with initial findings also supporting
the use of the Serotonin–Norepinephrine Reuptake Inhibitor (SNRI) venlafaxine and the antipsychotic agent risperidone. For treatment-resistant PTSD there was initial evidence supporting the effect of the alfa1-antagonist prazosin on sleep problems, although trials with atypical antipsychotics as a treatment augmentation showed mixed results.

Watts et al. performed a meta-analysis in 2013 in which they analysed the efficacy of each of the treatment modalities pharmacotherapy, psychotherapy and somatic therapy separately (13). In the meta-analysis of antidepressants, the authors found only SSRIs (paroxetine, fluoxetine and sertraline) and venlafaxine to be superior to placebo with a medium effect size. Additionally, they found risperidone to be efficient compared to placebo both as monotherapy and as an augmentation to other psychotropics and found topiramate to be the only effective treatment among the anticonvulsants. Overall, they found that the effect size of psychotherapy was larger than for pharmacotherapy - which was at least partly explained by differences in control group (waitlist controls studies having larger effect sizes than placebo/active treatment controls) and the publication bias for psychotherapy studies.

A review published in 2015 by Hoskins et al. included only randomised controlled trials (RCT’s) that compared specific pharmacological agents to each other or to a placebo (only three of the 51 RCT’s did not include a placebo arm) and where the participants did not receive trauma-focused therapy during the study period (11). The majority of the trials (n=31) were on SSRI. The meta-analysis found small but statistically significant evidence for SSRI as a group and for venlafaxine, fluoxetine and paroxetine as single pharmacological agents compared to placebo, but found inadequate evidence for most other psychotropics investigated.

As this brief overview shows, recommendations for pharmacological treatment of PTSD have gradually changed over the last decade from SSRIs only to also including venlafaxine. When we were designing our trial PTF3, initial findings were starting to be published on the possible effectiveness of venlafaxine for PTSD in non-refugee populations, but only one small study on refugees had ever investigated the effects of venlafaxine in trauma-affected refugees (17). This study had several severe methodological limitations, among these only 5 patients in the venlafaxine group which were all men who often receive poorer treatment results than women
in trials, which could therefore have diminished the effects for the venlafaxine group. Accordingly the study did not provide sufficient evidence to draw any conclusions about the effects of venlafaxine for this population. Due to numerous differences between trauma-affected refugees and other populations of PTSD patients, results cannot readily be transferred from one group to another which will be further discussed below. Thus, we found there was a need for larger and methodological sound randomised trials in order to make further conclusion on the efficacy of venlafaxine compared to SSRIs in refugees with PTSD.

The combination of pharmacotherapy and psychotherapy

The evidence for a cumulative effect of pharmacotherapy and psychotherapy is scarce. A Cochrane review by Hetrick et al. from 2010 on combined pharmacotherapy and psychological treatment methods in patients with PTSD only identified four studies which could be included in the review and found that there was not enough evidence to conclude whether the two treatment modalities combined were more effective than psychotherapy or pharmacotherapy alone (18). CTP’s own recent study, which compared combined treatment to single modality treatment and a waitlist control, also failed to demonstrate a synergy effect for the combination group (10), while other studies have found an add-on effect of psychotherapy to pharmacological treatment (19). Most official international guidelines, including the Danish MTV report mentioned above, still recommend a combination of pharmacotherapy, psychotherapy and psychosocial treatment methods for complex PTSD (15).

The psychotherapy methods recommended for treating PTSD at the time of the design of the present study were primarily trauma-focused cognitive behavioral therapy (TF-CBT), Eye Movement Desensitization and Reprocessing (EMDR) and Stress Management (SM) (20). However, over the last few years a growing body of evidence has supported the use of different types of exposure therapies, with initial evidence for a phase-oriented approach (21). Despite this, a review from 2015 found the head-to-head evidence to be too scarce to determine the effectiveness of one type of therapy over another (14).
Manualised psychotherapy for trauma-affected refugees

Standardising psychotherapy in a transcultural setting is a major challenge, yet is necessary to some degree since treatment based solely on preferences of individual providers and patients makes it difficult to establish evidence for the different types of psychotherapy. Most psychotherapy methods used in refugee health settings are originally developed for and tested on other groups of PTSD-patients, but have, in some cases, been adapted towards the target group. Previously, these adaptations have primarily aimed at tailoring the treatment to one particular cultural group, not to a group of trauma-affected refugees of mixed cultural origins (22). However, most refugee health settings accommodate clients from a diverse range of ethnic, cultural and linguistic backgrounds. Accordingly, treatment manuals often need to be applicable across cultures, which is increasingly acknowledged by researchers in the field (23,24).

Differences between refugees and other trauma-affected populations

The differences between refugees and other groups of PTSD patients are numerous (5). Survivors of civilian trauma have often been exposed to a single traumatic event while refugees typically have a history of multiple and prolonged traumatization (25). Moreover studies have shown that childhood traumas, which are frequently found among trauma-affected refugees (26), are associated with greater risk of PTSD in those with multiple traumas (27). Non-refugee PTSD patients also have the advantage of generally remaining in their habitual social, cultural and linguistic context after the traumatic event. Refugees, in contrast have, by definition, been forced to flee their home countries, leaving almost everything that defines their identity behind. As a consequence of these drawbacks, trauma-affected refugees often present a more complex symptom pattern than those incorporated within the current PTSD diagnosis (28). In recent research this is often referred to complex PTSD, which is now proposed as a separate diagnostic entity for the upcoming ICD-11 (29–31).

Due to the differences mentioned above, as well as the biological differences discussed in paper 1, it is questionable whether treatment approaches developed for other groups of PTSD-
patients can readily be translated to the treatment of refugees. Pragmatic approaches towards dealing with these differences will be further discussed later in this thesis.

Predictors for treatment outcome

While a considerable number of studies have been conducted on pre- and post-migration predictors of PTSD and other trauma-related mental health disorders among refugees (2,32–35), predictors of treatment outcome have received less attention. Although some of the factors that influence the development of PTSD may also play a role in its maintenance, it seems unlikely that predictors of mental health are identical to predictors of treatment outcomes.

Many of the existent papers on treatment predictors concern both baseline variables such as gender, along with variables that are not measurable at baseline such as for example number of treatment sessions attended. In the remaining part of this thesis, the term predictor of treatment outcome is however used solely about outcome correlated variables that are clearly measurable at baseline.

Two papers have been published on the same study population investigating the possible predictive value of gender, exposure to torture, offender status, baseline depression and anger, as well as dissociative symptoms on the treatment outcomes in the same refugee population (36,37). The authors found male gender and offender status to be significant negative predictors of treatment outcome, but found no significant associations between treatment outcome and any of the remaining variables. A couple of other papers chiefly concerned with mental health changes also touched upon predictors of treatment outcome (10,38). Additionally, some studies have been conducted on asylum seekers investigating whether uncertainty about the outcome of the asylum process has a negative effect on treatment outcome (39,40). Although more studies exist when it comes to other groups of PTSD patients, research on this important topic is still limited.

In studies on refugees with PTSD, offender status (36), a high symptom baseline score (38) and the receipt of state benefits have been found to be negative predictors of treatment outcome
Variables found to be negative predictors of treatment outcome in studies on other groups of PTSD patients were, amongst others, comorbid general anxiety disorder, high suicide risk, living alone (42), alcohol abuse and anger (43). Female gender has been found to be positively correlated with treatment outcome or maintenance of the treatment effect, both in populations of refugees and other PTSD populations (13,36,42,44).

Increasing knowledge about predictors of treatment outcome is of utmost importance. Identifying psychosocial factors that influence treatment outcome provides us with a better understanding of the obstacles patients and clinicians face during treatment and offer us possible explanations when facing challenges in receiving desired treatment outcomes. Even more importantly, identifying predictors of treatment outcome is a crucial step towards offering individualised treatment on an evidence basis, which would potentially lead to better treatment outcomes as well as higher patient satisfaction.

2. Aim and objectives

The overall aim of the present PhD thesis is therefore to generate new knowledge on pharmacological treatment and predictors of treatment outcome for trauma-affected refugees in order to optimise treatment outcome for this patient group.

The objective of paper 1 was to provide an overview of available literature on pharmacological treatment of trauma-affected refugees and to discuss the transferability of results from studies on non-refugee PTSD patients.

The objective of paper 2 was to present the study protocol of the randomised clinical study PTF3 including a presentation of the design, methods and outcome measures of the trial.

The objective of paper 3 was to examine differences in effects of venlafaxine and sertraline on PTSD, depression, anxiety, life quality, somatisation, pain, functional impairments and social functioning in trauma-affected refugees.

The objective of paper 4 was to examine possible psychosocial predictors of treatment outcome for trauma-affected refugees, using a newly designed instrument, the CTP predictor index.
3. Methods

The literature review

The databases PubMed, psycINFO, EMBASE, and the Cochrane library were systematically searched. The last search was performed on the 26th of September 2013. In addition, reference lists of the existing reviews were searched.

Papers were included if they described a specific psychopharmacological intervention for adult refugees (18 years old or above), diagnosed with PTSD and/or depression and if the outcome of the intervention was described, either qualitatively or quantitatively. The process of paper inclusion and exclusion is displayed in figure 1.

PTF3

The majority of the papers of this thesis (paper 2-4) concern the randomised controlled trial PTF3. The study was a randomised 2-armed pragmatic trial using sertraline as an active control to venlafaxine. Patients in both groups were offered a 6-7 month bio-psycho-social treatment programme combining pharmacotherapy, manualised psychotherapy and social counselling. In the study’s protocol paper (paper 2), the planned study design is comprehensively described. The following method description should therefore be seen as supplementary to the one of paper 2, i.e. to provide further descriptions of procedures when needed as well as provide additional information in the few occasions where changes have occurred from the original design.

Setting

CTP was established in 2008 (at that time named Psychiatric Trauma Clinic for Refugees) as part of the public Mental Health Services in the Capital Region of Denmark. During the initial years, the patient group was restricted to trauma-affected refugees, but from 2013 onwards the clinic also served other groups of migrant psychiatric patients, although refugees still constituted the largest patient group. The research group and activities at CTP have grown substantially over the years. Although both qualitative and quantitative studies have been performed, the main
focus has so far been on clinical outcome studies due to the gaps in evidence described above. Consequently, most clinical work presently forms part of pilot studies of new treatment options (41,45) or randomised clinical trials (3 have been completed, 1 is ongoing). Results from the trials are used to implement new treatment strategies and create new research hypotheses.

PTF3 was the third randomised clinical trial at CTP. The first randomised trial in the clinic was PTF1, a 2x2 factor trial comparing a combination of pharmacotherapy and psychotherapy to each of the two individually and to a waiting list control group (10). PTF2 was a randomised psychotherapy trial comparing stress management and cognitive restructuring, the results of which have not yet been published.

*The Treatment and Research Integrated Model (TRIM)*

From the establishment of CTP, the research activities have been closely connected with the treatment programmes. In an attempt to standardise data collection during the different studies, the clinic’s own Treatment and Research Integrated Model, TRIM, was developed and implemented (5). The aim of the model was to generate research data of high quality with minimal extra cost and time commitment from the clinic. The key components of TRIM are the tick-box format of medical records, the development and implementation of manuals for all treatment offered and the performance of regular ratings.

CTP’s medical record is designed as a tick-box system in order that information from the initial assessment, treatment sessions and contacts with the social counsellor can be directly entered into our research database. All clinicians therefore automatically collect data as a part of their everyday clinical work, which allows studies with a high number of participants. Moreover, fairly large amounts of data can be collected for the individual patient, since tick-boxes make data collection fast and easy as most information used in studies is routinely collected for clinical purposes. For PTF3, 744 different variables were collected - and if patients participated in a standard treatment course, the number of variables added up to 2.522, as many variables were collected repeatedly at each session with the patient. Needless to say, only a fraction of this information has been used in this thesis.
Manuals have been developed for both the medical and psychotherapeutic treatment and for the work carried out by the social counsellors in order to standardise treatment. Each time a new randomised trial is commenced, manuals are revised based on clinical experience and research results from previous trials. The development of manuals for PTF3 is briefly described below.

To date, outcome measures for the randomised studies at CTP have consisted of a core set of self-report and observer-rated questionnaires to which extra ratings can if relevant, be added for the specific studies. The standard outcome measures as well as the extra ratings added for PTF3 are further described in the method section of this thesis.

**Ethics**

Concerns have been raised about ethical issues surrounding the conduct of randomised controlled trials amongst refugees seeking treatment for trauma-related mental disorders. From the outset, the principle adopted by CTP has been that examining the evidence is essential to providing effective treatment for trauma-affected refugees. A failure to do so risks perpetuating treatments which lack empirical support and thus may be ineffective, creating an important ethical concern in itself (46).

PTF3 (as well as the other studies at CTP) have been conducted in accordance with the Helsinki protocol and patients were only included if written informed consent was obtained. Once a patient was referred to the clinic, written information about the study was sent to the patient along with a letter offering practical information concerning the forthcoming assessment process. Written information about the study was available in five languages: Arabic, Farsi, English, Bosnian and Danish, encompassing the native language of almost 90% of patients in PTF3. Patients were encouraged to consider bringing a relative or a friend to the initial assessment interview if they deemed this helpful. Patients who did not wish to take part in research were offered a treatment programme similar to that of the sertraline group. Patients who did not wish to receive pharmacological treatment, could not, for obvious reasons, take part in the trial, but were also offered a similar treatment programme, only without the pharmacological component.
Study approval and monitoring

The trial was approved by the ethics committee (H-3-2012-020), The Danish Medicines Agency (2011-006228-19.) and the Danish Data Protection Agency (2007-58-0015). Additionally, the data collection was monitored by the Good Clinical Practice (GCP) Unit at Copenhagen University Hospital.

Randomisation

Randomisation by envelope was performed, stratified by gender and the level of severity of PTSD symptoms on the basis of the Harvard Trauma Questionnaire (please see below). The randomisation list was devised by the Department of Biostatistics at the University of Copenhagen.

Participants

Participants were recruited from the total group of patients who had their first appointment at CTP between April 2012 and September 2013, as the original inclusion period was extended by three months on permission from relevant authorities. Inclusion criteria for the study were the following:

- Being a refugee or family reunified to a refugee
- Being 18 years or above
- Having a history of at least one severe psychological trauma
  (imprisonment/torture/inhuman and degrading experiences or punishment/organised violence, prolonged political persecution and harassment/experiences of war, civil war or similar conditions)
- Fulfilling the diagnosis of PTSD and/or depression according to ICD-10 research criteria
- Being motivated for receiving treatment
- Providing informed consent to participate in the study
Exclusion criteria were the following:

- Having a severe psychotic disorder or bipolar diagnosis (ICD-10 F2x or F.301 - F.31.9). Psychotic experiences related to trauma-related psychopathology did not lead to exclusion as such symptoms are prevalent among trauma-affected refugees.
- Currently abusing drugs or alcohol
- Being in need of acute admission to a psychiatric hospital
- Being pregnant or breastfeeding or being a woman in the reproductive age with a wish to conceive during the project period.
- Not providing written informed consent

The PTSD and depression diagnoses were determined through a clinical interview by one of the CTP doctors applying ICD-10 criteria for each of the diagnoses in a diagnostic algorithm. Psychotic and bipolar disorders were excluded using the SCAN interview, with chapter 1 and 14 used for screening, chapter 10 for bipolar disorders and chapter 16-19 for psychotic symptoms. All doctors performing these interviews were certified SCAN raters. Trauma-related psychotic symptoms alone were not an exclusion criterion, as these are relatively common in this PTSD patient group (47,48). It was therefore registered in the patient file whether the content of the psychotic feature was related to the patient’s past trauma or not.

Patients were systematically enquired about their use of drugs and alcohol and this was registered in the patient file. Objective measures such as an alcohol breath tester were available, but were only used in cases were the clinician suspected that the patient were being dishonest about current abuse.

From 1 April 2012 until 15 September 2013 a total of 407 patients were screened for the trial, from which 207 patients were included in the study. The participants’ flow through the trial is depicted in figure 2. The included patients were randomised to one of the two groups - 98 to the venlafaxine group and 109 to the sertraline group. The last patient finalised the treatment programme in September 2014.
The treatment programme

The full treatment programme was intended to last six-seven months and consisted of a combination of pharmacological, psychotherapeutic and psycho-social interventions. The pharmacological treatment to which the patient was randomised was the only element that differed between the two groups, as all treatment modalities where manual-based (please see below). The overall treatment programme followed a phase-based approach consisting of two phases.

During phase 1 (the first two months) the patient was offered six sessions with the medical doctor as well as introductory sessions with the psychologist and social counsellor. If the patients were in need of further social counselling, follow-up sessions were arranged. During phase 2 (the last four-five months) the patient was offered 4 sessions with a doctor, 16 sessions with the psychologist and at least one follow-up session with the social counsellor. If patients and clinicians agreed on extra sessions, these were all registered in the patient record.

Each patient had a designated medical doctor/psychiatrist and psychologist throughout the treatment programme. If patients were in need of an interpreter, whenever possible, the same interpreter assisted the patient during the entire programme.

Pharmacological treatment and psycho-education

During the treatment programme each patient was offered a total number of ten sessions with the medical doctor/psychiatrist. Sessions were scheduled to take place weekly during phase 1 and monthly during phase 2. During these sessions the pharmacological treatment to which the patients were randomised was initiated and the doses were gradually increased, if possible up to the maximum recommended dose – 200 mg daily for sertraline and 375 mg daily for venlafaxine. Compliance was measured by pill count and pharmacological completers defined as patients who completed a minimum of eight consecutive weeks of the pharmacological treatment to which they were randomised.

In addition to the trial medicine, all patients were offered supplementary treatment with mianserin if they suffered from severe sleep disturbances, which is the case for many patients
with PTSD. The combination of sertraline supplemented with mianserin in case of sleep disturbances was first line pharmacological treatment at CTP before the PTF3 trial commenced. If treatment with antipsychotic drugs was necessary from a clinical point of view, the patient would either continue with the antipsychotic treatment he/she was already receiving or begin treatment with perphenazine. However, during the study period, perphenazine was taken off the Danish pharmaceutical market and we therefore decided to replace it with quetiapine in accordance with the recommendation for first line antipsychotic treatment in the clinical guidelines for the Capital Region of Denmark at the time being (49). As CTP kept a stock of perphenazine for almost the entire remaining study period, if is however estimated that only a very limited number of patients were affected by this change.

Whenever possible, patients were gradually taken off any other psychopharmacological treatments they were receiving when entering the study. The termination or switching of psychotropics were conducted in accordance with the Maudley Prescribing Guidelines (50). All psychotropics mentioned above were provided free of charge during the entire treatment programme, regardless of whether the patient was participating in the study or not.

As side effects are common for both venlafaxine and sertraline, it was expected that the majority of patients would have mild side effects during parts of the study. Changes in the patients’ physical condition were registered at each medical doctor session, but only unexpected or serious events/side effects were systematically collected and reported to the ethics committee and the Danish Medicines Agency in accordance with Danish legislation at the time being.

Supplementary to the pharmacological treatment, psycho-education was performed on a range of topics such as symptoms of PTSD and depression, healthy lifestyle, sleep disturbances and chronic pain. Twelve different one-page handouts were used in the study, all of which have been developed at CTP and improved based on the experiences of previous trials. The psycho-education handouts were available in five different languages of which the English version is depicted in appendix A. The patient and the doctor jointly decided the relevant topic for each session based on the current needs of the individual patient. This approach was aimed to make
the treatment programme flexible, yet standardised as all clinicians followed the same manual. The main topics of each session were registered in the patient file in accordance with the TRIM (5).

**The manualised psychotherapy**

Each patient was offered one introductory session and 16 therapeutic sessions with a psychologist. The introductory session was in phase 1, before or immediately at the outset of the treatment period. All psychotherapy treatment sessions took place during phase 2.

The therapy provided was based on the same manual, for both groups. The manual was developed by the psychologists employed at CTP, based on the available literature and the experiences with the three manuals previously used during the randomised trials at the clinic. The result was a manual with flexible CBT including elements from TF-CBT, acceptance and commitment therapy (ACT) stress management and mindfulness. All methods were adapted to fit the patient group. As the patients came from many different cultures and had frequently adapted to their current cultural context to some extent, we could not rely on manuals developed to fit one specific culture. Instead we sought to shift the focus from “How are our patients different from one another” into “What have our patients got in common that makes us believe that they have some of the same needs when it comes to treatment”. Accordingly, we sought to base the manual on concepts and means of communication that are understandable across languages and cultural mindsets i.e. pictures with reference to the patients’ current lives. For example, most of our patients use public buses as their primary means of transport. In an adapted form of ACT we therefore used a drawing of a bus to discuss the patient’s strategies for dealing with distressing memories. These were pictured as “annoying passengers” that you cannot get to leave “the bus” (i.e. they will always remain in one’s life), but that you might learn to put behind “the yellow line” - a line on the floor behind the driver’s seat, designed to keep passengers from compromising the attention and vision of the driver. More examples from the PTF3 psychotherapy manual can be found in a previously published paper (51).
In addition, we knew from previous trials that patients varied substantially in cognitive functioning and reflectiveness and furthermore that a lot of matters of daily living such as socio-economic problems tended to influence the content of psychotherapy sessions. The psychologists therefore found it difficult to follow manuals strictly. On the other hand, we had to obtain a certain amount of standardisation into the psychotherapy in order to be able to ensure that both the treatment groups received roughly the same psychotherapeutic treatment. In an attempt to meet this challenge we created a flowchart that psychologists were to follow as a guide towards which methods they were to use depending on the prerequisites of the individual patient. The flowchart is depicted in appendix B. As with the medical doctors, the psychologists completed a methodology chart in the patient record after each session, thereby documenting the methods used and whether the patient had completed the planned homework. All psychologists attended manual supervision sessions regularly.

**Social counselling**

All patients were offered at least two sessions with a social counsellor during the trial: one at the beginning and one towards the end of the treatment. During the first session the social counsellor collected socio-demographic information from the patient and reviewed the social situation of the patients and his/her family in order to determine whether there were any social issues that required immediate attention. The social counsellor then informed the patient about relevant local community activities (i.e. groups for vulnerable refugee women) as well as provided information about the CTP social counselling group programme described below. During the treatment programme the social counsellor also facilitated contact to the social-services office and other relevant institutions and was in charge of meetings with the patients’ relatives.

Through the CTP social counselling group programme patients were offered the opportunity to participate in group counselling once a month. Sessions concerning the following three topics were offered in a fixed rotation:

- The structure of the Danish municipal administration and social services
- Financial issues and the tax system
Citizenship, social support and leisure activities

Groups were of mixed gender and divided according to language. There were Arabic, Farsi, Bosnian and Danish groups; encompassing the vast majority of the language groups at CTP. If patients spoke other languages they could still attend the Danish group with a personal interpreter provided by the clinic.

**Blinding**

Neither doctors nor patients were blinded in this study, while the raters who administered the Hamilton Depression Scale and the Hamilton Anxiety Scale (please see below) were blinded to the time of the interview (baseline or follow-up interview) and to the intervention group. A team of medical students trained at CTP administered the Hamilton scales. Inter-rater reliability was maximised by group ratings every six-eight weeks.

**Outcome measures**

The outcome measures in the trial were a combination of self-report ratings and observer ratings.

*Primary outcome measure*

- The primary outcome measure was the *first 16 questions in the Harvard Trauma Questionnaire, (HTQ) part IV*, which covers all PTSD symptoms in both DSM-IV and ICD-10. HTQ is a self-report rating scale designed to monitor the severity of PTSD in different patient groups, among these trauma-affected refugees (52). It is internationally recognised and validated in several different languages. Each individual item is rated on a 1-4 Likert scale with 4 corresponding to the highest severity level of symptoms. The total score constitutes the mean of the scores of the individual items. The cut-off value traditionally used for PTSD is 2.5, although the cross-cultural validity of the cut-off has been questioned (53).
Secondary outcome measures

- **Hopkins Symptom Check List-25 (HSCL-25)** is a self-report rating scale used to monitor the severity of anxiety and depression symptoms, which has been used in several studies with trauma-affected refugees and similar populations (53,54). It consists of 25 items; 10 anxiety symptoms and 15 depression symptoms, each symptom rated on a 1-4 Likert scale with 4 corresponding to the highest severity level of symptoms.

- **Social Adjustment Scale Self Report (SAS-SR) short version** is a self-report rating scale used to monitor changes in social functioning (55). It is a shorter version of a 54-item rating scale. The short form used in this study consists of 24 items rated 1-5, with 5 being the highest level of functional impairment.

- **WHO-5** is a five-item self-report rating scale used to monitor life quality in different groups of psychiatric patients (56). Each item is scored between 0-5, with 5 corresponding to the highest quality of life. The total score is calculated by adding all the scores of the items and multiplying this score by 4, so that the total score of the rating scale ranges between 0 and 100, with 100 indicating the highest life quality.

- **The somatisation items of SCL-90**, a self-report rating scale widely used within psychiatry in general, where the section of the scale used in this study being the one that monitors somatic complaints (57). Symptoms are rated on a 1-5 Likert scale, with 5 being the highest level of symptoms.

- **Visual Analogue Scale (VAS)** used to monitor pain in four different body areas: the head, upper extremities, lower extremities and the neck/back. It is self-report rating scale where the patient marks the symptom intensity on a 10 cm. long line with 10 corresponding to the worst possible pain. VAS scales have previously been used to assess pain severity in trauma-affected refugees (58)

- **Sheehan Disability Scale (SDS)** is a self-report rating, consisting of three different VAS scales used to measure different areas of functioning: family life, work and social networks (59). The VAS scales range from 1-10, with 10 representing the largest
functional impairments. The total score is the accumulated score from the three subscales, accordingly ranging from 0-30.

- **Crisis Support Scale (CSS)** is a seven-item self-rating scale used to monitor the social support experienced after a traumatic event among different groups of PTSD patients (60,61). Scores range from 1-7, with 7 indicating the highest level of social support.

- **Global Assessment of Functioning (GAF)** consists of two numerical observer rating scales used to evaluate overall severity of symptoms and level of functioning in adults. In clinical settings it has been used to monitor treatment effect in many different groups of psychiatric patients including, among others, trauma-affected refugees (62). On each of the two scales scores range between 0-100, with 100 being the optimal score of both scales.

- **Hamilton Depression and Anxiety Ratings Scales (HAM D+A)** are observer rating scales based on a semi-structured interview (63). They have been used in different areas of psychiatry for many years to monitor progression in depression and anxiety symptoms. HAM D consists of 17 items, while HAM A consists of 14 items. Each item is scored either from 0-2 or 0-4, with 2/4 being the highest level of symptoms.

We had originally included the Goal Attainment Scale (GAS), a method of scoring the extent to which patient’s individual goals are achieved in the course of an intervention (64), in the study design. However, during the study the psychologist reported severe problems with the use of this scale, with a very low percentage of patients being able to complete it. Consequently, we decided to discontinue the use of the scale.

Patients completed most self-report ratings three times during the study: At the initial psychiatric assessment (baseline rating), immediately before starting psychotherapy, and at the end of the treatment programme (follow-up rating). If the initial psychiatric assessment was conducted more than two months before the patient’s first consultation with a doctor, a new rating was conducted at the first treatment session with the doctor. This new rating was then
used as the baseline rating. SAS-SR and CSS were completed twice during the study: at the first and final consultations with the social counsellor.

In regard to the observer ratings, GAF was completed on the same occasions as the self-report ratings by the medical doctor in charge of the patient’s treatment. The blinded Hamilton interviews were conducted twice: at the beginning and the end of the treatment programme.

Additionally, patients were encouraged to complete a patient satisfaction questionnaire at the end of the treatment programme. The questionnaire was anonymised so that only the research personnel had access to the code linking the patient to the questionnaire.

*Translations of self-report ratings*

Self-report ratings and the satisfaction questionnaire were available in 5-6 languages at CTP: Danish, English, Arabic, Bosnian, and Farsi and, for some of the ratings, also in Russian. If the ratings were not available in the patient’s preferred language, an interpreter would assist the patient.

As mentioned in the preface, most of the ratings used in PTF3 had been used in several previous studies at the clinic (10,24,41). Therefore, most of the work of identifying validated translations of self-rating scales had already been conducted before the current trial took place. The self-report ratings added for PTF3 was the SAS-SR and the CSS, which were included in order to obtain some measures for social functions and social support in the study population. The SAS-SR was available in several validated translations, while the CSS were available in only a few of the languages used in the clinic. Where no translation was available, the English version of the questionnaire was translated using standard translation and back translation procedures: Two bilingual interpreters translated the English version to the new language and produced a new version by comparing their translations. The new version was back translated into English by a third interpreter and compared to the original English version. Wherever mismatches occurred, the third interpreter would discuss these with one of the interpreters producing the original version until agreeing on final version of the translation.
The CTP Predictor index

An index of potential psychosocial predictors (hereafter the CTP Predictor Index) was specifically developed for the current study in order to systematically investigate the relationship between potential psychosocial predictors and treatment outcome. Since there is a dearth of evidence when it comes to psychosocial predictors of the treatment outcomes of PTSD patients, the selection of items for the CTP predictor Index was principally based on clinical experience from previous studies at CTP. All groups of practitioners (psychiatrists, medical doctors, psychologists and social counsellors) working at CTP contributed to the development of the index, assisted by external researchers from relevant fields.

The CTP index consists of 15 potential predictors: 5 rated by the medical doctor/psychiatrist, 5 rated by the psychologist, and 5 rated by the social counsellor. The items rated by the medical doctor concerned the patient’s upbringing, mental health and previous treatment attempts, as well as chronic pain. The items rated by the psychologist related to the patient’s prerequisites for engaging in psychotherapy, and the items rated by the social counsellor related to the patient’s social situation, such as employment status and dwelling.

Each item in the index is rated on a 0-4 Likert scale (4 being the best score) in accordance with an instruction sheet. The total score of the rating scale ranges from 0-60. The index, as well as the instructions for scoring, are displayed in appendix C.

The index was completed at the practitioner’s first session with the patient, either before the treatment programme commenced or during one of the initial treatment sessions.

Other possible predictors of treatment outcome

Finally, we wanted to analyse the possible predictive values of some baseline variables which, in other studies, have been found to be predictors of treatment outcome. Accordingly, we analysed the predictive values of age, gender, refugee status (refugee versus being family reunified), torture exposure, previous stays in refugee camps (outside Denmark) or asylum centres (in Denmark), the duration of their stay in Denmark, and the depression and anxiety symptom level at baseline (measured by the Hamilton rating scales).
Data analyses

All statistical analyses were conducted in STATA 14. The scores of the rating scales as well as the CTP Predictor Index were recorded as missing if more than half of the single scale items were uncompleted.

Baseline data were analysed for group differences using chi-square and t-tests. The differences between follow-up and baseline were analysed using paired t-tests for these patients who had completed a follow-up rating. The primary analyses of post-treatment differences between the sertraline and venlafaxine groups were regression models that included baseline scores on each rating scale and an indicator variable for treatment group as predictors and the score on the rating scale as outcome. The regression analyses were conducted using Full Information Maximum Likelihood (FIML), which incorporates all available information including pre-treatment scores for patients without post-treatment scores. The structural equation modelling procedure “sem” of Stata 14 was used to conduct these analyses with robust standard errors.

Although we conducted both intention-to-treat analyses and analyses of pharmacological completers only, we chose to weight the intention-to-treat analyses in the reporting of the results. As PTF3 was a pragmatic trial, our main interest was to report results for the entire patient group, not only for those that complied with the clinicians’ instructions.

Pearson correlations were calculated between the overall score on the CTP Predictor Index and the baseline to follow-up score difference for those of the outcome scales that are used as standard ratings in PTF studies at CTP (all rating scales used in PTF3 except the SAS-SR and the CSS). Correlations between the individual items in the CTP Predictor Index and the symptom score changes from baseline to follow-up were analysed for the rating scales measuring PTSD, depression and anxiety symptoms: The HTQ, HSCL-25, HAM D and HAM A, with the HSCL-25 divided into subscales for depression and anxiety symptoms. In addition, we calculated the correlations between three subscale scores: Items scored by medical doctor, items scored by psychologist and items scored by social counsellor.
Associations between baseline variables and changes in PTSD symptoms measured on HTQ were analysed using unpaired t-tests (dichotomous variables) or Pearson correlations (continuous measures). Furthermore, we performed multiple regression analyses to evaluate effects of individual predictors in models incorporating all variables with significant associations to HTQ changes in the bivariate analyses.

4. Results

The literature review

Altogether, fifteen studies were found eligible for inclusion. Eleven studies primarily focused on antidepressants: two randomised controlled trials (one on pharmacotherapy alone and one comparing antidepressants alone with antidepressants in combination with psychotherapy), six observational studies and three case studies. The last four studies were on other pharmacological agents: two were on the use of the alpha-1-adrenergic receptor antagonist prazosin and two were on the alpha-2-agonist clonidine. No studies that primarily focused on anxiolytics or antipsychotics were identified.

Studies on antidepressants

The only RCT comparing several types of antidepressants was a study on a total number of 32 Bosnian refugees comparing sertraline, paroxetine and venlafaxine in a randomised open-label design (17). Outcome measures were PTSD symptoms measured by the PTSD Symptom Scale (PSS), depression symptoms assessed by the Beck Depression Inventory (BDI) and symptoms’ severity and level of functioning on GAF. All three groups showed a statistically significant improvement in PTSD symptoms after six weeks. Despite this, all patients still met diagnostic criteria for PTSD. Mean BDI scores decreased significantly in the sertraline and paroxetine group, but not in the venlafaxine group. GAF scores increased significantly in all three groups.

The RCT comparing antidepressants alone with antidepressants in combination with psychotherapy was performed on ten female refugees from Cambodia (19). Outcome measures were the Clinician-Administered PTSD Scale (CAPS) and the HSCL-25. Patients receiving
combined treatment showed an improvement on all scales. The sertraline only group did not improve on the CAPS re-experiencing and hyperarousal items, but on all other measures.

Another study compared antidepressants or psychotherapy alone with antidepressants in combination with psychotherapy but not in a randomised design (65). The participants were 50 male Bosnian refugees and the primary outcome measure was PTSD symptoms measured on the Watson Questionnaire. No significant association was found between treatment type and changes in PTSD-symptoms.

The remaining five observational studies included 12-56 patients and were all on a mixture of at least two groups of antidepressant, often in combination with either other classes of psychotropic (anxiolytics or antipsychotics) or other treatment modalities such as psychotherapy (66–70). All except one study (69) included at least one validated PTSD questionnaire (observer or self-report) among the outcome measures; however, in one of the papers no baseline scores were reported, making it impossible to calculate baseline to follow-up changes (67). All of the remaining studies reported an improvement in the majority of the patients, although p-values and effect sizes were only reported for one of the studies (70).

The three antidepressant case studies described cases treated with TCAs or MAOIs (71–73). None of the studies reported treatment effect using quantitative measures, solely qualitative descriptions of improvement.

Studies of prazosin

Two studies were conducted on prazosin – one retrospective study including 23 refugees (74) and one case study (75). The rating instruments used in the retrospective study were the Clinician Global Impression-Change (CGI-C) and CAPS scores for nightmares (a combination of the scores for nightmare frequency and intensity). These observer ratings were, however, not completed during the treatment course, but retrospectively based on patient files. On this basis the authors found some improvement in the majority of patients. The case study only included qualitative descriptions of improvement (75).
**Studies on clonidine**

The two studies on clonidine were both observational studies by the same first author, including 4-12 patients (76,77). In the study with 12 participants, clonidine was assessed as augmentation to TCAs. A checklist adapted from DSM-III-R served as outcome measure for PTSD symptoms, for which half of the patients had some improvement (76). In the other study, the effect of clonidine alone on sleep disturbances in PTSD patients was assessed using polysomnography data as an outcome measure in combination with qualitative descriptions of symptoms from patients (77). Interestingly, all patients reported increased sleep duration and fewer nightmares two weeks after the start of treatment, in contrast to the polysomnography data which showed a slight decrease in total sleep time after initiation of clonidine.

**PTF3**

A total of 207 patients were included in the study. Of these, data on 195 patients (94.2%) were available for intention-to-treat analyses. A total group of 156 patients (75.4%) completed a minimum of eight consecutive weeks of pharmacological treatment in accordance with the group to which they were randomised (n = 68 in the venlafaxine group and n = 88 in the sertraline group). Although the distribution of completers between the two groups was skewed, the difference was not significant (p=0.08). Patient inclusion and exclusion is displayed in figure 2.

**Characteristics of the study population**

The population in this study consisted of trauma-affected refugees (75%) and family members reunited with a refugee (25%) seeking psychiatric treatment. Participants originated from a range of countries, the vast majority (77 %) being the Middle East, with Iraq as the biggest contributor (34% of the total sample). The gender distribution was 60% men and 40% women. The age of the participants ranged from 18 to 63 years, with the mean being 44. The time from arrival to Denmark ranged from less than one up to 29 years, the mean time in Denmark being almost 15 years.
Psychiatric comorbidity

Although the psychopathology inclusion criterion was PTSD and/or depression in accordance with ICD-10 research criteria, all but one patient fulfilled the diagnosis of PTSD and almost 99% of patients qualified for a depression diagnosis. Additionally, 41% fulfilled the ICD-10 diagnosis of enduring personality change after catastrophic experience (F.62.0). Almost 12% were registered as having another comorbid psychiatric disorder of which not all were however specified in accordance with ICD-10 in the patient files. The vast majority of the diagnoses were anxiety disorders, with generalised anxiety (F.41.1) being the most frequent.

Trauma history and flight

To be included in the study patients had to have a history of at least one severe trauma. Almost half of the population (48%) had been exposed to torture at some point, with men constituting a significantly larger part (82%) of the tortured group. A little more than half (53%) of the total population had been imprisoned and 25% had lived in a refugee camp before arrival in Denmark. Other frequent trauma types included serving as a soldier (26%) or experiences of war as a civilian (94%).

Social status

Trauma does not only impact upon the patients’ mental health but can also alter social functioning, networking and caregiving abilities. Around 25% of the patients were living alone at the time they entered the study and 69% of the patients had children under the age of 18. The patients in the study had a range of social problems, most noticeably, only 7% were working or studying although roughly half of the patients had more than 10 years of education from their home country. A little over 16% either had no permanent dwelling or were living in a property that the social counselor found inadequate to meet the family’s needs. Almost one in five patients (19%) had no contact with people outside their own ethnic group, indicating very poor integration with the surrounding society.

Most of the baseline characteristics of the study population including the distribution between the two treatment groups are displayed in table 1. The only variable with a borderline
significant difference in distribution between groups was torture (p=0.054), as 55% in the venlafaxine group and 42% in the sertraline group had been exposed to torture. However, we did not find any significant correlation between exposure to torture and changes on HTQ (please see below), or any of the remaining rating scales except the somatisation items of SCL-90, so this skewedness is unlikely to bias results.

**The treatment programme**

Patients received a mean number of eight medical doctor sessions, ten psychologist sessions and two social counsellor sessions with no significant differences between the two groups. Mean treatment length was 6.3 months. The mean dose of sertraline was 96.21 mg and the mean dose of venlafaxine was 125.41 mg. A total number of 63 patients (69.23%) in the venlafaxine group and 80 patients (76.92%) received add-on mianserin at some point during the study with a mean dose of 13.57 mg (no significant group difference). A total of 19 patients in the venlafaxine group (20.88 %) and 23 patients in the sertraline group (22.12%) received treatment with antipsychotics at some point, although many of these were phased out during the study.

**Attrition and pharmacological side-effects**

Twelve patients (seven patients in the venlafaxine group and five in the sertraline group) were excluded from the study: four due to pregnancy, two due to hospital admissions (one to psychiatric and one to somatic ward), one was wrongly included in the study (was not a refugee/family reunited to refugee), one moved to another part of Denmark, two changed their minds about initiating treatment at CTP and two withdrew informed consent.

As side effects are common for both venlafaxine and sertraline, it was expected that many patients would have mild side effects during parts of the study, which from clinicians’ reports also seemed to be the case. However, only ten of the 39 non-completers were reported to have discontinued their medication due to side-effects, while three patients had to switch drugs during the trial: two could not tolerate venlafaxine but could tolerate sertraline and one only tolerated venlafaxine. These three patients were kept in the group to which they were
randomised during the intention-to-treat analyses but were registered as non-completer for the completer analyses.

**Changes from baseline to follow-up**

We analysed differences between baseline and follow-up for those patients in the intention-to-treat sample that had completed ratings, both at baseline and at follow-up, using paired t-tests. The primary outcome measure HTQ was completed both at baseline and follow-up by 154 patients. For the other ratings, the number of patients who had completed the rating at both baseline and follow-up ranged between 123 (GAF-F) and 158 (HAM-D). Overall, we found small but significant improvements in both the sertraline and the venlafaxine group on a number of the rating scales used. Changes from baseline to follow-up are displayed in table2.

*PTSD, depression and anxiety*

On both the HTQ and HSCL-25 we found a significant improvement from baseline to follow-up for both groups, although slightly larger for the sertraline group on both ratings.

On the blinded Hamilton ratings, we found a borderline significant improvement on the HAM-D for the sertraline group only (p=0.054), although no significant changes were found on the HAM-D for the venlafaxine group. On the HAM-A, we found no significant change for either of the groups.

A total of 21 patients moved from above to below 2.5 cut-off score on the HTQ, while two patients moved from below to above cut-off.

*Somatic symptoms*

On the SCL-90 somatisation scale and the VAS-scales for pain, no significant improvements were found for any of the groups. An extremely small, but significant deterioration was found for the VAS-arm in the venlafaxine group.
Quality of life, social functioning, functional impairments and overall symptoms

For the WHO-5 we found a significant improvement for the sertraline group only. On the SDS, we found a significant improvement for the sertraline group, but a non-significant deterioration for the venlafaxine group. The score of SAS-SR improved for both groups, although again slightly larger improvements were found for the sertraline group. No significant changes were found for the CSS. For the GAF, significant improvements were found for both groups on both GAF-S (largest for the sertraline group) and GAF-F (largest for venlafaxine group).

Differences in effect between the venlafaxine and the sertraline group

The group differences between the sertraline and venlafaxine group were analysed with Full Information Maximum Likelihood, which means that we were able to use data from all 195 patients included in the intention-to-treat sample.

No significant treatment difference was found on the primary outcome measure HTQ. On the other outcome measures, we found a significant difference between the treatment groups on SDS only and borderline significant differences on VAS-leg (p=0.053) and WHO-5 (p=0.07). These group differences were all in favour of sertraline. Group differences are displayed in table 3.

Differences between the intention-to-treat sample and the pharmacological completers

The sample of patients who completed a minimum of eight consecutive weeks of the pharmacological treatment to which they were randomised (n=156), was analysed using the same methods as for the intention-to-treat sample. The completer analyses are presented in appendix D. To rule out the possibility that those completing the pharmacological treatment programme were the patients with less severe PTSD symptoms we checked for baseline differences in HTQ-scores between completers and non-completers, but found no significant difference.

Changes from baseline to follow-up

The results were generally in accordance with those of the intention-to-treat analyses. Improvement on the HTQ and HSCL-25 was slightly larger in completer analyses as were the
majority of the GAF-scores. A significant improvement was found on VAS-headache for the venlafaxine group. The improvement for venlafaxine became borderline significant on the WHO-5, while the improvement on SAS-SR for the venlafaxine group became non-significant.

Group differences

Almost all significant or borderline significant group differences identified in the intention-to-treat analyses disappeared in the completer analyses, possibly due to the lack of statistical power with a smaller number of patients. The only significant group difference was on the VAS-leg, again in favour of sertraline.

The CTP predictor index

The correlations between the total score on the CTP-predictor index and the rating scale score changes from baseline to follow-up were analysed using Pearson correlation (r), and the results are displayed in table 4. Statistically significant correlations were found for most of the ratings. For the HTQ, the correlation was borderline significant (r = 0.15, p=0.06). Pearson’s r ranged between from 0.18 to 0.29 for the ratings on which changes from baseline to follow up was significantly correlated to the CTP predictor index score. The only ratings where score changes were not significantly correlated to the score of the CTP predictor index were two of the VAS scales for pain and the GAF-functioning scale.

The correlation between the single items of the CTP Predictor and changes in PTSD, depression and anxiety symptoms are displayed in table 5. Employment status was the only item from the index found to have a significant positive correlation with an improvement in PTSD symptoms measured on the primary outcome measure, the HTQ. Improvements in self-reported depression symptoms measured by HSCL-25 were negatively correlated to previously receiving psychiatric treatment without effect, being in chronic pain, a long duration of mental health problems, limited social relationships and poor integration. In regard to self-reported anxiety symptoms on the HSCL-25, improvement correlated negatively with poor acceptability of psychotherapy, few cognitive resources, few social relationships and poor integration. Observer-rated depression symptoms on HAM-D were negatively correlated to previous
unsuccessful treatment attempts, chronic pain, as well as low scores on the upbringing and all psychotherapy-related items. Observer-rated anxiety symptoms on HAM-A were also significantly correlated to all psychotherapy-related items as well as social relationships.

**Other predictors of treatment outcome**

Associations between baseline variables and baseline to follow-up changes measured on the HTQ are displayed in appendix E. Improvements in HTQ score were positively associated with female gender, younger age, being family reunited with a refugee (vs. being a refugee), shorter duration of stay in Denmark, and lower levels of depression and anxiety at baseline. The remaining variables analysed (a history of exposure to torture, stay in refugee camp, and stay in asylum centre) showed no significant association to HTQ changes.

In multiple regression analyses (including all baseline variables significantly associated to HTQ changes), gender was the only variable with a significant association to changes in HTQ score ($\beta = 0.19$, $p=0.04$), although the association between duration of stay in Denmark and HTQ changes was borderline significant ($\beta = 0.07$, $p=0.051$). The remaining variables were no longer significantly associated with HTQ score changes.

**Patient satisfaction**

Patient satisfaction was generally high. Of the 158-160 patients completing the items of overall satisfaction with their treatment at CTP, 78% indicated that they were generally satisfied and only 3% indicated that treatment had not been worth the time spent at all. Satisfaction and acceptability was larger for psychotherapy than for pharmacological treatment (87% satisfactory rate for psychotherapy vs. 66% for pharmacological treatment), possibly due to the side effects of pharmacological treatment, experienced by some patients.

Patients were also asked to specify their answer to the question about their overall satisfaction. Many patients indicated that they had felt very welcome and were satisfied with the contact to the staff at CTP:

“This is not a clinic. This is a warm, sweet family. Here I feel welcome to share my feelings”
“In the clinic, everyone is good, right from the first to the last [person]. Everything is ok, don’t replace them”

Many also indicated that talking to someone about their problems relieved their symptoms:

“I am from a country with many wars where nobody listens to my pain. Here I felt that I could speak freely with no fear.”

“When I come here things are difficult, when I’ve spoken to the psychologist I feel better”

Although not all patients experienced an effect of the treatment provided, many yet still indicated that they were glad that someone had been willing to try to help them and listen to their stories:

“I got a chance for someone to listen to me“

“They tried helping me and treated me like a normal person”

Several patients indicated that external factors had negatively impacted their treatment outcome:

“The situation was a little special because a lot of things happened right when I started treatment at the clinic. If not all these things had happened, then I could have recovered totally”

“It was good, but after they [the authorities?] have moved me, it is difficult for me to return [to the clinic] due to the long travel distance”

5. Discussion

The effect and tolerability of sertraline and venlafaxine

In the present study sertraline had a slightly better outcome than venlafaxine on several secondary outcome measures, although no difference was found on the primary outcome measure, the HTQ. The relatively large number of outcome measures in this study implies a risk of random findings of significant group differences which will statically be the case with 5% of the findings when a significance level of p = 0.05 is applied. Thus, one may speculate if the small,
but borderline significant difference observed on for example the VAS scale for leg pain reflects a true group difference. However we found a fairly consistent tendency throughout ratings for the sertraline group having a slightly better outcome, even where no statistically significant difference was identified. This is in line with the findings of the one previously conducted study by Smajkic et al., comparing sertraline and venlafaxine (and paroxetine) in trauma-affected refugees (17). Smajkic et al. found that all three antidepressants produced a statistically significant improvement by week six in PTSD symptom severity (PTSD Symptoms Scale) while venlafaxine seemed to be less effective than the two SSRIs in reducing symptoms of depression. Although we did not find significant group differences on the HSCL-25 and Hamilton depression scales in our study, we did find a borderline significant group difference on the WHO-5 life quality questionnaire, which has previously been used as a screening tool for depression (56).

There are several possible explanations for the differences in effect found in our study. As with Smajkic et al. (17) we had a higher dropout from the venlafaxine than from the sertraline group. Moreover, in our study we found the mean dose of venlafaxine to be relatively low (125 mg daily) although clinicians were instructed to aim for a daily dose of 375 mg unless intolerable pharmacological side-effects occurred. Smajkic et al. did not report actual mean doses, but aimed for a daily venlafaxine dose of 150 mg (17). Venlafaxine’s effect on noradrenaline reuptake is dose-dependent, starting on doses of around 225mg daily. When the daily dose is lower, it acts on serotonin reuptake only, like a common SSRI (12,78). In addition, we found that several of the differences in effect identified between the sertraline and venlafaxine group disappeared in completer analyses. Although our study was not specifically designed to provide an explanation of the group differences identified, these findings suggest the tolerability rather than the effect to be the problem when treating trauma-affected refugees with venlafaxine.

It is, however, also a possibility that the differences in effect on PTSD symptoms of sertraline and venlafaxine are relatively small, even when treating non-refugee PTDS patients with sufficient doses of venlafaxine. A study with head-to-head comparisons of sertraline and venlafaxine treatment efficacy (mean dose of venlafaxine = 225 mg,) in a general PTSD population found only small differences in effect (79) which has also been the conclusion of some of the existent meta-analyses (13), although others find venlafaxine to be superior (11).
The overall effect of the treatment programme

In general, we found some small but significant differences between baseline and follow-up for both groups on the primary and a number of the secondary outcome measures in the study. The study design, with no placebo or control group, does not, however, allow us to conclude whether the improvements detected were due to an effect of the treatment programme provided or due to symptom fluctuation over time. Nonetheless, there are a number of factors indicating that the improvements detected might be at least partly due to treatment.

Some studies have found that PTSD symptoms among refugees appear to diminish over time (80). However, the patients in PTF3 had been in Denmark for a very long time (close to 15 years as a mean) when referred to CTP, and yet demonstrated a very high level of both mental health symptoms and somatic complaints. This probably has to do with the selection of the patients, as CTP is a highly-specialised unit within the Danish public healthcare system, to which the most chronic and complicated cases are referred. In addition, a long duration of stay in Denmark was found to be a negative predictor of treatment outcome in PTF3, both in univariate and multivariate analyses. Therefore, we find it unlikely that the overall burden of symptoms in this group of patients would diminish if they were left untreated, especially over a shorter period of time.

Improvements on the HTQ and HSCL-25 were enlarged in completer analyses as were improvements on a number of the other ratings. Since there were no differences in HTQ-scores between completers and non-completers at baseline, the enhanced improvements are probably due to better effects for pharmacological treatment completers, which again suggest a certain impact of treatment.

Finally, a previous randomised study conducted at CTP found a small but significant effect of sertraline on some secondary outcome measures when compared to waiting list controls (10). It therefore seems likely that at least part of the change found in PTF3 is due to the pharmacological treatment too.
Predictors of treatment outcome

With the CTP Predictor Index we attempted to first operationalise the assessment of different variables concerning psychosocial resources, and then test them as predictors in a large treatment outcome study. Overall, we found that the CTP Predictor Index total score was significantly correlated with changes on most rating scales, although only borderline significant for the primary outcome measure, the HTQ. For the single items of the CTP predictor index, we found employment status to be the only single item significantly correlated to HTQ changes, while a number of items significantly correlated with changes in depression and anxiety symptoms. The size of the correlation coefficients were small to moderate for both the total score and single items’ correlations to outcome measures.

While the modest correlations for the individual items may not, given the large number of factors that can possibly influence treatment outcome, be that surprising, we did expect the total score of the index to have a stronger correlation to outcome than the individual item scores. A possible explanation for the modest size of the correlations between the total score of the index and treatment outcome could be that baseline to follow-up changes on the outcome measures in this study were not generally large, which makes it more difficult to identify strong outcome predictors than if treatment effects had been larger. Some may then argue that there is then no point in searching for treatment outcome predictors in a patient population with such limited improvements. On the other hand, if we do not attempt to identify the predictors of treatment outcome, we cannot develop better treatment matching strategies, and therefore we will miss the opportunity to actually improve the results of treatment for a complex and chronic patient group with a high burden of disease.

Challenges in performing randomised trials with trauma-affected refugees

Methodological challenges are prevalent in conducting research with trauma-affected refugees. Given the heterogeneity of refugee groups in relation to culture, language and psycho-social resources, performing randomised trials is not an easy task, yet necessary if we want to gather some evidence for treatment efficiency in pragmatic “real-life” settings.
Randomisation and control groups

Randomisation is one of the key issues discussed in connection to research in the field, as the process somewhat denies the clinician the opportunity to use his/her experience and clinical skills to judge how to tailor treatments to individual needs (5). However, clinical decisions are influenced by a range of factors, preferences and proclivities of the individual treatment provider, which tend not to be based on evidence. As a consequence, there is insufficient knowledge about the actual effects of the different treatment modalities applied according to individual clinical judgements.

Concerns have also been raised regarding the ethical implications of allocating refugees to control conditions such as waitlists. Even when comparing two active treatments, people may argue that one of the active treatments is usually anticipated to be more effective than the other. PTF3 is a very good example that such anticipations do not always hold true. Although we, based on experience and research from other fields, hypothesised that venlafaxine would be as effective and possibly better than sertraline, our findings demonstrated the opposite. This is one reason why we, despite the obvious value of clinical experience, need the evidence from treatment effect studies when choosing treatment modalities for trauma-affected refugees, as in every other medical field.

The design of our study did not allow us to draw final conclusions as to overall effects of the treatment programme, since no placebo or waitlist control group was included. When the present study was designed, the first RCT at CTP (PTF1), which included a waitlist control group, had just been completed in our clinic (10). Preliminary findings suggested that there was some effect of the treatment provided and because this first trial suggested an effect of sertraline compared to the waitlist control group, we found it less important to include a waitlist control group in the present study and found it more important to achieve larger samples in the pharmacological treatment groups. However, the analyses of PTF1 are now completed and in the light of the relatively small effect sizes found in PTF1 (10) it would have been an advantage to be able to compare the effects of the two pharmacological treatments with a waitlist control group. Including a waitlist control group might on the other hand have been ethically
questionable due to changes in access to treatment for trauma-affected refugees in Denmark that happened in the time period between the two studies. During the time when PTF1 was conducted there was a considerable waiting time for specialised treatment for refugees in most of Denmark, which was the main reason that a waitlist control group was deemed ethical. However, at the time of the present study this waitlists had been markedly reduced. Consequently, we did not find it ethically acceptable to withhold participants in PTF3 from immediate treatment, when potentially beneficial treatments were readily available.

However, in settings where there already is a waiting list due to lack of resources, it might be both pragmatic and ethical to use the waiting list period as a control condition. This could either be as controls for similar patients in active treatment or the waiting list acting as their own controls in a cross-over design. In the longer term this might actually help shorten waiting lists, since more effective treatment and individualisation of treatment based on sound evidence might diminish treatment length as well as costs.

**Outcome measures**

Validity as well as appropriateness of ratings are important questions when it comes to measuring treatment outcomes in refugee populations with diverse cultural and linguistic backgrounds. As previously mentioned, most ratings and translations were already in use before PTF3 was commenced. Although used in previous studies, ratings had not been validated specifically for our population. Hollifield et al. reviewed a range of rating scales used in refugee health studies, some of which were also used in the present study. The found the HTQ and HSCL-25 to be fairly well-validated, but found the majority of the remaining ratings scales reviewed to be poorly validated for refugee groups (25).

Using the same standardised measures across cultures makes it possible to measure treatment effects in a mixed group of trauma-affected refugees and to compare symptoms between ethnic subgroups. On the other hand, symptoms might not be expressed in the same way in different ethnic and cultural groups, and using standardised measures inhibits us from measuring culturally specific syndromes (81). However, it is hard to know to what extent cultural idioms of
distress apply to a population where many have been living in Denmark for a very long time and therefore constitute a cultural mixture of original and adapted cultures.

The majority of outcome measures utilised in our study were self-reported ratings and no observer ratings of PTSD symptoms were included. Before the study commenced we considered the inclusion of clinician-administered CAPS ratings, a commonly used outcome measure in PTSD studies. However, CAPS is a very comprehensive and time-consuming measure, particularly for patients who need assistance from an interpreter, and preliminary experiences from a pilot project at CTP using SCAN interviews (data yet unpublished) raised concerns about the patients’ ability to participate in lengthy rating sessions. On this basis we decided not to include CAPS as an outcome measures in PTF3. There appears to be a need for shorter observer ratings of PTSD, preferably developed expressly for trauma-affected refugees.

In addition to this, concerns have been raised about solely relying on symptom measures (PTSD, depression, anxiety etc.) of treatment outcomes, as these do not take into account the broader issues of cultural and social adaptation experienced by refugees (25). Accordingly, in PTF3 we added measures of social functioning and level of social support to the measures of symptoms and life quality already used. The SAS-SR, a measure of self-reported social functioning, is developed to monitor changes over a treatment course, but, to my best knowledge, has not been used in refugee populations previously (55). The CSS, a measure for social support after trauma, is not originally developed as a treatment effect monitoring tool, but has been used as such in one previous study with refugees, where significant baseline to follow-up changes were detected (61). Similar to the other ratings used in PTF3, neither the SAS-SR nor the CSS have been validated in our specific population, although the study population in which the CSS was previously used was quite similar to ours (61). Although both have been used in other psychiatric populations and have certain face validity towards the social problems of our patient group, the lack of validation of the instruments in refugee settings may, as previously mentioned, pose a potential problem.

While acknowledging the problems with the ratings used in this study and similar studies in the field, standard measures provide a core set for continuity and comparability of findings. Ideally
however, additional or alternative psychometric tools will, over time, be developed in order to measure treatment outcomes for trauma-affected refugees more specifically.

Blinding towards treatment allocation

The blinding of patients and clinicians presents a difficult challenge given that issues of mistrust and even paranoia are not uncommon features of trauma-affected refugees. Insisting on blinding would therefore most probably lead to a very low participation, causing a substantial selection bias that might compromise the validity of the conclusions made. The benefits of more excessive blinding in the present study design would therefore have been limited. Most outcome measures were self-ratings and the clinical impression was that patients did not generally have any pre-assumptions that one of the drugs would be more efficient than the other. The only measure completed by the medical doctors in charge of treatment was GAF. The results of the PTF3 with no difference in effect between groups at GAF speak against systematic bias in the doctors’ completion of the GAF ratings. Blinded Hamilton observer ratings were carried out in PTF3, as in previous randomised studies at CTP.

Measures of compliance

Non-compliance has been found to be a substantial problem in studies with refugees or other migrant populations (73,74,75). This might be due to a range of factors, such as cultural beliefs, linguistic problems, misunderstandings between patient and doctors and social factors such as stigma surrounding mental health disorders (85,86).

Around 75% of the patients in PTF3 completed at least eight weeks of treatment in accordance to the pill count. However, we had some problems with the validity of pill count method, which might have influenced study results. As the study population comprised cognitively impaired patients, problems of remembering the medication at each consultation loomed large. Consequently, when determining compliance levels, we would often have to rely on the medical possession rate, rather than the actual number of pills left at each consultation. This made it difficult to determine to what extent patients precisely complied with given instructions for certain periods of time during the study. Even with patients who did bring their medication to
each consultation, we did not have an objective measure to prove that the patient had actually been taking his/her medication, and had to solely rely on the patient’s word.

Blood tests as compliance measures have some advantages over pill counts. They are an objective measure of whether the patients are taking the medication and also provide some indication of whether the blood level of the medication is within a therapeutic range. On the other hand, a blood test provides us with a snapshot of the given day when it has been taken and does not tell us anything about compliance during the remaining study period. Moreover, it is an invasive measure to which some patients may object. The most precise information about compliance can potentially be obtained by combining the two methods. However, this may not always be possible due to economic, practical or ethical considerations.

**Generalisability of results**

The patients included in PTF3 seem to be fairly representative of patients treated in similar facilities in Denmark. A study by Palic et al. from 2014 included patients from three different specialised refugee outpatient clinics in Denmark (87). Participants in this study were roughly similar in terms of gender distribution (45.5% female vs. 40.0% in PTF3), age (mean 40.5 years old vs. 43.7 in PTF3), region of origin (with Middle Eastern countries as the biggest contributors in both studies, although Bosnians constituted a smaller proportion of the population in PTF3) and had resided in Denmark for almost as long as the participants in PTF3 (mean 12.5 years vs. 14.6 years in PTF3). The number of survivors of torture (31 vs. 48 % in PTF3) and patients imprisoned (36 vs. 53 % in PTF3) were larger in PTF3, while the amount of patients with war-related trauma was equivalent in the two studies (93 vs. 94%).

In regard to generalisability to other health care settings, one should bear in mind that our study was conducted in specialised refugee units in the secondary health care system and patient populations therefore most probably constituting a more chronic sample than refugees seen in the primary healthcare system or in non-specialised psychiatric facilities.

Due to the structure of the Danish asylum system, it is typically only refugees who have already been granted asylum that can receive non-acute treatment in the Danish public health system
to which CTP belongs. Refugees in the asylum phase receive health services from the Danish Red Cross and therefore no asylum seekers were included in the study. This may be a potential limitation in relation to the generalisability of our results internationally, where the organisation of the health sector differs from the Danish model. Moreover, in countries with larger refugee populations, some mental health clinics have specialised in treating only specific cultural groups, to which the methodology and results from this study may not apply, or only to a certain extent.

Comparability between trauma-affected refugees and other PTSD patients

It is far from simple to transfer results from clinical trials on western non-refugee patients to patient samples from other parts of the world as genetic, cultural and trauma-related factors can influence treatment efficiency. This does not mean that results from trials on non-refugee PTSD patients are not useful when it comes to designing treatment programmes and trials for trauma-affected refugees – and vice versa. There are, however, a range of both biological and non-biological differences that should be taken into account, both when designing studies and when interpreting the results.

Biological differences

A number of studies have found differences in pharmacogenetics between ethnically different populations. The cytochrome CYP450s, among these the CYP2C9, CYP2C19 and CYP2D6 accounts for substantial part of phase I drug metabolism in the liver. CYP2D6, in particular, is involved in the metabolism of a range of psychotropics, among these venlafaxine and sertraline (88). Based on the activity levels of CYP2D6, individuals are classified as ultrarapid metabolisers, extensive metabolisers, intermediate metabolisers or poor metabolisers. In a paper by Noerregaard (89), the prevalence of the cytochrome CYP450, CYP2D6 ultrarapid metabolisers is estimated to be up to 30% in Middle Eastern populations. However, many different gene alleles interfere with the activities of CYP2D6, rendering it far from simple to draw final conclusions about the activity of the enzyme in different ethnic groups, not to mention the clinical implications (88,90). The only certain way to determine the CYP2D6 activity level in an individual or a study population will therefore be through blood tests.
Other biological factors might similarly differ among ethnic groups. Differences in the genes responsible for protein binding, such as the serotonin transporter gene, might also affect the efficiency of many antidepressants acting primarily on serotonin reuptake (89). Equally, side effects might differ and be observed on lower doses than expected.

Furthermore, dietary factors have previously shown to significantly influence drug metabolism (85). It is, however, difficult to determine to what extent this and other similar cultural features are relevant in the PTF3 population, where the majority of patients have been living in Denmark for a substantial amount of time and might at least partly have adapted to local customs.

**Differences in trauma history, culture and social context**

Numerous researchers in the field have suggested that extreme trauma, such as extended periods of imprisonment and torture, might cause a far more complex trauma reaction than the symptoms described by the current PTSD diagnosis (28). Additionally, refugees frequently live with a number of ongoing stressors during the treatment period, such as insecure residency status, struggles in building a new life in a society often fundamentally different from their country of origin and fears for family left under threat in conflict areas in their homeland (91). This also means that the effects of the treatment provided, including the effects of the pharmacological treatment, might be smaller than expected from studies on other groups of PTSD patients.

Some of these differences might not only be an issue when comparing results from non-refugee and refugee populations, but have also been found when comparing war veterans to civilian PTSD patients. Soldiers have also often been exposed to a series of traumatic events and have been living under extreme stress for a prolonged period. Similarly, newer research also suggests treatments to be less efficient in trauma-affected soldiers than in other PTSD populations (13,92). Needless to say, there are a range of evident differences between western war veterans and non-western refugees – biologically, culturally and in life circumstances after the trauma. Despite these differences, the two groups might still be more comparable in psychopathology and treatment outcome, compared to civilian survivors of single trauma.
Accordingly, when designing new treatment effect studies with trauma-affected refugees, we might rather build upon the knowledge gained from treatment effect studies on war veterans than studies of civilian trauma survivors.

**Methodological considerations**

*The literature review*

The study had certain limitations. Only well-known databases were searched and we did not actively try to identify unpublished studies or study protocols. This decision was made on the basis of the purpose of this paper, which was primarily to provide an overview for clinicians and researchers in the field. Therefore, all the included papers should be easily accessible to others interested in a more comprehensive exploration of any of the studies.

The study populations were limited to refugees with trauma-related disorders since the intention was to provide guidance for clinicians and researchers working with this patient group. Studies on similar groups such as asylum seekers and internally displaced people were not included as important differences exist between refugees and internally displaced people. Refugees rely on a health system in which they belong to a minority, whereas internally displaced people are generally cared for by a health system with which they are familiar. Nonetheless, internally displaced people might experience different problems such as limited access to treatment or a lack of minimum standards for the quality of the care provided. Therefore, treatment programmes and research projects designed for refugees in a western country might not be at all suitable for internally displaced people in a low income country and vice versa.

*PTF3*

The PTF3 trial also had some limitations, of which most have been discussed above. Blinded observer ratings were carried out, but neither patients nor treatment staff were blinded to treatment allocations. The study did not include a waiting list or placebo control group, which makes us unable to draw final conclusions of the effects of the treatment programme. Pill
counts, but without blood tests, were used to determine compliance, resulting in some uncertainty about the actual amounts of medicine taken.

The CTP Predictor Index used in PTF3 was designed for the present study and must be tested in other studies, particularly given the modest sizes of the correlations identified. Moreover, we did not test the inter-rater reliability of the CTP predictor index in the present study, which should be performed for future studies, as the items rated by the psychologist in particular included subjective components.

The employment status item of the CTP Predictor Index included information related to both employment and income, making it hard to determine which of the two has the largest impact on treatment outcome. Although it is hard to separate these two variables completely, it could be worthwhile adding a separate item for the total household income in order to analyse the independent effects of the two variables. Similarly, there might be other items which could be separated into two or specified further for future use in the index.

The study also contains important strengths. Unlike most studies in the field, participants were randomised, which reduces selection bias and improves comparability between the two intervention groups. We systematically analysed the predictive value of a number of variables collected in a structured format, in order to minimise the risk of random findings. Moreover, we aimed to avoid unnecessarily restricting inclusion in order to make the patient group similar to the population treated at other refugee healthcare facilities, both in Denmark and worldwide.

6. Lessons learned from PTF3: Clinical implications and future research

PTF3 did not only generate new knowledge on pharmacological treatment and treatment predictors for trauma-affected refugees but has also provided me with valuable experience that I would like to share with clinicians and researchers working with similar populations. The recommendations in this section are therefore based on a combination of the results of the study and lessons learned while conducting the trial.
Clinical implications

PTF3 has some clinical implications. Sertraline had a slightly better outcome than venlafaxine on several secondary outcome measures, although no differences were found on the primary outcome measures, the HTQ. As mentioned above, this is in line with the findings of the one existing similar study (17). Due to these findings suggesting a slightly better effect of sertraline as well as the advantages in tolerability discussed above, we continue to recommend SSRIs as the first line pharmacological treatment for trauma-affected refugees.

In addition to this, we found changes from baseline to follow-up which were likely to be at least partly due to the treatment the patients received. Although the changes were small, this was expected with our patient group of refugees with a history of multiple trauma and a very high rate of comorbid mental health disorder alongside PTSD, as well as a range of somatic complaints and social problems. The treatment programme provided included pharmacological treatment, psycho-education and manualised psychotherapy adapted to the patient group and social counselling. As the study was designed to measure difference in effect between two pharmacological treatments and not the effects of the other single components of the treatment programme, we cannot conclude to what extent the individual treatment modalities contributed to the overall change. Although the overall evidence of the add-on effect of psychotherapy to pharmacological treatment is scarce (18), some studies have found an add-on effect on psychotherapy to pharmacological treatment (19,93) - and vice versa (94). Moreover, most treatment effect studies of psychotherapy for trauma-affected refugees have demonstrated some effect (13). As social problems are evidently present in this patient group we recommend that treatment programmes for refugees with severe trauma-related psychopathology should include pharmacological treatment as well as psycho-education, psychotherapy and social counselling. Manuals used in this study have been continuously adapted to suit the patient group, resulting in high overall patient satisfaction as well as satisfaction with the psychotherapy provided. We therefore recommend that treatment manuals used in refugee health settings are adapted towards the prerequisites and needs of the patient group.
During PTF3 we provided voluntary group lectures by our social counsellors on topics such as residency rules and regulations, advice on financial debt and the tax system, the structure of the Danish municipal administration and social services relevant to refugees. Unfortunately, only a minority of the patients in PTF3 (29 persons, equal to 15% of the intention-to-treat sample) participated in any of these sessions, with clinicians reporting the group format to be an issue for a large proportion of the patients. Similarly, a previous pilot study on group physiotherapy at CTP had a fairly low (around 30%) acceptance rate for participation, primarily due to reluctance to participate in group sessions (45). Although not always clearly articulated, it is our impression that the reluctance to participate in groups concerned the suspicion and mistrust that is often part of the clinical presentation of our patient groups, as previously discussed in this thesis. With such low acceptability, we cannot uncritically recommend group treatment to become an integrated part of treatment for trauma-affected refugees with severe psychopathology, despite the possible benefits of groups for those choosing to participate. Despite this, it might be an acceptable format for some refugee patients, in particularly those with less PTSD symptoms and no comorbid diagnose of enduring personality change after catastrophic experience.

Recommendations for future studies

Despite the challenges discussed in this thesis and in a previously published paper (5), it is possible to perform randomised trials with trauma-affected refugees, as we have demonstrated with PTF3 and previous studies conducted at CTP.

In the PTF3 study we investigated two out of the numerous pharmacological agents which are used in refugee health settings around the world, despite the current lack of knowledge on their effects for this patient group. Our choice of pharmacological agents for the trial was based on the available evidence at the time of the study, where venlafaxine had only been investigated in one very small study on trauma-affected refugees, but had shown promising results in other groups of PTSD patients. We therefore hypothesised that venlafaxine might equally be beneficial to trauma-affected refugees, but needless to say needed to test this hypothesis in the population concerned, due to the numerous differences between refugees and non-refugee
PTSD patients discussed elsewhere in this thesis. Although our study has enhanced the knowledge on the efficacy of sertraline and venlafaxine in trauma-affected refugees, there is still an urgent need for large-scale randomised studies on both trauma-affected refugees and other PTSD-populations researching the efficacy of pharmacological agents typically used in the field such as the different classes of antidepressants, antipsychotics and psychotropics used to treat insomnia and nightmares. In addition, studies are needed in relation to the tolerability of the different pharmacological agents in non-western PTSD patients.

The CTP Predictor Index used in this study showed significant correlations with a range of ratings, many of which are used in refugee healthcare settings worldwide. However, correlation coefficients were not large, which has also similarly posed a problem in predictor studies with other groups of PTSD patients (95). As discussed, the modest size of the correlations is possibly due to a large number of variables influencing treatment outcome - each factor only accounting for a limited part of the variability in patients’ treatment outcome. Although it might therefore not be easy to identify strong treatment outcome predictors, it is yet still necessary to continue the exploration in order to potentiate treatment outcome for the individual patients by matching the treatment provided to the prerequisites of the individual patient. We therefore encourage researchers in the field to include analyses of possible treatment outcome predictors in future trials.

Potential concerns about vulnerability and the risk of retraumatisation of refugee patients by participating in research and completing self-report ratings have not been borne out by our experiences from this and previous studies at CTP. The vast majority of our patients seem to regard the completion of questionnaires as a reasonable part of the assessment process, particularly once an explanation is given that the process assists in monitoring progress of treatment (5).

As discussed, we recognise the shortcomings of the outcome measures used in this study as regards capturing the complexity of somatic, social and mental health problems presented by trauma-affected refugees. Nonetheless, using standard measures provides a core set for continuity and comparability of findings. The implementation of research into the clinical daily
routines i.e. by the TRIM method (5) might also contribute to a higher percentage of patients accepting research participation and also make research projects less costly. We therefore encourage practitioners in the field to implement standardised measures of treatment outcome as an integrated part of clinical practices. Additionally, we encourage work on the development and evaluation of more comprehensive and precise outcome measures as well as a fine-tuning of existent measures towards capturing core features presented by refugee patients.

The choice of compliance measures in pharmacological studies will inevitably have to be based on both practical and ethical considerations. As discussed above, pill count as the sole measure of compliance cannot be recommended in studies on trauma-affected refugees with some degree of memory impairment. After the termination of PTF3, blood tests for somatic disorders such as diabetes and low D-vitamin levels have become an integrated part of the initial assessment at CTP and appear to be less problematic than expected for most of our patients. At CTP we are currently exploring the possibilities of including blood tests as a supplementary measure of compliance in future pharmacological studies and encourage other researchers in the field to do the same. Routine blood tests also offer the possibility of studying other interesting phenomena with clinical implications, such as the distributions of genotypes for CYP450s influencing metabolism among our patients. As mentioned, previous studies have found the distributions of gene alleles involved in drug metabolism to differ between ethnic groups, thereby influencing both the effect and tolerability of psychotropic in groups of ethnic minority patients (88). In addition to this, recent research suggests several CYP450 enzymes to be moderators of the development of psychopathology such as depression and suicide risk (96). Although outside the scope of the present thesis, this might imply novel possibilities for future studies.

7. Conclusion

The study presented in this thesis is the largest pharmacological trial ever conducted in the field of trauma-affected refugees and has important methodological qualities such as the randomisation of participants, which most studies in the field are currently lacking. We found no difference in treatment effect between the sertraline and venlafaxine group on the primary
outcome measure, the HTQ, but found significant/borderline significant group differences on the SDS, WHO-5 and the VAS scale for leg pain, all in favour of sertraline. As sertraline additionally seems to be better tolerated by our patient group, we recommend SSRIs as first line pharmacological treatment for trauma-affected refugees.

Moreover, we presented the CTP predictor index of psychosocial resources and evaluated its correlation with treatment outcome of a number of rating scales often used in refugee mental health settings. We found that psychosocial resources were significantly correlated to treatment outcomes in most of rating scales used in the study, but that correlations coefficients were modest in size and encourage researchers in the field to study treatment outcome predictors further.

The results and lessons learned from this study are largely transferrable to similar refugee health facilities in Denmark and, with certain reservations, to refugee healthcare facilities internationally. The design is fairly simple and manuals were used for all interventions, which makes the study easy to reproduce in similar or larger settings. I therefore hope that this thesis will inspire research groups, both in Denmark and internationally, to conduct further studies of the effect of pharmacological treatment and treatment outcome predictors for trauma-affected refugees.
8. Tables and Figures

FIGURE 1
Flowchart illustrating the literature search, article in- and exclusion

<table>
<thead>
<tr>
<th>Excluded on abstract</th>
</tr>
</thead>
<tbody>
<tr>
<td>B: 65</td>
</tr>
<tr>
<td>N: 674</td>
</tr>
<tr>
<td>NMI: 84</td>
</tr>
<tr>
<td>C: 12</td>
</tr>
<tr>
<td>R: 10</td>
</tr>
<tr>
<td>R: 10</td>
</tr>
<tr>
<td>RO: 10</td>
</tr>
<tr>
<td>S: 10</td>
</tr>
<tr>
<td>SF: 10</td>
</tr>
</tbody>
</table>

| Duplicates: N=187 |

| Studies for possible inclusion N=46 |

| Articles found by reference search of reviews, reference lists N=2 |

| Studies for final inclusion N=15 |

Abbreviations used in Figure 1:
B: Book
N: Not an intervention study (as defined in method section)
NMI: Not a medical intervention study
C: Study on children/adolescents
R: Reviews on medical treatment of traumatised refugees
RO: Review, other types
S: Study of somatic intervention
SF: Study protocol
NIS: Intervention not specified
199 were not included in the study due to:
- Did not fulfill criteria for treatment at CTP (n=124)
- Did not fulfill inclusion criteria for the study (n=10)
- Were excluded due to exclusion criteria (n=10)
- Did not sign informed consent to participate (n=55)

12 were withdrawn from the study due to:
- Pregnancy (n=4)
- Admission to psychiatric hospital (n=1)
- Somatic illness (n=1)
- Moved away (n=1)
- Wrongly included (n=1)
- Did not initiate treatment program (n=2)
- Withdrew informed consent (n=2)

39 did not take prescribed medicine for eight consecutive weeks during the study due to:
- Drop out of the treatment program (n=17)
- Side effects to medication (n=10)
- Not wanting to start pharmacological treatment (n=3)
- Did not want to change present medication to allocated antidepressant (n=1)
- Reason not specified (n=8)

Figure 2: Participants flow through the PTF3 trial

406 patients were referred to CTP during the inclusion period

207 signed informed consent to participate in the study

98 was randomised to V1

109 was randomised to S2

91 eligible for intention-to-treat analyses

104 eligible for intention-to-treat analyses

68 pharmacological completers

88 pharmacological completers
### Table 1: Baseline characteristics for the PTF3 study population

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>All (n=207)*</th>
<th>Group V1 (n= 98)*</th>
<th>Group S2 (n= 109)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic information</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male gender</td>
<td>124 (60.2)</td>
<td>61 (62.2)</td>
<td>63 (58.3)</td>
</tr>
<tr>
<td>Country of origin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ex-Yugoslavia</td>
<td>20 (9.7)</td>
<td>11 (11.2)</td>
<td>9 (8.3)</td>
</tr>
<tr>
<td>Iran</td>
<td>28 (13.6)</td>
<td>13 (13.3)</td>
<td>15 (13.9)</td>
</tr>
<tr>
<td>Iraq</td>
<td>71 (34.5)</td>
<td>34 (34.7)</td>
<td>37 (34.3)</td>
</tr>
<tr>
<td>Afghanistan</td>
<td>28 (13.6)</td>
<td>10 (10.2)</td>
<td>18 (16.7)</td>
</tr>
<tr>
<td>Lebanon</td>
<td>26 (12.6)</td>
<td>12 (12.2)</td>
<td>14 (13.0)</td>
</tr>
<tr>
<td>Other</td>
<td>33 (16.2)</td>
<td>18 (18.4)</td>
<td>15 (13.9)</td>
</tr>
<tr>
<td>Diagnosis (ICD-10) in addition to PTSD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>204 (98.6)</td>
<td>96 (97.96)</td>
<td>108 (99.08)</td>
</tr>
<tr>
<td>Enduring personality change after catastrophic experience (F.62.0)</td>
<td>80 (40.8)</td>
<td>38 (41.30)</td>
<td>42 (40.38)</td>
</tr>
<tr>
<td>Other psychiatric disorder</td>
<td>24 (11.7)</td>
<td>12 (12.24)</td>
<td>12 (11.11)</td>
</tr>
<tr>
<td>Trauma history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imprisonment</td>
<td>110 (53.4)</td>
<td>57 (58.8)</td>
<td>53 (48.6)</td>
</tr>
<tr>
<td>Torture**</td>
<td>99 (48.1)</td>
<td>54 (55.1)</td>
<td>45 (41.7)</td>
</tr>
<tr>
<td>Refugee camp</td>
<td>52 (25.7)</td>
<td>22 (22.9)</td>
<td>30 (27.5)</td>
</tr>
<tr>
<td>Psychosocial status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education &gt;10 years from home country</td>
<td>98 (50.8)</td>
<td>50 (53.2)</td>
<td>48 (48.5)</td>
</tr>
<tr>
<td>Presently employed/studying</td>
<td>14 (7.0)</td>
<td>7 (7.3)</td>
<td>7 (6.8)</td>
</tr>
<tr>
<td>Living alone all the time</td>
<td>51 (25.8)</td>
<td>21 (21.9)</td>
<td>30 (29.4)</td>
</tr>
<tr>
<td>Have got children less than 18 years old</td>
<td>137 (68.8)</td>
<td>68 (70.8)</td>
<td>69 (67.0)</td>
</tr>
<tr>
<td>Mean(SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>43.7 (9.7)</td>
<td>43.2 (9.6)</td>
<td>44.0 (9.7)</td>
</tr>
<tr>
<td>Years since arrival in Denmark</td>
<td>14.6 (7.3)</td>
<td>14.1 (7.1)</td>
<td>15.1 (7.4)</td>
</tr>
</tbody>
</table>

*Not all variables available for the entire patient group  
** Group difference borderline significant, p=0.054
**Table 2: Score differences between baseline and follow up ratings, PTF3**

**Symptom self-ratings**

<table>
<thead>
<tr>
<th>Rating</th>
<th>Group (n)</th>
<th>Mean baseline score (SD)</th>
<th>Mean follow-up score (SD)</th>
<th>Difference (SD)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HTQ</td>
<td>Sertraline (85)</td>
<td>3.24 (0.37)</td>
<td>3.02 (0.56)</td>
<td>-0.22 (0.55)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HTQ</td>
<td>Venlafaxine (69)</td>
<td>3.21 (0.39)</td>
<td>3.06 (0.55)</td>
<td>-0.15 (0.46)</td>
<td>0.01</td>
</tr>
<tr>
<td>HSCL-25</td>
<td>Sertraline (84)</td>
<td>3.02 (0.43)</td>
<td>2.84 (0.64)</td>
<td>-0.18 (0.60)</td>
<td>0.01</td>
</tr>
<tr>
<td>HSCL-25</td>
<td>Venlafaxine (66)</td>
<td>3.09 (0.44)</td>
<td>2.96 (0.56)</td>
<td>-0.13 (0.44)</td>
<td>0.02</td>
</tr>
<tr>
<td>SCL-90</td>
<td>Sertraline (81)</td>
<td>2.43 (0.81)</td>
<td>2.37 (0.91)</td>
<td>-0.06 (0.93)</td>
<td>0.58</td>
</tr>
<tr>
<td>SCL-90</td>
<td>Venlafaxine (66)</td>
<td>2.60 (0.79)</td>
<td>2.58 (0.77)</td>
<td>-0.02 (0.60)</td>
<td>0.79</td>
</tr>
<tr>
<td>VAS-Back</td>
<td>Sertraline (79)</td>
<td>6.62 (2.91)</td>
<td>6.60 (2.90)</td>
<td>-0.02 (3.29)</td>
<td>0.94</td>
</tr>
<tr>
<td>VAS-Back</td>
<td>Venlafaxine (65)</td>
<td>7.48 (2.31)</td>
<td>7.27 (2.26)</td>
<td>-0.21 (2.05)</td>
<td>0.42</td>
</tr>
<tr>
<td>VAS-Arm</td>
<td>Sertraline (80)</td>
<td>5.72 (3.44)</td>
<td>5.72 (3.48)</td>
<td>0.00 (3.49)</td>
<td>1.00</td>
</tr>
<tr>
<td>VAS-Arm</td>
<td>Venlafaxine (64)</td>
<td>5.66 (3.32)</td>
<td>6.43 (2.64)</td>
<td><strong>0.77 (2.69)</strong></td>
<td>0.03</td>
</tr>
<tr>
<td>VAS-Leg</td>
<td>Sertraline (80)</td>
<td>6.56 (3.19)</td>
<td>6.07 (3.13)</td>
<td>-0.49 (2.58)</td>
<td>0.09</td>
</tr>
<tr>
<td>VAS-Leg</td>
<td>Venlafaxine (64)</td>
<td>6.89 (2.94)</td>
<td>7.01 (2.51)</td>
<td>0.12 (2.62)</td>
<td>0.71</td>
</tr>
<tr>
<td>VAS-Head</td>
<td>Sertraline (80)</td>
<td>7.07 (2.42)</td>
<td>6.45 (3.06)</td>
<td>-0.62 (3.13)</td>
<td>0.08</td>
</tr>
<tr>
<td>VAS-Head</td>
<td>Venlafaxine (64)</td>
<td>7.15 (2.71)</td>
<td>6.56 (2.63)</td>
<td>-0.59 (2.58)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

HTQ, HSCL-25, SCL = 1-4 (1 best score), VAS = 0-10 (0 best score)
### Life quality/level of functioning self-ratings

<table>
<thead>
<tr>
<th>Rating</th>
<th>Group (n)</th>
<th>Mean baseline score (SD)</th>
<th>Mean follow-up score (SD)</th>
<th>Difference (SD)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO-5</td>
<td>Sertraline (85)</td>
<td>13.04 (14.04)</td>
<td>22.33 (25.04)</td>
<td><strong>9.29 (22.4)</strong></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>WHO-5</td>
<td>Venlafaxine (67)</td>
<td>14.51 (15.46)</td>
<td>17.85 (19.26)</td>
<td>3.34 (18.11)</td>
<td>0.14</td>
</tr>
<tr>
<td>SDS</td>
<td>Sertraline (80)</td>
<td>24.54 (5.39)</td>
<td>21.71 (8.18)</td>
<td><strong>-2.84 (7.76)</strong></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>SDS</td>
<td>Venlafaxine (67)</td>
<td>22.52 (6.10)</td>
<td>23.16 (6.51)</td>
<td>0.63 (2.44)</td>
<td>0.48</td>
</tr>
<tr>
<td>SAS-SR</td>
<td>Sertraline (86)</td>
<td>3.00 (0.73)</td>
<td>2.72 (0.76)</td>
<td><strong>-0.28 (0.69)</strong></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>SAS-SR</td>
<td>Venlafaxine (71)</td>
<td>3.00 (0.68)</td>
<td>2.84 (0.67)</td>
<td><strong>-0.16 (0.66)</strong></td>
<td>0.04</td>
</tr>
<tr>
<td>CSS</td>
<td>Sertraline (86)</td>
<td>21.91 (8.63)</td>
<td>22.64 (7.52)</td>
<td>0.73 (7.44)</td>
<td>0.37</td>
</tr>
<tr>
<td>CSS</td>
<td>Venlafaxine (72)</td>
<td>22.28 (7.20)</td>
<td>22.33 (6.82)</td>
<td>0.05 (6.28)</td>
<td>0.95</td>
</tr>
</tbody>
</table>

WHO-5 = 0-100 (100 best score), SDS = 0-10 (0 best score), SAS-SR = 1-5 (1 best score), CSS = 1-7 (7 best score)
### Observer ratings

<table>
<thead>
<tr>
<th>Rating</th>
<th>Group (n)</th>
<th>Mean baseline score (SD)</th>
<th>Mean follow-up score (SD)</th>
<th>Difference (SD)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAM-D</td>
<td>Sertraline (89)</td>
<td>23.84 (5.53)</td>
<td>22.29 (8.10)</td>
<td>-1.55 (7.49)</td>
<td>0.054</td>
</tr>
<tr>
<td>HAM-D</td>
<td>Venlafaxine (69)</td>
<td>23.61 (5.44)</td>
<td>22.52 (7.71)</td>
<td>-1.09 (6.86)</td>
<td>0.19</td>
</tr>
<tr>
<td>HAM-A</td>
<td>Sertraline (88)</td>
<td>26.84 (6.75)</td>
<td>26.31 (9.80)</td>
<td>-0.53 (9.10)</td>
<td>0.58</td>
</tr>
<tr>
<td>HAM-A</td>
<td>Venlafaxine (69)</td>
<td>27.09 (6.15)</td>
<td>26.23 (8.92)</td>
<td>-0.86 (8.28)</td>
<td>0.39</td>
</tr>
<tr>
<td>GAF-S</td>
<td>Sertraline (68)</td>
<td>47.50 (5.74)</td>
<td>51.37 (8.18)</td>
<td><strong>3.87 (6.39)</strong></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>GAF-S</td>
<td>Venlafaxine (56)</td>
<td>48.16 (5.35)</td>
<td>51.84 (7.15)</td>
<td><strong>3.68 (8.10)</strong></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>GAF-F</td>
<td>Sertraline (67)</td>
<td>48.55 (6.71)</td>
<td>50.27 (8.24)</td>
<td><strong>1.72 (6.55)</strong></td>
<td>0.04</td>
</tr>
<tr>
<td>GAF-F</td>
<td>Venlafaxine (56)</td>
<td>48.75 (5.41)</td>
<td>51.77 (7.49)</td>
<td><strong>3.02 (6.74)</strong></td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

HAM = 0-4 (0 best score), GAF = 0-100 (100 best score)

Overview over rating scores at baseline and follow-up for the intention-to-treat sample. Numbers in brackets after group indicates the number of patients included in this analysis, which are all patients who have completed a follow-up rating.

**Bold** = Statistically significant improvement

**Bold and Italic** = Statistically significant worsening
**Table 3: Regression coefficients for group differences at follow up**

*Adjusted for baseline rating scores*

**Intention to treat sample (n=195)**

<table>
<thead>
<tr>
<th>Rating</th>
<th>Regression coefficient (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HTQ</td>
<td>0.07 (-0.09 – 0.22)</td>
<td>0.40</td>
</tr>
<tr>
<td>HSCL</td>
<td>0.07 (-0.1 – 0.23)</td>
<td>0.42</td>
</tr>
<tr>
<td>SCL</td>
<td>0.12 (-0.12 – 0.35)</td>
<td>0.31</td>
</tr>
<tr>
<td>SDS</td>
<td>2.31 (0.10 – 4.52)</td>
<td>0.04*</td>
</tr>
<tr>
<td>WHO-5</td>
<td>-5.79 (-12.05 – 0.46)</td>
<td>0.07</td>
</tr>
<tr>
<td>VAS-neck/back</td>
<td>0.28 (-0.49 - 1.05)</td>
<td>0.48</td>
</tr>
<tr>
<td>VAS-arms</td>
<td>0.70 (-0.13 - 1.54)</td>
<td>0.10</td>
</tr>
<tr>
<td>VAS-legs</td>
<td>0.72 (-0.01 – 1.45)</td>
<td>0.053</td>
</tr>
<tr>
<td>VAS-head</td>
<td>0.02 (-0.80 -0.85)</td>
<td>0.95</td>
</tr>
<tr>
<td>SAS-SR</td>
<td>0.10 (-0.09 – 0.29)</td>
<td>0.29</td>
</tr>
<tr>
<td>CSS</td>
<td>-0.35 (-2.18 - 1.47)</td>
<td>0.71</td>
</tr>
<tr>
<td>GAF-F</td>
<td>1.35 (-0.93 – 3.63)</td>
<td>0.25</td>
</tr>
<tr>
<td>GAF-S</td>
<td>0.06 (-2.40 – 2.52)</td>
<td>0.96</td>
</tr>
<tr>
<td>HAM-D</td>
<td>0.19 (-1.94 – 2.33)</td>
<td>0.86</td>
</tr>
<tr>
<td>HAM-A</td>
<td>-0.57 (-3.19 – 2.04)</td>
<td>0.67</td>
</tr>
</tbody>
</table>

**Bold:** In favor of Sertraline

**Italic:** In favor of Venlafaxine

**Bold and *:** Statistically significant
Table 4: Correlation coefficients, the CTP predictor index total score

<table>
<thead>
<tr>
<th>Rating</th>
<th>Pearson’s r (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HTQ</td>
<td>0.15 (-0.01 – 0.30)</td>
<td>0.06</td>
</tr>
<tr>
<td>HSCL-25</td>
<td><strong>0.25 (0.10 – 0.40)</strong></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>WHO-5</td>
<td>-0.22 (-0.37 – -0.06)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>SCL-90 (somatisation)</td>
<td><strong>0.21 (0.05 – 0.36)</strong></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>SDS</td>
<td>0.19 (0.03 – 0.34)</td>
<td>0.02</td>
</tr>
<tr>
<td>VAS-neck/back</td>
<td><strong>0.18 (0.02 – 0.33)</strong></td>
<td>0.03</td>
</tr>
<tr>
<td>VAS-arms</td>
<td><strong>0.26 (0.10 – 0.41)</strong></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>VAS-legs</td>
<td>-0.03 (-0.19 – 0.13)</td>
<td>0.72</td>
</tr>
<tr>
<td>VAS-head</td>
<td>0.14 (-0.02 – 0.30)</td>
<td>0.09</td>
</tr>
<tr>
<td>HAM-D</td>
<td><strong>0.29 (0.14 – 0.43)</strong></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HAM-A</td>
<td><strong>0.27 (0.12 – 0.41)</strong></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>GAF-F</td>
<td>-0.16 (-0.33 – -0.02)</td>
<td>0.08</td>
</tr>
<tr>
<td>GAF-S</td>
<td><strong>-0.23 (-0.39 – -0.05)</strong></td>
<td>0.01</td>
</tr>
</tbody>
</table>

Correlations between the CTP predictor index total score and the changes between baseline and follow-up on outcome measures. **Bold** = Statistically significant correlation.
Table 5: Correlation coefficients for the items of the CTP predictor index

<table>
<thead>
<tr>
<th>Item</th>
<th>HTQ</th>
<th>HSCL-depression</th>
<th>HSCL-anxiety</th>
<th>HAM-D</th>
<th>HAM-A</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pearson (95% CI)</td>
<td>P</td>
<td>Pearson (95% CI)</td>
<td>P</td>
<td>Pearson (95% CI)</td>
</tr>
<tr>
<td>Items rated by medical doctor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motivation</td>
<td>0.03</td>
<td>0.72</td>
<td>0.11</td>
<td>0.18</td>
<td>0.09</td>
</tr>
<tr>
<td></td>
<td>(-0.13-0.19)</td>
<td></td>
<td>(-0.05-0.27)</td>
<td></td>
<td>(-0.07-0.25)</td>
</tr>
<tr>
<td>Upbringing</td>
<td>0.02</td>
<td>0.81</td>
<td>0.13</td>
<td>0.12</td>
<td>-0.12</td>
</tr>
<tr>
<td></td>
<td>(-0.14-0.18)</td>
<td></td>
<td>(-0.03-0.28)</td>
<td></td>
<td>(-0.17-0.15)</td>
</tr>
<tr>
<td>Previously treated without measurable effect</td>
<td>0.12</td>
<td>0.14</td>
<td>0.20</td>
<td>0.01</td>
<td>0.13</td>
</tr>
<tr>
<td></td>
<td>(-0.04-0.27)</td>
<td></td>
<td>(0.04-0.35)</td>
<td></td>
<td>(-0.03-0.28)</td>
</tr>
<tr>
<td>Chronic pain</td>
<td>0.11</td>
<td>0.17</td>
<td>0.25</td>
<td>&lt;0.01</td>
<td>0.11</td>
</tr>
<tr>
<td></td>
<td>(0.05-0.27)</td>
<td></td>
<td>(0.09-0.39)</td>
<td></td>
<td>(-0.05-0.27)</td>
</tr>
<tr>
<td>Chronicity of mental condition</td>
<td>0.08</td>
<td>0.35</td>
<td>0.19</td>
<td>0.02</td>
<td>0.048</td>
</tr>
<tr>
<td></td>
<td>(-0.08-0.23)</td>
<td></td>
<td>(0.03-0.34)</td>
<td></td>
<td>(-0.11-0.21)</td>
</tr>
<tr>
<td>Medical doctor subscale – total score</td>
<td>0.12</td>
<td>0.15</td>
<td>0.29</td>
<td>&lt;0.01</td>
<td>0.12</td>
</tr>
<tr>
<td></td>
<td>(-0.04-0.27)</td>
<td></td>
<td>(0.13-0.43)</td>
<td></td>
<td>(-0.05-0.27)</td>
</tr>
<tr>
<td>Item</td>
<td>HTQ</td>
<td>HSCL-depression</td>
<td>HSCL-anxiety</td>
<td>HAM-D</td>
<td>HAM-A</td>
</tr>
<tr>
<td>--------------------------------------------------</td>
<td>--------------</td>
<td>-----------------</td>
<td>--------------</td>
<td>----------------</td>
<td>----------------</td>
</tr>
<tr>
<td><strong>Item</strong></td>
<td>Pearson (95% CI)</td>
<td>Pearson (95% CI)</td>
<td>Pearson (95% CI)</td>
<td>Pearson (95% CI)</td>
<td>Pearson (95% CI)</td>
</tr>
<tr>
<td>Items rated by psychologist</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Understanding of the concept of therapy</td>
<td>0.10 (-0.06-0.25)</td>
<td>0.08 (-0.08-0.24)</td>
<td>0.32</td>
<td>0.09 (-0.07-0.25)</td>
<td>0.27</td>
</tr>
<tr>
<td>Receptiveness/acceptability to psychological treatment</td>
<td>0.08 (-0.08-0.23)</td>
<td>0.34</td>
<td>0.10 (-0.06-0.26)</td>
<td>0.23</td>
<td>0.16 (0.00-0.31)</td>
</tr>
<tr>
<td>Reflectivity</td>
<td>-0.03 (-0.19-0.13)</td>
<td>0.72</td>
<td>0.00 (-0.16-0.16)</td>
<td>0.99</td>
<td>0.19 (0.04-0.34)</td>
</tr>
<tr>
<td>Motivation for active participation</td>
<td>0.11 (-0.05-0.27)</td>
<td>0.16</td>
<td>0.14 (-0.02-0.30)</td>
<td>0.08</td>
<td>0.13 (-0.03-0.28)</td>
</tr>
<tr>
<td>Cognitive resources</td>
<td>0.13 (-0.03-0.28)</td>
<td>0.12</td>
<td>0.13 (-0.04-0.28)</td>
<td>0.13</td>
<td>0.19 (0.03-0.34)</td>
</tr>
<tr>
<td>Psychologist subscale – total score</td>
<td>0.10 (-0.06-0.25)</td>
<td>0.22</td>
<td>0.11 (-0.05-0.27)</td>
<td>0.17</td>
<td>0.15 (-0.01-0.30)</td>
</tr>
<tr>
<td>Item</td>
<td>HTQ Pearson (95% CI)</td>
<td>HTQ P</td>
<td>HSCL-depression Pearson (95% CI)</td>
<td>HSCL-depression p</td>
<td>HSCL-anxiety Pearson (95% CI)</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>----------------------</td>
<td>--------</td>
<td>----------------------------------</td>
<td>-------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>Social relations</td>
<td>0.11(-0.06-0.26)</td>
<td>0.20</td>
<td>0.27(0.11-0.42)</td>
<td>&lt;0.01</td>
<td>0.19(0.03-0.34)</td>
</tr>
<tr>
<td>Education</td>
<td>-0.06(-0.22-0.11)</td>
<td>0.49</td>
<td>-0.07(-0.23-0.09)</td>
<td>0.39</td>
<td>-0.08(-0.24-0.08)</td>
</tr>
<tr>
<td>Dwelling</td>
<td>0.04(-0.12-0.20)</td>
<td>0.63</td>
<td>0.01(-0.16-0.17)</td>
<td>0.93</td>
<td>0.07(-0.09-0.23)</td>
</tr>
<tr>
<td>Employment status</td>
<td>0.18(0.02-0.33)</td>
<td>0.03</td>
<td>0.02(-0.14-0.18)</td>
<td>0.81</td>
<td>0.06(-0.10-0.22)</td>
</tr>
<tr>
<td>Integration</td>
<td>0.10(-0.06-0.26)</td>
<td>0.24</td>
<td>0.27(0.11-0.42)</td>
<td>&lt;0.01</td>
<td>0.22(0.06-0.37)</td>
</tr>
<tr>
<td>Social counsellor subscale</td>
<td>0.08(-0.09-0.24)</td>
<td>0.35</td>
<td>0.17(0.01-0.32)</td>
<td>0.04</td>
<td>0.14(-0.02-0.30)</td>
</tr>
</tbody>
</table>

**Correlations between single items on the CTP predictor index and the changes of PTSD, depression and anxiety symptoms from baseline and follow-up.**

**Bold**=Statistically significant correlation
**Table 6: Associations between HTQ changes and baseline variables**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean HTQ change (SD)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (n=92)</td>
<td>0.11 (0.45)</td>
<td>0.02</td>
</tr>
<tr>
<td>Female (n=62)</td>
<td>0.31 (0.57)</td>
<td></td>
</tr>
<tr>
<td>Torture exposure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (n=74)</td>
<td>0.16 (0.55)</td>
<td>0.49</td>
</tr>
<tr>
<td>No (n=79)</td>
<td>0.22 (0.47)</td>
<td></td>
</tr>
<tr>
<td>Refugee status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Refugee (n=113)</td>
<td>0.13 (0.48)</td>
<td>0.04</td>
</tr>
<tr>
<td>Family reunified (n=40)</td>
<td>0.32 (0.56)</td>
<td></td>
</tr>
<tr>
<td>Refugee camp</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (n=37)</td>
<td>0.13 (0.37)</td>
<td>0.47</td>
</tr>
<tr>
<td>No (n=115)</td>
<td>0.20 (0.55)</td>
<td></td>
</tr>
<tr>
<td>Asylum centre</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (n=89)</td>
<td>0.14 (0.53)</td>
<td>0.11</td>
</tr>
<tr>
<td>No (n= 60)</td>
<td>0.28 (0.50)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>Correlation coefficients, r</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-0.20</td>
<td>0.01</td>
</tr>
<tr>
<td>Duration of stay in Denmark</td>
<td>-0.19</td>
<td>0.02</td>
</tr>
<tr>
<td>Depression score (HAM-D) at baseline</td>
<td>-0.22</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Anxiety score (HAM-A) at baseline</td>
<td>-0.21</td>
<td>0.01</td>
</tr>
</tbody>
</table>

**Associations between baseline variables and changes in HTQ score during the treatment course in univariate analyses. Bold: Statistically significant**
9. References


52. Mollica RF, Caspi-Yavin Y, Bollini P, Truong T, Tor S, Lavelle J. The Harvard


67. Boehnlein JK, Kinzie JD, Sekiya U, Riley C, Pou K, Rosborough B. A ten-year


74. Boynton L, Bentley J, Strachan E, Barbato A, Raskind M. Preliminary findings concerning the use of prazosin for the treatment of posttraumatic


81. Hinton DE, Kredlow MA, Pich V, Bui E, Hofmann SG. The relationship of PTSD to key somatic complaints and cultural syndromes among Cambodian refugees attending a psychiatric clinic: the Cambodian Somatic Symptom


90. Ingelman-Sundberg M. Genetic polymorphisms of cytochrome P450 2D6 (CYP2D6): clinical consequences, evolutionary aspects and functional


Pharmacological treatment of refugees with trauma-related disorders - What do we know today?

Authors

Charlotte Sonne (corresponding author)
Competence Centre for Transcultural Psychiatry/University of Southern Denmark
Mental Health Centre Ballerup
Maglevaenget 2
2750 Ballerup
Denmark
Email: charlotte.sonne@regionh.dk

Jessica Carlsson
Competence Centre for Transcultural Psychiatry
Mental Health Centre Ballerup
Maglevaenget 2
2750 Ballerup
Denmark
Email: jessica.carlsson.01@regionh.dk

Per Bech
Mental Health Centre North Zealand
Dyrehavevej 48
3400 Hilleroed
Denmark
Email: per.bech@regionh.dk

Erik Lykke Mortensen
Institute of Public Health and Center for Healthy Aging
University of Copenhagen
Oester Farimagsgade 5
1353 Copenhagen K
Denmark
Email: elme@sund.ku.dk
Abstract

**Introduction:** There is a dearth of evidence for pharmacological treatment for refugees with trauma-related disorders. As guidance for clinicians and researchers the present paper aims to provide an overview of available literature on the subject and discuss the transferability of results from studies on other Post Traumatic Stress Disorder (PTSD) patients.

**Methods:** A review of treatment outcome studies on PTSD and depression among refugees was carried out. Searches were performed in PubMed, psycINFO, EMBASE and the Cochrane library using MeSH/Thesaurus terms as well as free text words. Abstracts (and if necessary full papers) were reviewed by the first author and all types of studies (except reviews) describing specified pharmacological interventions were included.

**Results:** Fifteen studies were reviewed. Most studies were focusing on antidepressants.

**Discussion:** Included studies differed widely in method and quality. The majority were observational studies and case studies. Small sample sizes made statistical power questionable. Few studies reported effect sizes, confidence intervals and statistical significance of findings. Differences in pharmacogenetics, compliance and trauma reactions were discussed in relation to the transferability of results from studies on non-refugee populations.

**Conclusion:**

No specific pharmacological treatment for PTSD among refugees can be recommended on the basis of the available literature. The authors call for well-designed randomized trials on especially newer antidepressants and antipsychotics. Until such studies are available, clinical practice and design of trials could be guided by results from studies of other groups of PTSD patients. However, there may be important differences between refugees with trauma-related disorders and other PTSD patients.
Introduction

A review on the prevalence of PTSD among refugees estimated that around 30% of the world’s refugees suffer from Post-Traumatic Stress Disorder (PTSD) and approximately the same proportion suffers from depression, the two disorders often being comorbid (Steel et al., 2009). An approximate number of 18.2 million refugees worldwide make this patient group considerable in size as well as an important socio-economic challenge (Danish Refugee Council, n.d.). Although some researchers have published their own recommendations (Fabri, 1997; Jaranson & Quiroga, 2011; J David Kinzie, 2011), no common agreement has as yet been reached about best practice treatment of refugees with PTSD and other trauma-related disorders and a considerable variability in treatment programs still seems to be the rule rather than the exception (Başoğlu, 2006). This may not be surprising as most studies and official guidelines focus on other groups of PTSD patients, such as war veterans and victims of nature disasters or sexual assaults (Hetrick, Purcell, Garner, & Parslow, 2010; Stein, Ipser, & Seedat, 2009).

Uncritical generalization of results from studies on other groups of PTSD patients may be problematic for several reasons. As observed in numerous studies, refugees with trauma-related disorders usually report a large number of traumatizing events. In this aspect their history as well as their symptomatology differ from that of single trauma victims such as survivors of natural disasters (Steel et al., 2009). Other multi-trauma survivors such as war veterans have, unlike many refugees, often been brought up in a safe environment and usually return to their home country after the trauma. Having an intact social network and a basic knowledge of the health- and social system makes it easier for veterans to obtain appropriate help at an early stage. Refugees with trauma-related disorders on the other hand, usually lack these advantages. The asylum process in itself can be very stressful and even after obtaining residence status refugees often struggle with ongoing stressors such as challenges of cultural and social adaptation and worry for family members left behind. Together these factors might at least partly account for the fact that many refugees with trauma-related disorders present with a more widespread set of symptoms than those incorporated in the ICD-10 and DSM-IV PTSD diagnoses (Silove, 1999). Although not an official diagnosis this is often referred to as “complex PTSD” by clinicians and researchers in
the field (Resick et al., 2012). This broader set of symptoms as well as the lack of social support might result in treatment being less efficient than in non-refugee populations.

Apart from the psycho-social factors that differentiate refugees with trauma-related disorders from other PTSD patients, some studies has found a biological difference in the pharmacogenetics of patients from the Middle East and Asia compared to patients originating from western countries (Noerregaard, 2012). Although this is not yet thoroughly investigated, it may potentially affect the dose-response relationship and the effectiveness of these drugs when used in refugee health settings with primarily non-western populations as most drugs are usually tested and approved in western countries.

To study refugees as one homogenous group may rightly be challenged, as there will be many differences among patients from areas as different as Asia, Africa and the Middle East. However, despite those obvious differences, refugees also share a number of challenges independent of their country of origin. They have all been forced to leave their homes often under very traumatizing circumstances, and most do to some extent struggle with issues of cultural transition. Furthermore they all have to rely on a health system in which they belong to a minority biologically as well as culturally and where their background, needs and views of life often is poorly understood. Because of these similarities which are based on the very concept of being a refugee, we find it important to research refugees as an independent group despite the acknowledged intragroup variability.

There are quite a number of studies, reviews and met analyses on pharmacological treatment of non-refugee PTSD patients (Stein et al., 2009; Watts et al., 2013). However, there are very few reviews on the treatment of adult refugees with PTSD and almost all of these focus on psychosocial or psychological treatment options (Nickerson, Bryant, Silove, & Steel, 2011; Palic & Elklit, 2011), probably reflecting that the majority of treatment effect studies on traumatized refugees concerns non-pharmacological treatment options. In the present paper we have therefore decided to focus solely on pharmacological treatment of trauma-affected refugees, as it is equally important to review the evidence for the use of medication in treatment programs.

To our knowledge only one systematic review that including pharmacological treatment of adult refugees with trauma-related disorders has until now been published (Crumlish &
O’Rourke, 2010). This review included all possible treatment modalities and very few details were presented concerning pharmacological treatment. In this systematic review, only high quality RCTs were included and only two studies on pharmacological treatment. Needless to say, this is the correct procedure for a systematic review, but in the case of a very scarcely researched field, very strict study inclusion criteria may also lead to exclusion of knowledge that could be valuable in directing clinical practice and future research. Given the small number of studies, a broader literature overview seems to be appropriate, including a discussion of the transferability of results from general PTSD studies to the treatment of refugees with trauma-related disorders.

The aim of the present paper is therefore to provide an overview of the present knowledge on pharmacological treatment of refugees with trauma-related disorders by

- Examining the available literature on pharmacological treatment of adult trauma-affected refugees with PTSD and/or depression
- Discussing the transferability of studies on other groups of PTSD patients
- Discussing the implication of the findings for the direction of future research within the field.

**Method**

**Search strategy**

The databases PubMed, psycINFO, EMBASE, and the Cochrane library were systematically searched.

For PubMed, psycINFO and EMBASE a combination of the searches described below (MeSH/thesaurus terms as well as free text words was used). Due to the different features of the databases the exact phrasing of the words differed slightly although the same terms were searched for.

As for PubMed the following search was performed:

(((PTSD AND refugee*)) OR ((Refugee*) AND depression)) AND (((((pharmacolog*) OR medicin*) OR medical*) OR antidepressant*) OR antipsychotic*) OR Medication)
As for Embase and psycINFO the following search was performed:

(((PTSD AND refugee)) OR ((Refugee) AND depression)) AND (((((((((pharmacology) OR pharmacologic) OR pharmacologically) OR medical) OR medically) OR antidepressant) OR antidepressants) OR antipsychotic) OR antipsychotics) OR Medication)

As the Cochrane library is a much smaller database, it was searched solely for the word “refugee”.

The last search was performed on the 26th of September 2013.

Reference lists of the existing reviews were searched manually by the first author, resulting in two extra articles.

The first author went through all abstracts manually. In the few cases where no abstract could be obtained from any of the databases, the full paper was obtained if the relevance of the article could not be evaluated from the title.

As discussed above, trauma-affected refugees sometimes present with other symptoms than those included in the diagnoses of PTSD and depression. However, in order to make results from the present paper comparable with reviews on trauma-affected non-refugee populations, the authors decided to focus on PTSD and depression when developing the search strategy. Since those diagnoses are the most common among refugees with trauma-related disorders we assumed that papers focusing on other disorders would usually also include either of the two and that we would not risk missing essential literature.

**Study inclusion and exclusion**

Articles were included if they described a specified psychopharmacological intervention on adult refugees (18 years old or above), diagnosed with PTSD and/or depression and the outcome of the intervention was described, either qualitatively or quantitatively. All types of studies except reviews were included.

To be included articles had to be written in English, French, Spanish or Scandinavian languages (Danish, Swedish or Norwegian).
The search strategy described above identified a total number 965 studies (963 from databases and two from reference lists from reviews) of which 46 were of possible relevance. After reading through the 46 articles, 31 were excluded. Articles excluded were labeled as: 1) Books 2) Non-intervention articles (including articles that did not describe any relevant intervention as well as commentaries and letters to the editor) 3) Non-pharmacological interventions, including articles on other interventions such as psychotherapy or physiotherapy 4) Child studies if the study only dealt with child, adolescent or family interventions 5) Reviews on pharmacological interventions 6) Reviews on other subjects 7) Studies on somatic interventions only and 8) Study protocols. Articles were furthermore excluded if the intervention used was not specified (e.g. if the only description of medication was “antidepressants” with no further specifications) and labeled as “intervention not specified”.

The process of in- and exclusion is illustrated in Figure 1.

Results

Fifteen studies were found eligible for inclusion. An overview of the included studies is provided in table 1. The studies are divided into two categories: Studies primarily focusing on antidepressants (11 studies), and studies primarily focusing on other pharmacological agents (four studies). Within each category the studies are presented in a hierarchical order according to the level of evidence, with randomized controlled studies first and case studies last.

Studies primarily on antidepressants

Eleven studies with primary focus on antidepressants were identified, including two randomized controlled trials (RCTs). The first RCT was on pharmacotherapy alone. The second was an RCT comparing antidepressants alone with antidepressants in combination with psychotherapy. The remaining studies were six observational studies and three case studies.
Randomized controlled trials

The RCT on medication only was a study on adult Bosnian refugees in the US conducted by Smajkić et al. (Smajkić et al., 2001). The three antidepressants sertraline, paroxetine and venlafaxine were compared in a randomized open-label design. The number of participants was 32 not including eight drop outs, all from the venlafaxine group. Patients in the sertraline group (nine women, six men) received 50-100 mg daily, patients in the Paroxetine group (nine women, three men) received 20 mg daily and patients in the venlafaxine group (five men) received 37.5-75 mg daily. Six of the patients were additionally prescribed clonazepam. The study period was 6 weeks. PTSD symptoms were measured by the PTSD Symptom Scale (PSS) whereas depression symptoms were assessed by the Beck Depression Inventory (BDI). Furthermore the Global Assessment of Functioning (GAF) was included. Changes on the scale scores were analyzed using paired sample t-tests. All three groups (sertraline, paroxetine and venlafaxine) showed statistically significant improvement in PTSD symptoms after 6 weeks. Nevertheless all patients still met diagnostic criteria for PTSD after 6 weeks. Mean BDI scores decreased significantly in the sertraline and paroxetine group, but not in the venlafaxine group. The GAF scores increased significantly in all three groups.

The RCT comparing antidepressants alone with antidepressants in combination with psychotherapy was a study by Otto et al. on ten female Khmer-speaking Cambodian refugees (Otto et al., 2003). All ten had previously been treated with a selective serotonin reuptake inhibitor (SSRI) other than sertraline (no further description) in combination with 0.5-1 mg Clonazepam and still met DSM-IV criteria of PTSD despite the treatment. The ten participants were then randomized to either sertraline alone or sertraline in combination with ten sessions of Cognitive Behavioral Therapy (CBT). At the end of the treatment period participants from the sertraline group were taking a mean dose of 125 mg/day whereas participants from the combined treatment group were taking a mean dose of 100 mg/day. Outcome measures were the Clinician-Administered PTSD Scale (CAPS) and the Hopkins Symptom Checklist-25 (HSCL-25) for PTSD, depression and anxiety symptoms. The duration of the study was not reported. Patients receiving combined treatment were reported to have improvement on all scales. The sertraline alone group did not improve on the CAPS re-experiencing and hyperarousal
items, but on all other scales, although for some of them only slightly. No confidence intervals or P-values were reported. Effect size between groups was calculated as Cohen’s d, using the pooled standard deviation for both groups. Forty percent in each group reported at least one mild side effect but none of these resulted in treatment discontinuation.

Overall the Smajkić et al randomized controlled trial showed some effects of sertraline, paroxetine and venlafaxine on PTSD-symptoms (Smajkić et al., 2001). Furthermore, sertraline and paroxetine, but not venlafaxine, were found to be effective on depression. However, since the study did not include an untreated control group, the venlafaxine group in particular was very small and the authors only found a small difference between the groups, it is not possible to evaluate the extent to which the observed changes from baseline to evaluation reflect a real effect of the treatment or to spontaneous remission.

Otto et al. compared two treatment modalities: sertraline alone versus sertraline in combination with psychotherapy and found that to a certain extent the combination group had a better outcome (Otto et al., 2003). However, since all participants received sertraline and the study did not include untreated comparison groups, it is not possible to evaluate the effects of sertraline on the basis of this study.

In conclusion the two randomized controlled trials available do not provide unambiguous evidence on the effects of pharmacological treatment of refugees with trauma-related disorders.

**Observational studies**

A three year follow up study by Drozdek compared either antidepressants or psychotherapy alone with antidepressants in combination with psychotherapy (Drozdek, 1997). Out of an original population of 120 male Bosnian refugees, 50 of those fulfilling PTSD criteria were assigned to one of the three treatment groups: 1. group psychotherapy, 2. medication and 3. a combination of medication and group psychotherapy. Drozdek does not state whether the assignment to groups was randomized or according to participant/clinician choice and therefore the study is categorized as an observational study. The treatment lasted 6 months. The psychopharmacological agents used were tricyclic antidepressants (TCAs) (amitriptyline, clomipramine) and anxiolytics (diazepam, oxaxepam) in usual adult dosages. No significant
association was found between any of the three types of treatment and the PTSD diagnosis at any of the evaluation points.

A one-year follow up study was carried out by Boehnlein et al. on 12 Cambodian refugees who received monthly treatment for one year (J K Boehnlein, Kinzie, Ben, & Fleck, 1985). Two patients dropped out, but agreed to be contacted for follow up. PTSD symptoms were assessed with the PTSD section of the Diagnostic Interview Schedule (DIS). All patients had comorbid psychiatric diagnoses, depression being the most common. Patients were treated either with one or more TCAs (imipramine or amitriptyline), a monoamine oxidase inhibitor (MAOI) (phenelzine) or a combination of these medications. Some patients appear to have been treated with benzodiazepines and beta-adrenergic blockers as well, but this is not further specified in the article. In addition to the medical treatment all patients received “supportive therapy” mainly focusing on current problems.

After one year of treatment five of the initial 12 patients did not meet the diagnostic criteria for PTSD. Three others had improved but still met the diagnostic criteria. Three patients remained unchanged, and one had deteriorated. One of the two drop outs had worsened at follow up and one improved while still fulfilling the criteria for PTSD. No correlation was found between recovery and working/taking English classes. The authors stated that the impression was that the TCAs were helpful in treating PTSD and depression symptoms in 6 patients whereas benzodiazepines and propranolol seemed to be ineffective.

A ten-year follow up study was carried out by Boehnlein et al. on 23 adult Cambodian refugees (J K Boehnlein et al., 2004). The study population consisted of five males and 18 females who had all been in continuous treatment for PTSD for at least 10 years, with an average of 13.5 years of treatment. The antidepressive treatment consisted of either a SSRI or a TCAs (not further specified), in 16 individuals combined with either clonidine or prazozin to control nightmares. Furthermore, patients received supportive therapy and most participated in weekly socialization groups. The included rating scales were CAPS and the Hamilton Depression Rating Scale (HDRS).

Since baselines scores were not reported, changes from original scores could not be calculated. However, the authors divided the patients into those with good or poor outcome at the ten year follow up. Those with a poor outcome (n=10) had a CAPS score higher than
20 and a HDRS score higher than 20 whereas in those with a good outcome (n=13) had a CAPS score lower than 20 and the remaining three had CAPS scores corresponding to “mild symptoms”. The authors found that many patients suffered from an exacerbation of symptoms during the follow up period. Fourteen patients had at least one 3 month episode of severe recurrence of PTSD symptoms, often in connection with current stressors.

Kinzie et al. carried out a one-year prospective observational study on a mixed group of tortured refugees from Ethiopia, Somalia, Iran and Afghanistan (J D Kinzie et al., 2012). The study population of 22 torture survivors originated from a sample of 57 patients (criteria for selection not specified for the majority of the patients). Treatment consisted of supportive psychotherapy, education, counseling by ethnic counselors and medication. Thirteen patients were on SSRI’s, six on TCAs, one on buproprion and two on duloxetine. As add-on treatment seven patients received clonidine, one prazozin. Additionally, 11 patients were treated with antipsychotics, two for clear psychotic symptoms, the remaining nine for irritable and aggressive symptoms (usually with low doses of risperidone). PTSD symptoms were evaluated with HTQ and the Short Post-Traumatic Rating Scale Interview (SPRINT). Depression was measured by the Center for Epidemiological studies Depression Scale (CES-D). Scales were administered at intake and at a follow up visit 11-14 months after intake.

Improvements were reported on the majority of the rating scales in 20 out of 22 patients. Significant differences between intake and one-year follow up were observed, but the statistical analyses were not clearly described. Since neither changes on rating scales or specific medication were reported for the individual patients, it remains an open question whether there were any differences in treatment patterns between those that moved out of the pathological ranges on PTSD and depression and those that did not.

Schwartz-Langer et al. conducted an observational study on 13 refugees with trauma-related disorders (eight women, five men) from former Yugoslavia. (Schwarz-Langer, Deighton, Jerg-Bretzke, Weisker, & Traue, 2006). They were treated with a combination of psychotherapy, physiotherapy and medicine. Twelve patients were treated with SSRIs (sertraline, citalopram or fluvoxamine) and the last one with mirtazapine. Four were additionally treated with lorazepam, two with zopiclone, two with buspirone and eight patients also received olanzapine and one also flupentixol. All were additionally treated with psychotherapy and
physiotherapy. An evaluation of treatment results was conducted by examining therapy protocols for changes and by use of an evaluation form in which reduction in PTSD symptoms and sleep disorders were recorded during “a post hoc interview” which was not further described. All patients showed improvement in sleep behavior and most showed improvement in intrusive symptoms and hyperarousal. The authors found that the positive effect of antidepressant treatment normally started after several weeks of treatment.

Hinton et al. (Hinton, Kredlow, Bui, Pollack, & Hofmann, 2012) performed an observational study with 56 Cambodian refugees (59% women). The original study population consisted of 57 patients, diagnosed with PTSD using the Structured Clinical Interview for DSM (SCID). None of them had previously received psychopharmacological treatment. Paroxetine up to maximum dosage (not further specified) was used as first line treatment. Furthermore some patients received 0.5 mg clonazepam when needed. If patients remained symptomatic on this combination either mirtazapine or bupropion was added. Additional treatment consisted of supportive therapy and psycho-education. PTSD symptoms were evaluated after three and six months of treatment using the PTSD Checklist (PCL). The patients showed a significant improvement on PCL and other scales at the three months’, but not at the six months’ evaluation. Cohen’s d was 1.3 for the PCL.

The different observational studies investigated a range of different antidepressants in combination with other pharmacological agents such as anxiolytics and antipsychotics as well as different kinds of non-medical interventions. All but one study (Drozdek, 1997) found some improvement at all points of evaluation at least in part of the treated patients. One study did not include baseline data and as such did not measure an outcome but only status at follow up (J K Boehnlein et al., 2004). Therefore it is not really an outcome study, although named so by the authors.

Interestingly, the study by Drozdek was also the only one with a sort of control group, since the study included a group of PTSD patients who had refused treatment (Drozdek, 1997). Unfortunately, the results are reported somewhat ambiguously, making it difficult to compare data from the initial evaluation (after 6 months of treatment) with data from the three year follow up. At the initial evaluation 73% of those diagnosed with PTSD (presumably including the group that did not receive treatment, but this is not specified) no longer met
the diagnosis for PTSD whereas 90% of the group that refused treatment still met the diagnostic criteria. At the three year follow the authors clearly state that they compared treated and non-treated PTSD patients, and at that point 83 % of the treated, but only 60 % of the non-treated met the diagnostic criteria for PTSD. This may indicate that patients in the treated group were more severely ill than the patients refusing treatment, which is a possible bias in a non-randomized design.

The remaining studies did not include a control group which makes it difficult to evaluate the extent to which the observed changes from baseline to evaluation were due to a real treatment effect or reflected the natural course of the disease or other things happening to the patients in addition to treatment. This is further discussed in the limitations section.

Case studies

A case study by Frances and Kroll describes a 57 year old Hmong woman from Laos treated with up to 150 mg amitriptyline (Frances & Kroll, 1989). The patient reported improvement on the treatment. During two periods of non-compliance her symptoms returned. Cheung describes three cases (two women, one man) of Cambodian refugees with PTSD and depression living in New Zealand and treated with doxepine 20-50 mg (Cheung, 1993). All improved after two to five weeks of treatment. In two cases, attempts to reduce antidepressant dosages resulted in recurrence of symptoms whereas one remained improved when medication was stopped after six months. DeMartino et al. presented five cases of refugee patients, all women from Cambodia or Laos treated with MAOIs (DeMartino, Mollica, & Wilk, 1995). Symptoms of depression were monitored with the HSCL-25 and PTSD symptoms with a clinical checklist (not further described). All patients had tried TCAs for a minimum of 12 months with insufficient effect before MAOIs were initiated. Three were treated with 10-20 mg tranylcypromine, one with 30 mg isocarboxazid. All five cases showed some improvement.

The case studies described above included cases on TCAs and MAOIs. All found that their interventions were effective in the patients studied. However, interpretation of case studies is always ambiguous and they do not permit definitive conclusions about treatment effects.
Studies primarily focusing on other pharmacological agents

Four studies primarily on other pharmacological agents were identified. Two of the studies were on the use of the alpha-1-adrenergic receptor antagonist prazozin and its effect on nightmares in PTSD patients. The two remaining studies were on the alpha-2-agonist clonidine and its effect on nightmares as well as other PTSD- and depression symptoms. No studies primarily focusing on anxiolytics or antipsychotics were identified.

Studies of prazozin

Two studies were conducted on prazozin – one retrospective chart study and one case study.

Boynton et al. conducted a retrospective chart review on a mixed group of 23 refugees (15 women and eight men) with chronic PTSD (Boynton, Bentley, Strachan, Barbato, & Raskind, 2009). Rating instruments were the Clinician Global Impression-Change (CGI-C) and CAPS scores for nightmares (a combination of the scores for nightmare frequency and intensity). These scores, however, were not obtained during the treatment course, but retrospectively based on a chart review on charts from before the patients initiated treatment with prazozin and 8 weeks after a stable dose was achieved. Doses of prazozin ranged from 1-6 mg. Data were analyzed with paired sample t-test.

The authors found that the CAPS scores decreased significantly from baseline. The overall PTSD score as rated on CGI-C “markedly improved” in six patients, “moderately improved” in 11 patients and “minimally improved” in six patients. At the end of the study three cases were presented, all of them had improved on 2-3 mg prazozin (in two of the patients in combination with fluoxetine or sertraline).

Boehlein et al. briefly described two cases of refugee patients in a neurobiological paper on reduction of noradrenergic activity in PTSD (J K Boehlein & Kinzie, 2007). Both cases were treated with prazozin 1-2 mg, resulting in an improvement in nightmares and other intrusive symptoms.

Both the retrospective study and the case study on prazozin found some effect on nightmares and on some of the other PTSD symptoms. However, the methods used in the studies (retrospective design and a single case) raises the issue of whether the reported improvements reflect a real treatment effect.
Studies on clonidine

The two studies on clonidine were both observational.

Kinzie et al. described the use of add-on clonidine to a TCA (usually Imipramine) (J D Kinzie & Leung, 1989). Twelve Cambodian refugees with chronic PTSD were prospectively included in the study. Rating scales were the HDRS and a checklist for PTSD and depression adapted from the DSM-III-R (not further described). Patients were first treated with a TCA alone for 1-2 months, after which nine patients had 0.2-0.6 mg Clonidine added to their TCA treatment (of the original population one moved away and two did not receive clonidine, since they had improved sufficiently on TCAs alone). Furthermore, three patients improved with regard to depressive symptoms on TCAs only and two improved with regard to PTSD symptoms (how much they improved was not described but apparently not enough to withdraw them from the clonidine study). After 12-19 months of treatment with the TCA-clonidine combination five patients no longer met the criteria for major depression and two patients no longer met the criteria for PTSD. This appears to include the patients that improved on TCAs alone but still continued in the study. Sleeping difficulties was the symptom that improved in most patients.

Kinzie et al. also conducted a pilot study on four Cambodian female refugees all living in the US (J D Kinzie, Sack, & Riley, 1994). All had been diagnosed with chronic PTSD and major depressive disorder. No rating scales were used but changes in the frequency of nightmares as well as changes in other symptoms were reported by patients. Furthermore amount of sleep and sleep patterns were recorded with polysomnograph electrodes in the patient’s home, twice before initiating clonidine treatment and twice after. Initial dose was 0.1 mg clonidine, increasing after one week to 0.1 mg in the morning and 0.2 mg at bedtime.

All patients reported increased sleep and fewer nightmares two weeks after treatment start. The former was however in contrast to the polysomnograph data which showed a slight decrease in total sleep time after initiation of clonidine. All patients also reported a decrease in irritability and startle response, although not total absence.

The two studies both reported subjective improvement of PTSD symptoms after clonidine treatment although patient reports of increased sleep time was contrary to polysomnograph
findings in the second study (J D Kinzie et al., 1994). The first study aimed to use patients as their own controls, as they initially received TCAs with clonidine add-on after 1-2 months of treatment (J D Kinzie & Leung, 1989). However, the confusing reporting of results and the very different duration of treatment periods on TCA alone compared to the TCA-clonidine combination makes it difficult to draw any conclusions from the study.

Discussion

Fifteen studies were included in this study. The settings, the population, the study design and methods used for assessment of treatment outcome differed substantially and the quality of the included studies were generally low as discussed further below.

Limitations of included studies

The included studies suffer from a broad range of limitations. Generally, only small samples of patients were included, the biggest study being on 56 patients (Hinton et al., 2012), making it reasonable to question the statistical power of the studies. Probably due to this factor, few studies report effect sizes, confidence intervals and statistical significance of their findings. Needless to say, a randomized design is preferable when testing the efficiency of different types of pharmacological interventions. Observational studies focusing on pharmacological treatment can be useful in generating hypotheses for further research or to test the acceptability of a given treatment, but seldom provide clear answers as to the effect of a specific pharmacological intervention. Case studies can be used to report new clinical observations or rare phenomena, but are not appropriate for studying treatment effects.

Only one of the identified trials (Smajkić et al., 2001) compared different pharmacological agents in a randomized design. This study had, however, a number of other limitations such as few patients in each group, a large drop-out from one of the groups (leaving this group with only male participants), only small dosages of the antidepressants tested and no intention-to-treat analyses of the drop-outs. This together with no information about baseline differences between groups and no calculation of between-group effect size makes it doubtful that the reported differences between groups reflect a true difference in treatment effect. A non-medicated control group would have provided further information
about the real effect, but the lack of control group might be due to other factors, such as ethical issues.

Most of the studies identified were observational studies or case studies, which limits the direct clinical usefulness of their conclusions as stated above. In quite a few of these studies the patients were treated for several years during which other events apart from receiving treatment will inevitably happen to the participants. In studies with very small numbers or even just one or two patients, it is therefore not at all possible to discern how much of a given outcome is due to the treatment and how much is due to other factors such as receiving permanent citizenship, being reunited with one’s family etc. Likewise, negative current stressors might influence the outcome; this element is mentioned in several studies (J K Boehnlein et al., 2004; DeMartino et al., 1995; J D Kinzie & Leung, 1989).

Some studies merely provide a very brief description of the administered treatment and other studies only specify treatment for part of the treatment period (J K Boehnlein et al., 1985; J K Boehnlein et al., 2004; J D Kinzie et al., 2012). In most studies it is difficult to know what other treatment, if any, the described treatment was compared to. The Kinzie clonidine-TCA study reported that patients had tried a TCA alone before trying the TCA-clonidine combination (J D Kinzie & Leung, 1989). Out of the final study population of nine persons, three apparently improved on TCAs alone. However they were still present in the final evaluation of combined treatment, where they accounted for half of the patients that improved on depressive symptoms, even though they had actually improved before receiving clonidine. Furthermore the study patients were only treated with TCA alone for 1-2 months whereas the TCA-clonidine combination was given for 12-19 months. It could therefore easily be the case that a later onset of TCAs action caused the observed improvement, not the add-on clonidine.

In quite a few of the studies no ratings were used and only a brief qualitative description of the outcome provided (J K Boehnlein & Kinzie, 2007; Cheung, 1993; Frances & Kroll, 1989; J D Kinzie et al., 1994; Schwarz-Langer et al., 2006). A range of different rating scales were used in the remaining studies, some were validated and well known scales, others were study-specific or used in a very different context than the scale was intended for. For example in the study by Boynton et al., two rating scales developed to be used by clinicians
while interviewing the patients were scored retrospectively on the basis of the patient charts, by a psychiatrist who had apparently never met the patients (Boynton et al., 2009). Even the studies using standardized and validated rating scales do not always report the treatment outcome on the included scales. Kinzie et al. mention that HTQ is used throughout the study, but do not provide any scores on this rating scale at baseline or at treatment evaluation (J D Kinzie et al., 2012). DeMartino et al. claim that rating scales were used for monitoring symptoms, but scores are not reported (DeMartino et al., 1995).

Only one of the included studies (Smajkić et al., 2001) focused on newer types of antidepressants such as serotonin-noradrenaline reuptake inhibitors (SNRIs) which is peculiar, given the fact that in particular venlafaxine has demonstrated promising results on other groups of PTSD patients (Watts et al., 2013). Furthermore no studies investigate antipsychotics as the primary treatment and only few use antipsychotics as adjunctive treatment, again in contrast to other PTSD studies (Watts et al., 2013). This dearth of evidence reflects the lack of research tradition within the field. Although slowly changing, research on treatment outcome was not prioritized for many years, probably due to a mixture of political, ethical, practical and economic reasons. In particular, concerns have been raised about randomized studies in relation to the vulnerability and heterogeneity of refugee groups. However, an in-depth discussion of possible reasons for the lack of studies and the potential problems of randomization is outside the scope of the present paper., but has been discussed in another paper (Carlsson, Sonne, & Silove, 2014)

**Limitations of this study**

The present study has some limitations. Only well-known databases were searched and we did not actively try to identify unpublished studies or study protocols. This decision was made on the basis of the purpose of this paper, which is primarily to provide an overview for clinicians and researchers in the field. Therefore all the included articles should be easy accessible for anyone interested in having a closer look on any of the studies mentioned.

Only studies in English, French, Spanish or Scandinavian languages (Danish, Swedish or Norwegian) were included which could pose a possible limitation. However all studies in other languages were assessed based on the English abstract and no intervention studies
were excluded on the basis of the language criteria. Therefore this decision did not influence the results of the present review.

The study populations were limited to refugees with trauma-related disorders since the intention was to provide guidance for clinicians and researchers working with this patient group. Therefore studies on similar groups such as asylum seekers and internally displaced were not included. This limited the number of included studies, but the decision was made in order to focus on comparison of findings on refugees with trauma-related disorders.

Refugees rely on a health system in which they belong to a minority both culturally and biologically, as illustrated below. Internally displaced people on the other hand are under most circumstances cared for by a health system with which they are familiar, although they might experience different problems such as accessibility and lack of minimum standards for the quality of the care provided.

**Transferability of results from other groups of PTSD patients**

As briefly mentioned in the review by Crumlish and O’Rourke, evidence from pharmacological trials on other groups of western PTSD patients might prove adaptable to refugee populations (Crumlish & O’Rourke, 2010). As tempting as this may be, because of the lack of proper studies identified, results should only be generalized to traumatized refugees with caution for several reasons.

Some studies have suggested that there are differences in pharmacogenetics between ethnically different populations. Genotypes for cytochrome CYP450, responsible for the metabolism of a range of different drugs, may differ in different ethnicities. Studies have found that the prevalence of CYP450 2D6 ultra rapid metabolizers is up to 30% in Middle Eastern populations (Noerregaard, 2012). Although a large number of Middle Eastern patients will be normal metabolizers there is a much smaller frequency of rapid metabolizers among European patients and western psychiatrists may therefore not be aware of this issue when treating patients from Middle Eastern countries. Other biological factors might similarly differ among ethnic groups. A study by Lin et al. found a higher mean serum concentration in the blood of Asians than in Caucasians after injection of a similar dose of Haloperidol, suggesting a range of pharmacokinetic factors including absorption and hepatic first-pass metabolism as possibly responsible for the observed difference (Lin, Poland, Lau, &
Rubin, 1988). Differences in the genes responsible for protein binding, such as the serotonin transporter gene might also affect the efficiency of for example many antidepressants acting primarily on serotonin reuptake (Noerregaard, 2012). Likewise, side effects might differ and be observed on lower doses than expected. Lin et al. have also pointed out that dietary factors have previously shown to significantly influence drug metabolism (Lin & Shen, 1991).

Non-compliance is another problem that is addressed by several articles on mainly Southeast Asian refugees (De Lay & Faust, 1987; J. D Kinzie, Leung, Boehnlein, & Fleck, 1987), but also found to be a substantial problem among other groups of ethnic minorities (Blom et al., 2010). This might be due to a range of factors, going from beliefs about the causes of mental health disorders, beliefs about medication among the patients, their extended families and their social network, to barriers in the relationship between doctor and patient, such as language problems and different ideas about “the good doctor” and patient autonomy (Kortmann, 2010; Lin & Shen, 1991).

Finally, quite a few researchers in the field have suggested that extreme trauma, such as extended periods of imprisonment and torture, might cause a far more complex trauma reaction than the symptoms described by the current PTSD diagnosis (Silove, 1999). This also means that the effect of the treatment provided, including the effect of the pharmacological treatment, might be smaller than expected from studies on other groups of PTSD patients.

It is therefore far from simple to directly transfer results from clinical trials on western patients to patient samples from other parts of the world, and it requires attention to genetic, cultural and trauma related factors that can influence drug efficiency. However, this does not mean that results from trials on non-refugee PTSD patients are not useful when it comes to designing treatment programs and trials for traumatized refugees – only that this should be done in the light of the factors discussed. Especially in the design of new trials with traumatized refugees, all literature on the treatment of trauma related disorders should of course be taken into account.

**Conclusion and clinical perspectives**

On the basis of the literature identified for this review, it is not possible to recommend any specific pharmacological treatment over another. Antidepressants are presently the
pharmacological agent which has been most often investigated among refugees with trauma-related disorders although mainly in smaller observational studies, and any conclusions will therefore mirror the limitations of this study design. In our experience antidepressants are also the pharmacological agent most often used by clinicians when treating this patient group, probably based on results from studies on other groups of PTSD patients as well as on clinical experience. However, even though the value of clinical experience should not be underestimated, clinical judgment may be biased and – like findings from observational studies – need to be tested in rigorous trials. There is especially a lack of trials on newer antidepressants, but also on other antidepressants to either confirm or disprove results from the studies described in this paper. Treatment effect should be consistently measured by culturally appropriate and well-validated rating scales both in trials and in clinical practice.

Studies on antipsychotics (both as primary and supplementary treatment) as treatment for refugees with trauma-related disorders are almost totally absent, thereby causing major problems for evidenced-based treatment of complex trauma reactions with psychotic or psychotic-like symptoms.

For prazozin and clonidine only a very limited number of studies were identified on refugees with trauma-related disorders. There is however a growing body of literature supporting the effect of prazozin on nightmares in combat veterans and other groups of PTSD patients (Writer, Meyer, & Schillerstrom, 2014). Until results from well-designed trials are available, clinicians must to a large extent depend on a combination of clinical experience and research results from trials on other PTSD populations (Watts et al., 2013). They should, however, be aware of the challenges discussed above such as differences in culture, pharmacogenetics and compliance. Attention should be paid to effective dosages, which might differ from those recommended with respect to both treatment effect and side effects. Furthermore, psycho-education is considered to be highly important in order to secure compliance. Written information in all relevant languages should preferably be available at clinics treating refugees with trauma-related disorders. Compliance could also be secured by serum concentration blood tests, which can at the same time be used to guide dosages. If this is not possible, due to clinical or pharmacological issues, pill counting or similar methods can be pragmatic alternatives.
Acknowledgments

The authors would like to thank translator Susan Soendergaard for English proof reading of the manuscript.

Author Biographies

Charlotte Sonne, MD, is currently undertaking a PhD at the Competence Centre for Transcultural Psychiatry (CTP). She is the principal investigator on a randomized clinical trial concerning pharmacological treatment of trauma-affected refugees and is additionally studying psychosocial predictors for treatment outcome on the same population. She expects to finalize her PhD dissertation in the end of 2015 and is planning to proceed her research in a postdoc position, where her focus will be on her interventions for trauma-affected refugees.

Jessica Carlsson, MD, PhD, is the head of research at Competence Centre for Transcultural Psychiatry (CTP) and Associate Professor at the Medical Faculty, University of Copenhagen. Dr. Carlsson’s research areas are transcultural psychiatry, migration and mental health and trauma in refugee populations and outcome studies in trauma-affected refugees. She is presently the principal and co-supervisor of 7 PhD students at CTP. Her published works has a focus on trauma and mental health in refugee populations and in transcultural psychiatry with a focus on clinical psychiatry.

Per Bech, MD, Dr Sci, is professor of Clinical Psychometrics at the University of Copenhagen. His research area is clinical psychometrics with special focus on the measurement of symptom outcome in schizophrenia, mania, depression, anxiety, side-effects of treatment, and subjective well-being. He is presently the principal or co-supervisor to 6 PhD-students. He is member of the editorial boards in several international journals of psychiatry and is author or co-author of more than 400 papers. He has written and edited books on rating scales.

Erik Lykke Mortensen is trained as a psychologist and is a Professor of Medical Psychology. He has published in many fields of relevance to medical psychology, including clinical and epidemiological studies with a special focus on neuropsychology, psychometrics, mental
disorders and the role of psychological factors in physical disease. His primary contributions have been studies of the influence of prenatal and early postnatal factors on mental and physical development and studies of factors influencing age-related cognitive decline.

Funding information

The first author’s PhD studies are supported by the following private and public foundations: The research foundation for the Capital Region of Denmark, The research foundation of Mental Health Services - Capital Region of Denmark, Helsefonden and TRYG Fonden. None of these have had any influence on the design, content or publication of the present study.

References


Tables and figures

FIGURE 1
Flowchart illustrating the literature search, article in- and exclusion

Abbreviations used in Figure 1:
B: Book
N: Not an intervention study (as defined in method section)
NM: Not a medical intervention study
C: Study on children/adolescents
RM: Reviews on medical treatment of traumatized refugees
RO: Review, other types
S: Study of somatic intervention
SP: Study protocol
INS: Intervention not specified
**Table 1: Overview of included studies**

**Abbreviations used for interventions:**
- CBT: Cognitive behavioral therapy
- TCA: Tricyclic antidepressant
- MAOI: Monoamine oxidase inhibitors
- SSRI: Selective serotonin reuptake inhibitor

**Abbreviations used for rating scales:**
- PSS: PTSD Symptom Scale
- BDI: Beck Depression Inventory
- GAF: Global Assessment of Functioning,
- CAPS: Clinician-Administered PTSD Scale
- HSCL-25: Hopkins Symptom Checklist-25,
- DIS: Diagnostic Interview Schedule
- HDRS: Hamilton Depression Rating Scale
- HTQ: Harvard Trauma Questionnaire
- CED: Center for Epidemiological studies Depression Scale
- PCL: PTSD checklist
- SSI: Cambodian Somatic Symptom and Syndrome Inventory
- SF-12: Short form-12 health survey
- SDS: Sheehan Disability Scale
- CGI-C: Clinician Global Impression-Change

<table>
<thead>
<tr>
<th>Author</th>
<th>Intervention</th>
<th>Participants</th>
<th>Methodology</th>
<th>Evaluation</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smajkic et al (Smajkic et al., 2001)</td>
<td>Sertraline, Paroxetine, and Venlafaxine</td>
<td>N= 32 (completers only)</td>
<td>Non-blinded RCT</td>
<td>PSS</td>
<td>Sertraline and Paroxetine: Significant improvement on all scales</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PTSD Bosnian refugees in Chicago</td>
<td></td>
<td>BDI</td>
<td>Venlafaxine: Significant improvement on PSS and GAF but not on BDI.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>GAF</td>
<td>All remained PTSD positive</td>
</tr>
<tr>
<td>Author</td>
<td>Intervention</td>
<td>Participants</td>
<td>Methodology</td>
<td>Evaluation</td>
<td>Change</td>
</tr>
<tr>
<td>------------------------</td>
<td>------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------</td>
<td>---------------------------------------</td>
<td>-------------------</td>
<td>----------------------------------------------------------------------</td>
</tr>
<tr>
<td>Otto et al (Otto et al., 2003)</td>
<td>Sertraline alone versus Sertraline in combination with CBT</td>
<td>N=10 Khmer speaking women from Cambodia living in the US</td>
<td>Non-blinded RCT</td>
<td>CAPS</td>
<td>Combined treatment groups: Improvement on all scales. The Sertraline alone group: No improvement on the CAPS re-experiencing and hyperarousal items but on all other scales. No confidence intervals or P-values reported.</td>
</tr>
<tr>
<td>Drozdek (Drozdek, 1997)</td>
<td>Antidepressants or psychotherapy alone with antidepressants in combination with psychotherapy</td>
<td>N= 50 Male Bosnian refugees in the Netherlands</td>
<td>Observationel (no randomisation described for group allocation) including 3 year follow up</td>
<td>Watson Questionnaire (PTSD)</td>
<td>No significant association between treatment type and PTSD-symptoms</td>
</tr>
<tr>
<td>Boehnlein et al (J K Boehnlein, Kinzie, Ben, &amp; Fleck, 1985)</td>
<td>Antidepressants (TCA’s and/or MAOI’s), benzodiazepines, propranolol and “supportive therapy”</td>
<td>N= 12 Cambodian refugees living in the US</td>
<td>Observational</td>
<td>PTSD section of DIS</td>
<td>Five patients no longer PTSD positive Three patients improved but still PTSD positive The rest remained the same or got worse</td>
</tr>
<tr>
<td>Boehnlein et al (James K Boehnlein et al., 2004)</td>
<td>Antidepressants (SSRI or a TCA’s), clonidine or Prazozin and supportive psychotherapy</td>
<td>N= 23 Cambodian refugees living in the US</td>
<td>Retrospective 10 year follow up</td>
<td>CAPS HDRS</td>
<td>No baseline scores =&gt; not possible to calculate differences.</td>
</tr>
<tr>
<td>Author</td>
<td>Intervention</td>
<td>Participants</td>
<td>Methodology</td>
<td>Evaluation</td>
<td>Change</td>
</tr>
<tr>
<td>--------</td>
<td>--------------</td>
<td>--------------</td>
<td>-------------</td>
<td>------------</td>
<td>--------</td>
</tr>
<tr>
<td>Kinzie et al (J David Kinzie et al., 2012)</td>
<td>Antidepressants and antipsychotics, psychotherapy and counseling</td>
<td>N=22 Tortured refugees of mixed origin</td>
<td>Observational</td>
<td>HTQ SPRINT (PTSD) CED WHO-Quality of life-Brief SDS Self-invented scale analogue to SDS</td>
<td>HTQ: not reported Other scales: Improvement on all scales for 20 patients. Two did not improve on any scales</td>
</tr>
<tr>
<td>Schwartz-Langer et al (Schwarz-Langer, Deighton, Jerg-Bretzke, Weisker, &amp; Traue, 2006)</td>
<td>Mixed pharmacological treatment, psychotherapy and physiotherapy.</td>
<td>N=13 Refugees from former Yugoslavia, living in Germany</td>
<td>Observational</td>
<td>Therapy protocol changes and interview “post hoc” (not specified exactly when)</td>
<td>Improved sleep in all patients and improvement in intrusive symptoms and hyperarousal in most.</td>
</tr>
<tr>
<td>Frances and Kroll (Frances &amp; Kroll, 1989)</td>
<td>Amitriptyline</td>
<td>N=1 Hmong refugee from Laos</td>
<td>Case study</td>
<td>Qualitative descriptions only</td>
<td>Improvement of depressive symptoms</td>
</tr>
<tr>
<td>Cheung (Cheung, 1993)</td>
<td>Doxepine</td>
<td>N=3 Cambodian refugees</td>
<td>Case study</td>
<td>Qualitative descriptions only</td>
<td>Improvement of symptoms</td>
</tr>
<tr>
<td>Author</td>
<td>Intervention</td>
<td>Participants</td>
<td>Methodology</td>
<td>Evaluation</td>
<td>Change</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-----------------------------------------------</td>
<td>--------------------------------------------------------</td>
<td>---------------------</td>
<td>---------------------------------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>DeMartino et al</td>
<td>MAOI’s</td>
<td>N=5</td>
<td>Case study</td>
<td>Qualitative descriptions only</td>
<td>Improvement of most symptoms</td>
</tr>
<tr>
<td>(DeMartino, Mollica, &amp; Wilk,</td>
<td></td>
<td>Female refugees from Cambodia or Laos</td>
<td></td>
<td>Although rating scales are</td>
<td></td>
</tr>
<tr>
<td>1995)</td>
<td></td>
<td></td>
<td></td>
<td>mentioned scores are not</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>reported.</td>
<td></td>
</tr>
<tr>
<td>Boynton et al</td>
<td>Prazozin (in some patients in combination</td>
<td>N=23</td>
<td>Retrospective chart</td>
<td>CAPS (items on nightmares only)</td>
<td>CAPS Significant decrease</td>
</tr>
<tr>
<td>(Boynton, Bentley, Strachan,</td>
<td>with antidepressants)</td>
<td></td>
<td>review</td>
<td>CGI-C</td>
<td></td>
</tr>
<tr>
<td>Barbato, &amp; Raskind, 2009)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mixed group of refugees living in the US</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boehlein et al (James K</td>
<td>Prazozin</td>
<td>N=2</td>
<td>Case study</td>
<td>Qualitative descriptions only</td>
<td>Improvement of nightmares and other intrusive</td>
</tr>
<tr>
<td>Boehnlein &amp; Kinzie, 2007)</td>
<td></td>
<td>Refugees</td>
<td></td>
<td></td>
<td>PTSD symptoms</td>
</tr>
<tr>
<td>Kinzie et al (J D Kinzie &amp;</td>
<td>TCA and Clonidine</td>
<td>N=12 (9 completers)</td>
<td>Prospective</td>
<td>HDRS</td>
<td>HDRS: Average change from baseline: 16.3 points.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>depression adapted from DSM-III-R</td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Intervention</td>
<td>Participants</td>
<td>Methodology</td>
<td>Evaluation</td>
<td>Change</td>
</tr>
<tr>
<td>--------------------</td>
<td>--------------</td>
<td>----------------------------------</td>
<td>---------------------------</td>
<td>------------------------------------------------</td>
<td>------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Kinzie et al</td>
<td>Clonidine</td>
<td>N=4</td>
<td>Observational pilot study</td>
<td>Polysomnography data and qualitative descriptions</td>
<td>Improvement of PTSD symptoms according to patients but slight decrease of length of sleep measured by polysomnograph</td>
</tr>
<tr>
<td>(J D Kinzie, Sack, &amp; Riley, 1994)</td>
<td></td>
<td>Female refugees from Cambodia</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Paper 2

Treatment of traumatized refugees with Sertraline versus Venlafaxine in combination with psychotherapy – a randomized clinical study
Treatment of traumatized refugees with Sertraline versus Venlafaxine in combination with psychotherapy – study protocol for a randomized clinical trial

Charlotte Sonne1, Jessica Carlson1, Ask Ellit2, Erik Lykke Mortensen3 and Morten Ekstrom1

Abstract

Background: Sufficient evidence is lacking to draw final conclusions on the efficiency of medical and psychological treatments of traumatized refugees with PTSD. The pharmacological treatments of choice today for post-traumatic stress disorder are antidepressants from the subgroup selective serotonin reuptake inhibitors, especially Sertraline. The evidence for the use of selective serotonin reuptake inhibitors in the treatment of complex post-traumatic stress disorder in traumatized refugees is very limited. Venlafaxine is a dual-action antidepressant that works on several pathways in the brain. It influences areas in the brain which are responsible for the enhanced anxiety and hyper-arousal experienced by traumatized refugees and which some studies have found to be enlarged among patients suffering from post-traumatic stress disorder.

Design: This study will include approximately 150 patients, randomized into two different groups treated with either Sertraline or Venlafaxine. Patients in both groups will receive the same manual-based cognitive behavioral therapy, which has been especially adapted to this group of patients. The treatment period will be 6 to 7 months. The trial endpoints will be post-traumatic stress disorder and depressive symptoms and social functioning, all measured on validated rating scales. Furthermore the study will examine the relation between a psycho-social resources and treatment outcome based on 15 different possible outcome predictors.

Discussion: This study is expected to bring forward new knowledge on treatment and clinical evaluation of traumatized refugees and the results are expected to be used in reference programs and clinical guidelines.

Trial registration: ClinicalTrials.gov NCT01569685

Keywords: Refugee, PTSD, Depression, Trauma, Venlafaxine, Sertraline

Background

The treatment of traumatized refugees is one of the least researched areas within the field of psychiatry. Most research on post-traumatic stress disorder (PTSD) and other psychiatric conditions related to traumatic stress have been carried out on victims of other kinds of traumatic experience such as rape, traffic accidents or trauma related to war. There are reasons to believe that mental symptoms experienced after trauma relates to the type and intensity of the trauma. Most traumatic events (traffic accidents, robberies, natural disasters, etc.) are of limited duration. However, many refugees experience more or less constant or repeated trauma for months or even years, such as periods with daily exposure to torture during a long imprisonment. The current PTSD diagnosis often does not fully capture the severe psychological harm that occurs with such prolonged trauma. People such as refugees experiencing long-lasting trauma often report additional symptoms alongside formal PTSD symptoms, such as alterations in emotional control and dissociative symptoms. Although not a formal diagnosis in either the Diagnostic and Statistical Manual of Mental Disorders (DSM)
or the International Classification of Diseases (ICD) diagnostic system, this is often referred to as complex PTSD by clinicians and researchers within the field.

Apart from a history of repeated trauma in their country of origin, the process of forced immigration experienced by refugees is highly traumatic and dramatically impacts the lives of individuals and families [1,2]. It also tears apart the social structures that are often very important to people from highly collectivistic minded societies. Furthermore, the ways of understanding mental health problems often differ from the country of origin to the receiving country. With this in mind, the research results from studies conducted on other patient populations cannot simply be transferred to traumatized refugees. It is therefore problematic that the three available Cochrane analyses of PTSD have only been able to identify very few studies of traumatized refugees [3-5].

The Danish Medical Technology Report (MTV report), The treatment and rehabilitation of PTSD inclusive traumatized refugees [6], concluded that antidepressants from the subgroup of selective serotonin reuptake inhibitors (SSRIs), among these the drug Sertraline, are currently the drugs of choice for the treatment of PTSD. However, the report also concluded that SSRIs are inadequate as a treatment for complex PTSD. Some antidepressants from the subgroup of dual-action products, among these Venlafaxine, have shown promising results in clinical case reports [7] but have not been investigated thoroughly in randomized studies on traumatized refugees. Studies of other groups of PTSD patients conclude that both short-term and long-term Venlafaxine treatment is effective in PTSD [8,9]. Although the exact pathophysiology of PTSD still remains to be fully understood, the brain’s noradrenergic pathways are recognized to be involved. Venlafaxine acts on both serotonin and noradrenergic pathways in many areas in the brain. Among other structures it is believed to play a role in the regulation of the amygdala, which is currently held at least partly responsible for the enhanced anxiety and hyper arousal experienced by traumatized refugees. This gives us reason to believe that this drug could provide greater relief of cluster D PTSD symptoms in particular.

A Cochrane review from 2010 of combined pharmacological and psychological treatment of PTSD included only four studies, all conducted on a very limited number of patients [4]. The authors concluded: Further research into the clinical management of PTSD is required including large trials that use (i) reliable and clinically meaningful outcome measurements such as remission of PTSD, (ii) consistent measures of PTSD symptoms and (iii) functional outcomes, including those related to social and occupational function. Furthermore, the authors called for studies of homogeneous populations such as traumatized refugees.

The latest Cochrane review, as well as the MTV report mentioned above, consider social functioning to be an important issue, which could potentially be a trial endpoint on the same level as symptoms ratings [4,6]. Related to this issue is the current lack of understanding of the relationship between psychosocial resources and treatment outcome.

Objectives
The objectives are to: 1) examine differences in the treatment outcome of patients treated with Venlafaxine and Sertraline respectively; 2) study the relationship between changes in symptoms in PTSD / depression and changes in social functioning from baseline to post treatment evaluation; 3) investigate if pre-treatment ratings of patient resources correlate with the actual outcome of the treatment for the individual patient.

Methods
The study is a randomized clinical trial aiming to include approximately 200 traumatized refugees of which a minimum of 150 are estimated to complete the trial in accordance with the protocol. Patients are randomized into two groups treated with either Sertraline or Venlafaxine in combination with manual-based cognitive therapy, as described below. The treatment period is 6 to 7 months. Treatment outcome is evaluated in two ways, through self-ratings and blinded observer-ratings. Patients complete self-ratings on three occasions during the study, these are at the pre-treatment consultation (baseline), between phase 1 and 2 (please see below), and at the end of the treatment period. Blinded observer-ratings are carried out by a team of trained medical students who do not know to which intervention group the patient has been randomized. These ratings are carried out at the beginning and at the end of the treatment period. The rating scales are described in detail in the outcome section below.

Participants
The study is being carried out at the Psychiatric Trauma Clinic for Refugees (PTF), which is part of the Psychiatric Center Ballerup, situated in the Capital Region of Denmark. The different effects of two medical treatments in combination with psychotherapy are being studied on a relatively homogeneous group of adult (≥18 years of age) traumatized refugees who are referred to the PTF during the study period. Social functioning will be included as one of the trial endpoints and psychosocial predictors and their relation to treatment outcome will be analyzed.

The study will ultimately include approximately 200 patients over a period of 15 months. About 150 patients are expected to complete the study (based on previous studies at the PTF in a similar group of patients).
Patients are either referred to the PTF by their general practitioner (GP) or by a referring doctor in a specialist unit. If it seems likely that the patient belongs to the target group of the clinic, he or she will be invited to a pre-treatment consultation.

**Inclusion criteria**

The inclusion criteria are as follows: patients must be referred to PTF between 1 April 2012 and 31 June 2013; ≥ 18 years of age; have symptoms of PTSD in accordance with the ICD-10 research criteria; have had psychological trauma in the past; be motivated to undergo treatment; provide written informed consent.

**Exclusion criteria**

Patients will be excluded if they are suffering from serious psychotic disorder (defined by ICD-10 diagnosis F20 and F30.1-F30.9); are currently abusing drugs or alcohol (ICD-10 F1.1x-24-F1.x26); are in need of admission to a psychiatric hospital; do not give written informed consent, or are pregnant, breast feeding or plan to become pregnant during the project period.

If the patient fulfills the inclusion criteria, and is not excluded by the exclusion criteria, the patient is included and randomized to one of two intervention groups:

**Treatment groups**

Group V1 is assigned to treatment with Venlafaxine and manualised psychotherapy developed to fit the target group of the clinic. Group S2 is assigned to treatment with Sertraline and manualised psychotherapy developed to fit the target group of the clinic. In both groups treatment is planned to last between 6 and 7 months. The treatment and the ratings are shown in Figure 1. The different parts of the intervention are described in detail below.

**The intervention**

The intervention consists of a combination of medical, psychological and psychosocial treatment and is divided into two phases. During phase 1 (the first 2 months) the patient only has consultations with the doctor and receives no psychological treatment. During phase 2 (the last 4 months) the patient has sessions with both the doctor and the psychologist as described below. The patient meets with the social counsellor at least twice during the study period. If extra consultations are agreed, these are registered in the patient record (for example, if there are medical or psychosocial problems that need immediate attention).

**Medical intervention**

Each patient is offered 10 sessions with one of the medical doctors at the PTF. Sessions are scheduled to take place weekly during phase 1 and monthly during phase 2. During these sessions the medical treatment of the randomized group is initiated and monitored. If the patient suffers from extensive sleeping problems, Mianserin (10 to 30 mg) is given additionally in both groups. If at all possible, patients are taken off all other kinds of psychopharmacological treatment. In small doses Mianserin is believed to act primarily on sleep disturbances, not on symptoms of depression. Furthermore, Mianserin is given for the same indication in both groups of patients. Mianserin should not affect our ability to analyze differences in treatment response for Sertraline and Venlafaxine.
respectively, as there is no pharmacoological reason to believe that Mianserin interacts differently with either of the two drugs being compared in this trial.

In addition to the medical treatment, the patients receive psycho-education on topics such as symptoms of PTSD and depression, the rationale for treatment, healthy lifestyle, including exercise and proper diet, breathing and relaxation exercises, sleep disturbances, and chronic pain. Twelve different one-page handouts are available at PTf on a range of these topics (in five different languages). They are given to the patients to take home when a topic has been discussed during a treatment session. The patient and the doctor together decide the relevant topic for each session.

The medical and psycho-educational treatment is thoroughly described in a treatment manual followed by all doctors. The main topic of each session is registered in the patient record together with side effects of the treatment and any social problems that the patient has. Furthermore, a brief psychiatric evaluation is carried out by the doctor and noted using a tick-box system developed at PTf and used in previous studies.

Psychological intervention

Each patient is offered one introductory session and sixteen therapeutic sessions with a psychologist. The introduction session is in phase I, before or right at the beginning of the treatment period. The remaining sessions take place during phase 2.

All therapy is based on the same manual, which is primarily based on cognitive therapy with elements of trauma-focused therapy, acceptance commitment therapy (ACT), and mindfulness. The methods have been adapted to this patient group on the basis of the available literature and on experience of the three manuals previously used at the clinic.

After each session the therapist fills in a methodology scheme in the patient record, whereby registering the methods that were used during the session and whether the patient had completed planned homework. All psychologists regularly attend manual supervision sessions to ensure that therapy is in accordance with the manual and to avoid too much inter-therapist variation.

Psycho-social intervention

All patients are offered at least two appointments with a social counsellor during the project period: one at the beginning and one towards the end of the treatment. During these sessions patients are asked to complete two self-ratings that are related to social functioning and network; these are further described below. After the first session the social counsellor writes a letter to the patient's contact at the social services office describing the social problems that the patient might have. All contacts to external parties, including the patient's relatives, are registered in the patient record.

Group lectures

Group lectures are offered to all patients once a month. Three different lectures are offered, one on each of the following topics: the structure of the Danish municipal administration and social services, advice on financial debt and the tax system, and citizenship and possibilities for support and social activities. As lectures are offered every month in a fixed rotation the patients have two possibilities to attend each of the different lectures during a 6-month period.

Outcome

Data collection combines self-ratings and observer-ratings. Patients are asked to fill in self-ratings three times: at their first appointment at PTf (baseline), immediately before they start on phase 2, and at the end of the treatment period. Patients and doctors are not treatment-blinded, but a team of specially trained intervention-blinded medical students are carrying out Hamilton anxiety and depression ratings at baseline and at completion of the treatment. Interpreters assist the patients during both ratings and treatment sessions when needed. All the rating scales used in the study are validated and have previously been used in different cultural settings. At PTf they are available in five different languages.

Primary outcome measure

The Harva trauma questionnaire (HTQ) [10] is a self-administered rating scale used to monitor the severity of PTSD in different patient groups, among these, groups of traumatized refugees. It is internationally recognized and validated in several different languages. The first 16 questions in the HTQ part IV (symptoms) have been chosen to monitor PTSD symptoms, as they cover all PTSD symptoms in both DSM-IV and ICD-10.

Secondary outcome measures

The Hopkins symptom check list-25 (HSCL-25) [11] is a self-administered rating scale used to monitor the severity of anxiety and depression symptoms. It consists of 25 questions, 10 about anxiety symptoms and 15 about depression symptoms. The social adjustment scale self-report (SAS-SR) short version [12] is a self-administered rating scale used to monitor social functioning during treatment. It is a shorter version of a 54-question rating scale. The short form used in this study consists of 24 questions. The Hamilton depression and anxiety ratings scales (HAM-D-A) [13] are observer-administered rating scales based on a semi-structured interview. They have been used for many years in different areas of
psychiatry to monitor progression in depression and anxiety symptoms.

**Other psychometric instruments used in the study**

The following instruments were used: the WHO-5, a five-item self-administered rating scale used to monitor quality of life in different groups of psychiatric patients; the somatisation items of Symptom Check List-90 (SCL-90), a self-administered rating scale broadly used in the psychiatric field, using the part of the scale that monitors somatic complaints; pain in four different body areas measured using a visual analogue scale (VAS), a self-administered rating scale used to monitor pain in four different body areas, namely the head, arms, legs and neck/back; the Sheehan disability scale (SDS), a self-administered rating scale comprising three different VAS scales used to measure three different areas of functioning, namely family life, work and social networks; global assessment of functioning (GAF), an observer-administered rating scale used to evaluate symptoms and functioning level in adults. In clinical settings the GAF is used to monitor treatment effect in many different groups of psychiatric patients; goal attainment scaling (GAS), which is used to make the individual patient state his/her own measures for successful treatment outcome in a way that makes it possible to use it for treatment evaluation, and finally, the crisis support scale (CSS), a seven-item self-rating scale used to monitor the social support experienced after a traumatic event in different groups of PTSD patients.

**Psycho-social resources and relation to treatment outcome**

If a patient agrees to participate in the treatment program a ratings table (Figure 2) is completed in accordance with a manual explaining the rating of each item, to secure inter-rater reliability. This is done during the first session with the patient, which is scheduled before the actual treatment or at the beginning of the treatment program. The doctor completes the first five questions, the psychologist completes the next five, and the last five questions.

![Table: Rating of psychosocial resources in patients at PTF](image)

<table>
<thead>
<tr>
<th>Medical Areas</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Residence</td>
<td></td>
</tr>
<tr>
<td>Lightning</td>
<td></td>
</tr>
<tr>
<td>Recent treatment practice carried out without measurable effect</td>
<td></td>
</tr>
<tr>
<td>Chronic pain</td>
<td></td>
</tr>
<tr>
<td>Chronic psychiatric conditions</td>
<td></td>
</tr>
<tr>
<td>Psychiatric</td>
<td>Date</td>
</tr>
<tr>
<td>Understanding of the concept of therapy</td>
<td></td>
</tr>
<tr>
<td>Acceptability towards psychological treatment</td>
<td></td>
</tr>
<tr>
<td>Ability of medical indication</td>
<td></td>
</tr>
<tr>
<td>Motivation for active participation</td>
<td></td>
</tr>
<tr>
<td>Cognitive resources</td>
<td></td>
</tr>
<tr>
<td>Social contacts</td>
<td>Date</td>
</tr>
<tr>
<td>Personal relation</td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td></td>
</tr>
<tr>
<td>Housing</td>
<td></td>
</tr>
<tr>
<td>Work</td>
<td></td>
</tr>
<tr>
<td>Integration</td>
<td></td>
</tr>
</tbody>
</table>

Figure 2 Rating of psychosocial resources in patients at the Psychiatric Trauma Clinic for Refugees.
are completed by the social counselor. Based on the score, the patients are divided into three groups: high, moderate or limited psychosocial resources. These groups are not to be confused with the treatment groups.

The purpose of this part of the study is to investigate associations between psychosocial resources and treatment outcome. Consequently, after completed treatment, the patients are again divided into three groups, but this time in accordance with outcome (high, moderate or limited) measured by the primary outcome measure of the study. The psychosocial resource categorization is then compared with the outcome categorization in order to analyze whether there is a relation between psychosocial resources and the ability to benefit from the treatment. Furthermore, the individual rating items are analyzed to identify the strongest outcome predictors.

Randomization
The randomization list is made by the Biostatistics Department at the University of Copenhagen, while the randomization of the individual patient is carried out by a group of secretaries in a division of the Psychiatric Center in Ballerup that is independent of the PTF. Before randomization, stratification is made by gender and baseline HTQ score.

Data analysis
Sample size and power calculations
If the included 150 patients are divided into two groups of equal size, the power to detect a group difference of half of 1 SD on the rating scales will be 86%, while the power to detect a difference of 1 SD will be close to 100%. Differences of less than half of 1 SD are considered to be of marginal interest from a clinical point of view.

Statistical analysis
For analysis of objective 1, the outcome variables are the baseline, second and third ratings in both the primary and secondary outcome measures. With two intervention groups and three ratings, the design of the study may be described as a 2 x 3 factorial design with repeated measures of the last factor. Analysis of variance (ANOVA) with repeated measures of one factor can be used to analyze this design, but multi-level analysis will be more efficient if there are missing observations on one or more of the three ratings. In these analyses the main effect of the rating factor represent changes during the course of therapy, but the main focus is the interaction between the group and rating factor, corresponding to group differences in patterns of mean ratings. If differences between groups are calculated between the three ratings, group differences in differences scores correspond to this interaction. Group differences in multiple difference variables can be analyzed by multivariate analysis of variance (MANOVA), while single difference variables (for example, between the third rating and the baseline score) can be tested with a t-test for independent groups. Adjustments for the effect of baseline values on outcome variables and background factors (such as gender and age) can be done using analysis of covariance (ANCOVA)/linear regression, including multi-level models. Intention-to-treat analyses will be carried out alongside complete analyses.

For analysis of objective 2, the relationship between changes in social functioning and changes in symptoms can be calculated by bivariate or partial correlations, if adjustments are made for baseline or background factors as described above. For objective 3, from the baseline predictor table patients are divided into three groups according to the predicted treatment outcome and using relevant statistical methods. This categorization is compared with a categorization based on the actual treatment outcome. The degree of concordance can be evaluated with kappa coefficients or correlation coefficients based on the uncategorized ordinal measures of predicted and actual treatment outcome.

Ethics
The trial protocol has been approved by The Ethics Committee of the Capital Region of Denmark, the Danish Medicines Agency and the Danish Data Protection Agency. The project recognizes the Helsinki II Declaration. Participation in the project is voluntary and requires written, informed consent. Patients who do not wish to participate in the project still have the right to receive equal treatment at the PTF. Randomization is considered ethical, as current evidence cannot clarify whether one of the treatments offered to the patients is better than the other.

Publications
Three publications are planned after the conclusion of the data collection to describe 1) the effect of Sertraline versus Venlafaxine on trauma-related psychiatric disorder in refugees; 2) changes in social functioning in relation to PTSD and depression symptoms during a six-month treatment program for traumatized refugees, and 3) the relationship between psychosocial resources and treatment outcome in traumatized refugees.

Trial status
Patient inclusion in this trial started on 1 April 2012 and is scheduled to continue until 31 June 2013.

Abbreviations
ACT: acceptance and commitment therapy; ANCOVA: analysis of covariance; ANOVA: analysis of variance; CGI-C: clinical global impression; GAS: global assessment of functioning; GAS: goal attainment scaling; HAM-A: Hamilton anxiety scale;
FVT-10: Hamilton depression scale; HAM-D: Hamilton depression scale; HSC: Hopkins symptom checklist; HSR: Hopkins symptom checklist; ICD: International classification of diseases; MED: Medical Endpoints; MINAS: Minnesota multiphasic personality inventory; MMPI: Minnesota multiphasic personality inventory; PCL: PTSD; PTSD: post-traumatic stress disorder; SST: Self report of PTSD; TSS: Test screen; VAS: visual analog scale.

Competing interests
The authors CJS, JG, JS, AE, and ELM hereby declare that they have no competing interests.

Authors’ contributions
CS is the primary investigator of the study, designed the study and is the primary author of the protocol as well as this manuscript. JG is a co-investigator in the study, participated in the design of the study and helped to draft the protocol and this manuscript. AE helped to draft the protocol and has revised the manuscript critically. AE and ELM have been involved in the design of the study and helped to draft the protocol and the manuscript. A final reading and approved the final manuscript.

Acknowledgements
Acknowledgement is given to the clinical staff at the PTF for their contributions through the process of designing and implementing this study and the manuscript used in the treatment program; Janina Bjerg, Per Bents, Carlette Hoppenau, Niels Vinding, Christina Klimberg, Patrick Termut, Ina Paradisi, Vibe Schioldansen and Josephine Thomas.

Author details
1. Psychiatric Trauma Clinic for Refugees, Gretenro Hospital, c/o 3D, st. Veis Andersenvej 60, 2900 Hellerup, National Center for Psychiatry and Mental Health, Denmark, and Institute of Public Health and Center for Health Aging, University of Copenhagen, Øster Farimagsgade 5, 1353 Copenhagen K, Denmark.

Received: 18 October 2012 Accepted: 26 April 2013
Published: 11 May 2013

References

Paper 3

Treatment of trauma-affected refugees with venlafaxine versus sertraline combined with psychotherapy – a randomised study

Authors

**Charlotte Sonne** (corresponding author)
Competence Centre for Transcultural Psychiatry
University of Southern Denmark
Maglevaenget 2
2750 Ballerup
Denmark
Email: charlotte.sonne@regionh.dk
Phone: +45 3864 5178

**Jessica Carlsson**
Competence Centre for Transcultural Psychiatry
Mental Health Centre Ballerup
Maglevaenget 2
2750 Ballerup
Denmark
Email: jessica.carlsson.01@regionh.dk

**Ask Elklit**
University of Southern Denmark
National Center for Psychotraumatology
Campusvej 55
5230 Odense
Denmark
Email: aelklit@health.sdu.dk

**Per Bech**
Mental Health Centre North Zealand
University of Copenhagen
Dyrehavevej 48
3400 Hillerød
Denmark
Email: per.bech@regionh.dk

**Erik Lykke Mortensen**
Institute of Public Health and Center for Healthy Aging
University of Copenhagen
Øster Farimagsgade 5
1353 København K
Denmark
Email: elme@sund.ku.dk
Abstract

Objective: To examine differences in effect of venlafaxine and sertraline on Post-traumatic Stress Disorder (PTSD), depression and functional impairments in trauma-affected refugees.

Method: The study was a randomised pragmatic trial comparing venlafaxine and sertraline in combination with psychotherapy and social counselling. PTSD symptoms measured on the Harvard Trauma Questionnaire – part IV was the primary outcome measure. Other outcome measures included: Hopkins Symptom Check List-25, Social Adjustment Scale – short version, WHO-5 Well-being Index, Crisis Support Scale, Sheehan Disability Scale, Hamilton Depression and Anxiety scale, the somatisation items of the Symptoms Checklist-90, Global Assessment of Functioning scales and pain in four body areas rated on visual analogue scales.

Results: 207 patients were included in the trial (98 in venlafaxine and 109 in sertraline group). Of these, 195 patients were eligible for intention-to-treat analyses. Small but significant baseline to follow-up differences were found on the Harvard Trauma Questionnaire and a number of other ratings for both groups. No difference in treatment effect between the sertraline and venlafaxine group was found on the primary outcome measure, the Harvard Trauma Questionnaire. The Sheehan Disability Scale, WHO-5 and the visual analogue scale for leg pain displayed significant / borderline significant group differences, all in favour of sertraline.

Conclusion: Sertraline had a slightly better outcome than venlafaxine on several secondary outcome measures, but not on the primary outcome measure. Selective Serotonin Reuptake Inhibitors (SSRI) are recommended by the authors as first line pharmacological treatment for trauma-affected refugees.
Trial Registration: ClinicalTrials.gov NCT01569685

**Keywords:** Refugee; venlafaxine; sertraline; Stress Disorders, Post-Traumatic
Introduction

Despite a rapidly increasing amount of studies on the treatment of Post-Traumatic Stress Disorder (PTSD) in general, only few intervention studies have been carried out on the pharmacological treatment of trauma-affected refugees [1,2]. Therefore, clinical guidelines for the treatment of PTSD are based on reviews and meta-analyses which mainly include studies on non-refugee PTSD populations [3–6]. The single existent Cochrane review on combined pharmacotherapy and psychological treatment methods in patients with PTSD [5] identified only four studies that could be included in the review. These studies were all conducted on fairly small patient groups (the largest group had 65 participants for randomisation), and only one very small study (n=10) included refugees. The authors concluded that further research into the clinical management of PTSD was required, including trials with larger number of patients, using reliable and clinically meaningful outcome measurements such as remission of PTSD and functional outcomes. In addition, the authors called for studies of more homogeneous patient populations. While research on other groups of PTSD patients has burgeoned since, intervention studies concerning trauma-affected refugees are still limited in number and quality, and the vast majority are on psychological interventions only [7,8].

When the present study was designed, the only official Danish guideline for the treatment of PTSD was the Danish Medical Technology report (MTV) “The treatment and rehabilitation of PTSD including traumatised refugees” from 2008 [9]. It concluded that selective serotonin reuptake inhibitors (SSRI), including the drug sertraline, were the best-documented pharmacological treatment of PTSD. However, both the MTV report and a Cochrane review on
pharmacological treatment concluded that more trials are needed on patients with treatment refractory PTSD, such as that of many refugees, because SSRI seemed to be inadequate for these patients [6,9]. Several studies of the pharmacological treatment of PTSD on other groups of trauma-affected patients have pointed towards the selective Serotonin-Noradrenaline reuptake inhibitor venlafaxine as an alternative treatment option [3]. However, the results from studies on non-refugee patients cannot be uncritically transferred to trauma-affected refugees due to a range of differences in biomedical and psycho-social profiles as well as trauma history [2,10].

To the best of our knowledge, only one study has investigated the use of venlafaxine in trauma-affected refugees [11]. This open-label study, with a total number of 32 participants (5 in venlafaxine treatment), compared sertraline, paroxetine, and venlafaxine. All 3 antidepressants produced statistically significant improvement by week 6 in PTSD symptom severity (PTSD Symptoms Scale) while venlafaxine seemed to be less effective than the two other drugs in reducing symptoms of depression. However, the study had quite a few methodological problems (e.g. small groups sizes, gender imbalance among treatment groups, short study period, no intention-to-treat analyses), making results questionable.

Aim of the study

As stated above venlafaxine had shown promising results in non-refugee PTSD populations but had only been compared to SSRI in one small refugee study of limited quality. On this background, we found it appropriate to test the effects of venlafaxine versus an SSRI in a larger randomised trial in order to determine its effect in trauma-affected refugees. We therefore
designed a randomised clinical trial comparing venlafaxine with sertraline, which was the standard treatment at the Competence Centre for Transcultural Psychiatry, where the study was performed. The aim of the study was to examine differences in the effectiveness of venlafaxine and sertraline in reducing PTSD/depression symptoms and functional impairments in a group of trauma-affected refugees referred to treatment at the Competence Centre for Transcultural Psychiatry.

**Material and methods**

The trial was a randomised 2-armed pragmatic trial using sertraline as an active control to venlafaxine. In both groups a combination with manualised psychotherapy and social counselling were included. The method is described thoroughly below. Additionally, a protocol paper has been published previously [12].

**Participants**

The Competence Centre for Transcultural Psychiatry (CTP) is a highly specialised transcultural psychiatric outpatient facility situated in the Capital Region of Denmark. The largest patient group is refugees with trauma-related mental health problems, but migrants with other mental health problems are also treated at the clinic. Participants in the present study were recruited from the total group of patients who had their first appointment at CTP between April 2012 and September 2013. Patients were invited to 1-2 hour pre-treatment interviews with one of the clinic’s medical doctors in order to obtain psychiatric, medical, and trauma history, and to evaluate whether the patient belonged to the study target group and was motivated for treatment. If the patient fulfilled all inclusion but no exclusion criteria and gave written
informed consent, the patient was included in the study and randomised to one of the two treatment groups. Inclusion criteria were: being a refugee or family reunified to a refugee, being 18 years or above, having a history of at least one severe psychological trauma, fulfilling the diagnosis of PTSD and/or depression according to ICD-10 research criteria [13], being motivated for treatment, and giving informed consent to participate in the study. Exclusion criteria were: an ICD-10 F2x or bipolar diagnosis, current abuse of drugs or alcohol, in need of acute admission to a psychiatric hospital, being pregnant or breastfeeding or being a woman in the reproductive age with a wish to conceive during the project period.

The PTSD, depression and enduring personality change after catastrophic experience diagnoses were determined through a clinical interview by one of the CTP doctors, where ICD-10 criteria for each of the diagnoses were entered in a diagnostic algorithm. Psychotic and bipolar disorders were excluded using parts of the SCAN interview and all doctors performing these interviews were certified SCAN raters. Chapter 1 and 14 were used for screening, chapter 10 for excluding bipolar disorders and chapter 16-19 for excluding psychotic disorders. Trauma-related psychotic symptoms were not an exclusion criterion, as these are relatively common in this patient group and it was therefore registered in the patient file whether the content of the psychotic feature was related to the patient’s past trauma [14,15].

Patients were systematically enquired about their use of drugs and alcohol and this was registered in the patient file. Objective measures such as an alcohol breath tester were available, but were only used in cases were the clinician suspected that the patient were being dishonest about current abuse.
Patients who fulfilled the inclusion criteria, but did not wish to participate in the study, were offered the clinic’s treatment as usual (TAU), which was similar to the treatment provided to the sertraline group. If patients did not want pharmacological treatment, it was still possible to receive treatment but, for obvious reasons, not possible to participate in the study.

**Randomisation and blinding**

Randomisation by envelopes was performed, stratified by gender and level of severity of PTSD symptoms on the basis of Harvard Trauma Questionnaire (HTQ). The randomisation list was made by the Department of Biostatistics at the University of Copenhagen. The envelopes were administered by a group of secretaries at the central administration at the Mental Health Centre Ballerup who had no other contact with the clinical staff at CTP during the study.

Neither doctors nor patients were blinded in this study, while the raters administering the Hamilton Depression Scale (HAM-D) and the Hamilton Anxiety Scale (HAM-A) (please see below) were blinded to the time of the interview (baseline or follow-up interview) and to the intervention group. A team of medical students trained at CTP were administering the Hamilton scales. Inter-rater reliability was maximised by group ratings every 6-8 weeks.

**The intervention**

The study compared a venlafaxine group with a sertraline group. For both groups, the treatment programme was planned to last 6-7 months. Patients in both groups were offered a total of 10 sessions with a psychiatrist /medical doctor (in the rest of this article referred to as doctor) and 16 sessions with a psychologist. All patients were offered a session with a social worker at the
beginning and end of the treatment programme and, if needed, during the treatment programme as well. Furthermore, it was possible for the patients to participate in group meetings with the social worker once a month. For all patients, the exact numbers of consultations as well as theme(s) of the session were registered at each consultation using a tick box sheet in accordance with the Treatment and Research Integrated Model (TRIM) used at CTP [14].

*The venlafaxine group*

Venlafaxine was given as slow-release tablets. The start dosage was 37.5-75 mg/day. For the first six weeks (phase 1), doctors aimed to see patients weekly and gradually increased the dosage by 37.5-75 mg at each consultation if tolerated by the patient. During phase 2 (the remaining part of the treatment programme), patients met with their doctor approximately once a month. If side effects did not prohibit, dosage was increased at these visits. The dosage could be increased up to the maximum recommended daily dosage of 375 mg/day.

*The sertraline group*

At the time of the study, sertraline was first-line of pharmacological treatment at CTP. The recommended start dosage was 25-50 mg. Like the V1 group, patients in the S2 group met with the doctor once a week during phase 1 and once a month during phase 2. Sertraline dosage was increased gradually by 25-50 mg per week for the first 6 weeks, and then adjusted once a month to a maximum of 200 mg/day.
Patients in both groups were instructed to take the prescribed medicine daily unless intolerable side effects occurred, in which case they should contact their medical doctor at CTP immediately. In addition to the trial medicine, all patients were offered supplementary treatment with mianserin if they suffered from severe sleep disturbances, which is the case for many patients with PTSD. Although no patients with a psychotic disorder were included in the study, some patients did suffer from trauma-related psychotic symptoms. If treatment with antipsychotic drugs was necessary from a clinically point of view, the patient would either continue with the antipsychotic treatment he/she was already receiving or start treatment with perphenazine. However, during the study period, perphenazine was taken off the Danish pharmaceutical market and we therefore decided to replace it with quetiapine in accordance with the recommendation for first line antipsychotic treatment in the clinical guidelines for the Capital Region of Denmark at the time being. As CTP kept a stock of perphenazine for almost the entire remaining study period, it is however estimated that only a very limited number of patients were affected by this change.

Whenever possible, patients were gradually taken off any other psychopharmacological treatments they received when entering the study. All these psychotropics were given free of charge by the clinic to the patient during the entire treatment programme regardless of whether they were participating in the study or not.

**Compliance**

Compliance is one of the major issues in most pharmaceutical studies with refugees and immigrants. Despite many attempts to secure compliance (written instructions in the patient’s
own language, medical cards etc.), it was expected that many patients would have periods of poor compliance when, for example, running out of medicine, misunderstanding the dose or terminating pharmacological treatment without consulting the staff at the clinic.

Since frequent collection of blood samples could have a negative effect on the mental health of a patient group with a substantial amount of torture survivors, compliance was instead measured by pill count at each consultation with the doctor. If patients forgot to bring their medication to the consultation, this was noted in the patient file and days of compliance were then calculated as the medical possession ratio (the number of days for which the patients had sufficient medicine) during the data management phase of the study. If patients had at least eight consecutive weeks of pharmacological compliance during the study period they were defined as completers of the pharmacological part of the treatment programme.

**Measurements**

The treatment outcome was measured by a combination of non-blinded self-report ratings and blinded observer ratings. The primary outcome measure was self-reported PTSD symptoms assessed using the Harvard Trauma Questionnaire (HTQ), which has been developed primarily for trauma-affected refugees and validated in several languages and settings [15,16]. Secondary outcome measures included depression and anxiety symptoms measured on the Hopkins Symptom Check List-25 (HSCL-25) [17] and on the Hamilton Depression and Anxiety Ratings Scales (HAM-D+A) [19], social functioning measured on the Social Adjustment Scale Self Report (SAS-SR) short version [18], social support assessed on the Crisis Support Scale (CSS) [20] level of functioning assessed on the Sheehan Disability Scale (SDS) [21], quality of life assessed on the
WHO-Five Well-being Index (WHO-5) [22], the somatisation scale of SCL-90, pain in four
different body areas rated on Visual Analogue Scales (VAS) and levels of symptoms and
functioning assessed on the Global Assessment of Functioning (GAF) [23]. These measures were
all self-report ratings except the GAF-scores, which were completed by the doctor in charge of
the treatment and the HAM D+A which were completed by blinded assessors as described
above.

All self-report ratings were available in 5 languages: Danish, English, Farsi, Bosnian, and Arabic.
Some of the ratings were available in Russian as well. Apart from SAS-SR short version and CSS
all outcome measures were used in previous randomised clinical trials at the clinic and were
translated and implemented before this study commenced. In cases without a validated
translation, a translated version was produced by standard translation and back-translation
procedures. Whenever needed during ratings or treatment sessions, patients were assisted by
a professional interpreter if they wished so.

Patients completed most self-report ratings three times during the study: At the pre-treatment
interview (baseline rating), right before starting psychotherapy, and at the end of the treatment
programme (follow-up rating). If the pre-treatment interview was conducted more than two
months before the patient’s first consultation with a doctor, a new rating was conducted at the
first treatment session with the doctor and this new rating was then used as the baseline rating.
SAS-SR and CSS were completed twice during the study: at the first and last consultation with
the social counsellor. The blinded Hamilton interviews were also carried out twice: at the
beginning and the end of the treatment programme.
Study approval and monitoring

The study was approved by the local ethics committee (H-3-2012-020), The Danish Medicines Agency (2011-006228-19.) and the Danish Data Protection Agency (2007-58-0015). The study was furthermore monitored by the Good Clinical Practice (GCP) Unit at Copenhagen University Hospital.

Data management and statistics

Data was entered into the clinic’s Access database twice and discrepancies corrected according to the case record files. Scores on rating scales were recorded as missing if more than half of the scale items were unanswered. Analyses were performed using STATA 14.

Baseline data were analysed for group differences using chi-square and t tests. Differences between follow-up and baseline were analysed using paired t tests on those of the patients who had completed a follow-up rating. The primary analyses of post-treatment differences between the sertraline and venlafaxine groups were regression models that included baseline scores on each rating scale and an indicator variable for treatment group as predictors and the score on the rating scale as outcome. To conduct intention-to-treat analyses the regression analyses were conducted using Full Information Maximum Likelihood (FIML) which incorporates all available information including pre-treatment scores for patients without post-treatment scores. The structural equation modeling procedure “sem” of Stata 14 was used to conduct these analyses with robust standard errors.
Results

Participants

From 1 April 2012 until 15 September 2013 a total of 407 patients were screened for the trial: 124 did not fulfil criteria for treatment at CTP, 10 did not fulfil inclusion criteria for the study, 10 were excluded due to exclusion specified criteria, and 55 did not sign informed consent to participate in the study. The remaining 207 patients gave informed consent to participate in the study and were randomised – 98 to the venlafaxine group and 109 to the sertraline group. The last patient finalised treatment in September 2014. Participants’ flow through the trial is depicted in figure 1. Baseline characteristics for the two groups, including sociodemographic data, trauma history, and psychiatric diagnoses, are illustrated in Table 1. Almost 99% of the patients had comorbid depression and a little more than 40% was diagnosed with enduring personality change after catastrophic experience (F.62.0). Almost 12% were registered as having another comorbid psychiatric disorder of which not all were however specified in accordance with ICD-10 in the patient files. The vast majority of the diagnoses were anxiety disorders, with generalised anxiety (F.41.1) being the most frequent.

None of the analysed variables differed significantly between groups, although there was a borderline significant difference in distribution of torture survivors (p=0.054).

Attrition and compliance with treatment programme

Twelve patients (seven patients in the venlafaxine group and five in the sertraline group) were excluded from the study: four due to pregnancy, two due to hospital admissions (one to
psychiatric and one to somatic ward), one was wrongly included in the study (was not a refugee), one moved to another part of Denmark, two changed their minds about initiating treatment at CTP and two withdrew informed consent. Accordingly, 195 patients (94.2%) were available for intention-to-treat analyses.

A total group of 156 patients (75.4%) completed minimum 8 weeks of pharmacological treatment in accordance with the group to which they were randomised (n = 68 in the venlafaxine group and n = 88 in the sertraline group). The majority of the non-completers did take the allocated antidepressants during part of the treatment programme but either stopped before 8 weeks or took their medication irregularly during large parts of the treatment programme. Reasons reported for not completing 8 weeks of pharmacological treatment included dropping out of the CTP treatment programme (n=17), side effects to medication (n=10), not wanting pharmacological treatment after all (n=3) or not wanting to change present medication to allocated antidepressant (n=1). No reasons were reported for the rest of the non-completers.

**Pharmacological side effects**

As mild side effects are common for both venlafaxine and sertraline, it was expected that many patients would have side effects during parts of the study, which was also the case according to clinicians’ reports. Changes in the patients’ physical condition were registered at each medical doctor session, but only unexpected or serious events/side effects were systematically collected and reported to the ethics committee and the Danish Medicines Agency in accordance with Danish legislation at the time being.
Only ten patients withdrew from the trial because of side effects while three patients had to switch drugs during the trial: two did not tolerate venlafaxine but did tolerate sertraline and one only tolerated venlafaxine. These three patients were kept in the group to which they were randomised during the intention-to-treat analyses.

**Treatment**

Patients received a mean number of eight medical doctor sessions, 10 psychologist sessions and two social worker sessions with no significant differences between the two groups. Mean treatment length was 6.3 months. Mean dose of sertraline was 96.21 mg and mean dose of venlafaxine was 125.41 mg. A total number of 63 patients (69.23%) in the venlafaxine group and 80 patients (76.92%) received add-on mianserin at some point during the study with a mean dose of 13.57 mg (no significant group difference). A total of 19 patients in the venlafaxine group (20.88%) and 23 patients in the sertraline group (22.12%) received treatment with antipsychotics at some point, although many of these were phased out during the study.

**Outcomes**

*Differences between baseline and follow-up*

Table 2 illustrates the differences between baseline and follow-up for those of the patients in the intention-to-treat sample that had completed ratings both at baseline and at follow-up. The primary outcome measure HTQ was completed both at baseline and follow-up by 154 patients. For the other ratings, the number of patients who had completed the rating at both baseline and follow-up ranged between 123 (GAF-F) and 158 (HAM-D).
We found small but significant improvements in both the sertraline and the venlafaxine group on the primary outcome measure HTQ as well as on a number of other ratings: HSCL-25, SAS-SR, GAF-S and GAF-F. For the WHO-5 we found a significant improvement for the sertraline group only and on the blinded Hamilton ratings, there was a borderline significant improvement on the HAM-D, also in favour of the sertraline group (p=0.054). On the Sheehan Disability Scale, we found a significant improvement for the sertraline group, but a non-significant deterioration for the venlafaxine group. As for the VAS pain scales, we found no significant changes except on the VAS-arm for venlafaxine, where we found a significant deterioration.

Differences in effects between groups

Table 3 illustrates the group differences between the sertraline and venlafaxine group in the intention-to-treat sample analysed with Full Information Maximum Likelihood, which means that we were able to use data from all 195 patients included in the intention-to-treat sample. No significant treatment difference was found on the primary outcome measures. On the other outcome measures, we found a significant group difference on SDS only and borderline significant differences between the treatment groups on VAS-leg (p=0.053) and WHO-5 (p=0.07). These group differences were all in favour of sertraline.

Discussion

Our study is the largest study ever comparing different pharmacological treatment options for trauma-related psychiatric disorders among refugees. We found no statistically significant group differences on the primary or secondary outcome measures but found a significant difference on the SDS (level of functioning). Borderline significant differences were found on WHO-5
(quality of life) and on the VAS scale for leg pain. All these differences were in favour of sertraline. The relatively large number of outcome measures in this study implies a risk of random findings of significant group differences which will statically be the case with 5% of the findings when a significance level of $p = 0.05$ is applied. We however found a fairly consistent tendency throughout ratings for the sertraline group having a slightly better outcome, even where no statistically significant difference was identified which makes it less likely that the findings are random.

The most recent meta-analysis on mixed groups of PTSD patients has found the evidence for the effect of venlafaxine to be superior to that of sertraline [24]. Similarly, a meta-analysis from 2012 found a larger effect of venlafaxine on CAPS [25]. The fact that our study was not able to reproduce this finding could be due to a range of factors. One likely explanation could be the relatively low mean dose of venlafaxine that the patients received in the present study.

Venlafaxine’s effect on noradrenaline reuptake is dose-dependent starting on doses of around 225mg daily. When the daily dose is lower, it acts on serotonin reuptake only, like a common SSRI [25,26]. Other studies have furthermore suggested that there are biological differences between Caucasians and people from the Middle Eastern areas, including the percentage of fast metabolisers being substantially larger among Middle Eastern patients [10]. It is, however, also a possibility that the true differences between the effectiveness of sertraline and venlafaxine in treating PTSD are rather small as another meta-analysis from 2013 found only little difference in effect sizes [3].

During the study changes in the patients’ physical condition were registered at each medical doctor session, but only unexpected or serious events/side effects were systematically collected.
and reported. Therefore we cannot for certain conclude if side-effects occurred more frequent in the venlafaxine than in the sertraline group. The fact that we ended up with a relatively low dose of venlafaxine even though we aimed for maximum doses might however suggest that the acceptability of sertraline was larger than that of venlafaxine among the patients in the present study, similarly to what have been found in meta-analysis of other patient groups [27].

Overall we found some small but significant differences between baseline and follow-up for both groups on the primary and most of the secondary outcome measures (except the Hamilton ratings) as well as on some of the other ratings used in the study. As the patient sample in this study comprises severely trauma-affected refugees who have been referred to a highly specialised clinic, the rather small improvements are not surprising. The study design, with no placebo or control group, does not allow us to conclude whether the improvements detected are due to an effect of the treatment programme provided. A previous study, conducted at the same treatment facility as ours however, found a small but significant effect of sertraline on depression compared to waitlist controls, and it therefore seems likely that at least part of the change is due to the pharmacological treatment in the present study too [28].

As a high percentage of patients in both groups were taking a small dose of mianserin during at least part of the study, the sleep enhancing effect of mianserin might contribute to the overall change. If we believe the change we found between baseline and follow-up on the majority of ratings is at least partly due to the pharmacological treatment, it might very well be the effect of the combination of mianserin and the investigated antidepressants rather than sertraline or venlafaxine alone.
Around 21 percent of the total study population was taking antipsychotic medication at some point during the trial. Although there were no significant group difference in the use of antipsychotics, one cannot rule out that a possible considerable effect of antipsychotics on the patients’ PTSD might have hidden differences in effects between the two groups due to a ceiling effect. The general small pre-post treatment changes in both groups do however make this less likely.

The duration of the study was six months, during which the patients had to be gradually started up in pharmacological treatment, which means that patients usually had their antidepressants for substantially shorter time when evaluated at follow-up. It is therefore possible that part of the treatment effect only can be observed after a longer post-treatment period. For this reason, patients in the present study will be invited to follow-up interviews and ratings six and 18 months after the termination of their treatment programme.

**Limitations and strengths**

Our trial has certain limitations. Blinded observer ratings were carried out, but neither patients nor treatment staffs was blinded to treatment allocations. This decision was taken by an expert team of doctors at CTP with a substantial amount of experience with, and knowledge about, trauma-affected refugees. Due to the nature of the trauma previously experienced by many of the patients (torture experiences) and the subsequent complex PTSD with suspicion as a key feature, the clinicians found it likely that a majority of the patients would decline participation if blinded. A substantial selection bias would have been very unfortunate in this study since we were aiming to get a population and a set-up that were, to a large extent, comparable with any
other clinic in the field, making study results easy to implement elsewhere. In the current study
design, where most outcome measures were self-report ratings, the gains of blinding would
have been limited. In combination with the risk of greater selection bias, this was the basis for
the current pragmatic design where blinded observer ratings were chosen as recommended by
authors of similar studies in the field [11].

The study did not include a waitlist or placebo control group, due to both pragmatic and ethical
considerations. When the present study was designed, the first RCT at CTP (PTF1), which
included a waitlist control group, had just been completed in our clinic [30]. Preliminary
findings suggested that there was some effect of the treatment provided and because this first
trial suggested an effect of sertraline compared to the waitlist control group, we found it less
important to include a waitlist control group in the present study and found it more important
to achieve larger samples in the pharmacological treatment groups. However, the analyses of
PTF1 are now completed and in the light of the relatively small effect sizes found in PTF1 [30] it
would have been an advantage to be able to compare the effects of the two pharmacological
treatments with a waitlist control group. Including a waitlist control group might on the other
hand have been ethically questionable due to changes in access to treatment for trauma-
affected refugees in Denmark that happened in the time period between the two studies.

During the time when PTF1 was conducted there was a considerable waiting time for specialised
treatment for refugees in most of Denmark, which was the main reason that a waitlist control
group was deemed ethical. However, at the time of the present study this waitlists had been
markedly reduced. Consequently, we did not find it ethically acceptable to withhold participants
in the present study from immediate treatment, when potentially beneficial treatments were readily available.

Pill count was used to determine compliance. This is naturally a less secure method than blood test as patients could potentially hide poor compliance from the treatment staff by throwing away their medication. However, we chose the present method based on the assumption that some patients would find the frequent collection of blood samples unacceptable due to their trauma history. Blood tests as compliance measures do however hold some advantages over pill counts. They are an objective measure of whether the patients are taking the medication and also provide some indication of whether the blood level of the medication is within a therapeutic range, which is especially relevant in a non-western populations were percentages of fast drug metabolisers have been found differ from western populations. In the present study this difference could potentially have influenced the efficacy of the pharmacological agents investigated and it would therefore have been beneficial to know whether blood levels of the antidepressant agents had been within the therapeutic range.

The study also holds important strengths. Unlike most studies in the field, participants were randomised, which reduces selection bias and improves comparability between the two intervention groups. Furthermore, we aimed to avoid restricting the inclusion unnecessarily in order to make the patient group similar to the population treated at other refugee health care facilities both in Denmark and worldwide. Therefore, the results and lessons learned from this study are, to a large extent, transferrable to similar refugee health facilities. The design is fairly simple and manuals were used for all interventions, which makes the study easy to reproduce in similar or larger settings.
Conclusion

In the present study sertraline had a slightly better outcome than venlafaxine on several secondary outcome measures, although no difference was found on the primary outcome measures, the HTQ. As mentioned above this is in line with the findings of the one existing similar study conducted previously [11]. We therefore still recommend SSRIs as first line pharmacological treatment for trauma-affected refugees. Although differences between the two treatment groups were only found on a minority of the rating scales, this knowledge in itself is valuable and brings us one step closer to evidence-based pharmacological treatment for trauma-affected refugees. However, there is still an urgent need for large-scale randomised studies on both trauma-affected refugees and other PTSD populations in order to determine the efficacy of other pharmacological agents typically used in the field for example TCAs and newer antidepressants such as agomelatine.

Competing interest

The authors of this paper: Charlotte Sonne, Jessica Carlsson, Per Bech, Ask Elklit and Erik Lykke Mortensen all declare to have no competing interest towards the results of this study. The funding bodies of the trial had no influence on design, analysis, interpretation, drafting, manuscript, decision to publish, or any areas other than funding.
Author’s contributions

Charlotte Sonne was the primary investigator of the study, designed the study, performed the statistically analyses and was the primary author this paper. Jessica Carlsson was the co-investigator of the study, participated in the design and implementation of the study and helped to draft and critically review this paper. Ask Elklit and Per Bech have been involved in major decision during the study and revised the present paper critically. Erik Lykke Mortensen has been involved throughout the design of the study and has assisted the first author with statistical analyses and the drafting of this manuscript. All authors read and approved the final manuscript.

Acknowledgements

The authors wish to thank the following funding bodies from which the study has received grants: The Health Foundation (Helsefonden), The Tryg Foundation (TrygFonden), The Research foundation of the Capital Region of Denmark and the Research foundation for the Mental Health Services - Capital Region of Denmark.

The authors also wish to thank Senior Consultant Morten Ekstroem, head of CTP for his support throughout the design and implementation of the study. Furthermore the authors wish to thank the data management team: Laura Lindberg, Henriette Laugesen and Klement Dymi for their invaluable work in making data ready for analyses.
References

13. WHO. The ICD-10 Classification of Mental and Behavioural Disorders - Diagnostic criteria for research. 1993.


Tables and figures

199 were not included in the study due to:
- Did not fulfill criteria for treatment at CTP (n=124)
- Did not fulfill inclusion criteria for the study (n=10)
- Were excluded due to exclusion criteria (n=10)
- Did not sign informed consent to participate (n=55)

12 were withdrawn from the study due to:
- Pregnancy (n=4)
- Admission to psychiatric hospital (n=1)
- Somatic illness (n=1)
- Moved away (n=1)
- Wrongly included (n=1)
- Did not initiate treatment program (n=2)
- Withdrew informed consent (n=2)

39 did not take prescribed medicine for eight consecutive weeks during the study due to:
- Drop out of the treatment program (n=17)
- Side effects to medication (n=10)
- Not wanting to start pharmacological treatment (n=3)
- Did not want to change present medication to allocated antidepressant (n=1)
- Reason not specified (n=8)

Figure 1: Participants flow through the trial

406 patients were referred to CTP during the inclusion period

207 signed informed consent to participate in the study

98 was randomised to V1

109 was randomised to S2

91 eligible for intention-to-treat analyses

104 eligible for intention-to-treat analyses

68 pharmacological completers

88 pharmacological completers
Table 1: Baseline characteristics for the study population

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>All (n=207)*</th>
<th>Group V1 (n= 98)*</th>
<th>Group S2 (n= 109)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic information</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male gender</td>
<td>124 (60.2)</td>
<td>61 (62.2)</td>
<td>63 (58.3)</td>
</tr>
<tr>
<td>Country of origin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Ex-Yugoslavia</td>
<td>20 (9.7)</td>
<td>11 (11.2)</td>
<td>9 (8.3)</td>
</tr>
<tr>
<td>• Iran</td>
<td>28 (13.6)</td>
<td>13 (13.3)</td>
<td>15 (13.9)</td>
</tr>
<tr>
<td>• Iraq</td>
<td>71 (34.5)</td>
<td>34 (34.7)</td>
<td>37 (34.3)</td>
</tr>
<tr>
<td>• Afghanistan</td>
<td>28 (13.6)</td>
<td>10 (10.2)</td>
<td>18 (16.7)</td>
</tr>
<tr>
<td>• Lebanon</td>
<td>26 (12.6)</td>
<td>12 (12.2)</td>
<td>14 (13.0)</td>
</tr>
<tr>
<td>• Other</td>
<td>33 (16.2)</td>
<td>18 (18.4)</td>
<td>15 (13.9)</td>
</tr>
<tr>
<td><strong>Diagnosis (ICD-10) in addition to PTSD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Depression</td>
<td>204 (98.6)</td>
<td>96 (97.96)</td>
<td>108 (99.08)</td>
</tr>
<tr>
<td>• Enduring personality change after catastrophic experience (F.62.0)</td>
<td>80 (40.8)</td>
<td>38 (41.30)</td>
<td>42 (40.38)</td>
</tr>
<tr>
<td>• Other psychiatric disorder</td>
<td>24 (11.7)</td>
<td>12 (12.24)</td>
<td>12 (11.11)</td>
</tr>
<tr>
<td><strong>Trauma history</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imprisonment</td>
<td>110 (53.4)</td>
<td>57 (58.8)</td>
<td>53 (48.6)</td>
</tr>
<tr>
<td>Torture**</td>
<td>99 (48.1)</td>
<td>54 (55.1)</td>
<td>45 (41.7)</td>
</tr>
<tr>
<td>Refugee camp</td>
<td>52 (25.7)</td>
<td>22 (22.9)</td>
<td>30 (27.5)</td>
</tr>
<tr>
<td><strong>Psychosocial status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education &gt;10 years from home country</td>
<td>98 (50.8)</td>
<td>50 (53.2)</td>
<td>48 (48.5)</td>
</tr>
<tr>
<td>Presently employed/studying</td>
<td>14 (7.0)</td>
<td>7 (7.3)</td>
<td>7 (6.8)</td>
</tr>
<tr>
<td>Living alone all the time</td>
<td>51 (25.8)</td>
<td>21 (21.9)</td>
<td>30 (29.4)</td>
</tr>
<tr>
<td>Have got children less than 18 years old</td>
<td>137 (68.8)</td>
<td>68 (70.8)</td>
<td>69 (67.0)</td>
</tr>
<tr>
<td><strong>Mean(SD)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>43.7 (9.7)</td>
<td>43.2 (9.6)</td>
<td>44.0 (9.7)</td>
</tr>
<tr>
<td>Years since arrival in Denmark</td>
<td>14.6 (7.3)</td>
<td>14.1 (7.1)</td>
<td>15.1 (7.4)</td>
</tr>
</tbody>
</table>

*Not all variables available for the entire patient group
** Group difference borderline significant, p=0.054
Table 2: Score differences between baseline and follow up ratings

Symptoms self-ratings

<table>
<thead>
<tr>
<th>Rating</th>
<th>Group (n)</th>
<th>Mean baseline score (SD)</th>
<th>Mean follow-up score (SD)</th>
<th>Difference (SD)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HTQ</td>
<td>Sertraline (85)</td>
<td>3.24 (0.37)</td>
<td>3.02 (0.56)</td>
<td><strong>-0.22 (0.55)</strong></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HTQ</td>
<td>Venlafaxine (69)</td>
<td>3.21 (0.39)</td>
<td>3.06 (0.55)</td>
<td><strong>-0.15 (0.46)</strong></td>
<td>0.01</td>
</tr>
<tr>
<td>HSCL-25</td>
<td>Sertraline (84)</td>
<td>3.02 (0.43)</td>
<td>2.84 (0.64)</td>
<td><strong>-0.18 (0.60)</strong></td>
<td>0.01</td>
</tr>
<tr>
<td>HSCL-25</td>
<td>Venlafaxine (66)</td>
<td>3.09 (0.44)</td>
<td>2.96 (0.56)</td>
<td><strong>-0.13 (0.44)</strong></td>
<td>0.02</td>
</tr>
<tr>
<td>SCL-90</td>
<td>Sertraline (81)</td>
<td>2.43 (0.81)</td>
<td>2.37 (0.91)</td>
<td><strong>-0.06 (0.93)</strong></td>
<td>0.58</td>
</tr>
<tr>
<td>SCL-90</td>
<td>Venlafaxine (66)</td>
<td>2.60 (0.79)</td>
<td>2.58 (0.77)</td>
<td><strong>-0.02 (0.60)</strong></td>
<td>0.79</td>
</tr>
<tr>
<td>VAS-Back</td>
<td>Sertraline (79)</td>
<td>6.62 (2.91)</td>
<td>6.60 (2.90)</td>
<td><strong>-0.02 (3.29)</strong></td>
<td>0.94</td>
</tr>
<tr>
<td>VAS-Back</td>
<td>Venlafaxine (65)</td>
<td>7.48 (2.31)</td>
<td>7.27 (2.26)</td>
<td><strong>-0.21 (2.05)</strong></td>
<td>0.42</td>
</tr>
<tr>
<td>VAS-Arm</td>
<td>Sertraline (80)</td>
<td>5.72 (3.44)</td>
<td>5.72 (3.48)</td>
<td><strong>0.00 (3.49)</strong></td>
<td>1.00</td>
</tr>
<tr>
<td>VAS-Arm</td>
<td>Venlafaxine (64)</td>
<td>5.66 (3.32)</td>
<td>6.43 (2.64)</td>
<td><strong>0.77 (2.69)</strong></td>
<td>0.03</td>
</tr>
<tr>
<td>VAS-Leg</td>
<td>Sertraline (80)</td>
<td>6.56 (3.19)</td>
<td>6.07 (3.13)</td>
<td><strong>-0.49 (2.58)</strong></td>
<td>0.09</td>
</tr>
<tr>
<td>VAS-Leg</td>
<td>Venlafaxine (64)</td>
<td>6.89 (2.94)</td>
<td>7.01 (2.51)</td>
<td>0.12 (2.62)</td>
<td>0.71</td>
</tr>
<tr>
<td>VAS-Head</td>
<td>Sertraline (80)</td>
<td>7.07 (2.42)</td>
<td>6.45 (3.06)</td>
<td><strong>-0.62 (3.13)</strong></td>
<td>0.08</td>
</tr>
<tr>
<td>VAS-Head</td>
<td>Venlafaxine (64)</td>
<td>7.15 (2.71)</td>
<td>6.56 (2.63)</td>
<td><strong>-0.59 (2.58)</strong></td>
<td>0.07</td>
</tr>
</tbody>
</table>

HTQ, HSCL-25, SCL = 1-4 (1 best score), VAS = 0-10 (0 best score).
### Life quality/level of functioning self-ratings

<table>
<thead>
<tr>
<th>Rating</th>
<th>Group (n)</th>
<th>Mean baseline score (SD)</th>
<th>Mean follow-up score (SD)</th>
<th>Difference (SD)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO-5</td>
<td>Sertraline (85)</td>
<td>13.04 (14.04)</td>
<td>22.33 (25.04)</td>
<td><strong>9.29 (22.4)</strong></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>WHO-5</td>
<td>Venlafaxine (67)</td>
<td>14.51 (15.46)</td>
<td>17.85 (19.26)</td>
<td>3.34 (18.11)</td>
<td>0.14</td>
</tr>
<tr>
<td>SDS</td>
<td>Sertraline (80)</td>
<td>24.54 (5.39)</td>
<td>21.71 (8.18)</td>
<td><strong>-2.84 (7.76)</strong></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>SDS</td>
<td>Venlafaxine (67)</td>
<td>22.52 (6.10)</td>
<td>23.16 (6.51)</td>
<td>0.63 (2.44)</td>
<td>0.48</td>
</tr>
<tr>
<td>SAS-SR</td>
<td>Sertraline (86)</td>
<td>3.00 (0.73)</td>
<td>2.72 (0.76)</td>
<td><strong>-0.28 (0.69)</strong></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>SAS-SR</td>
<td>Venlafaxine (71)</td>
<td>3.00 (0.68)</td>
<td>2.84 (0.67)</td>
<td><strong>-0.16 (0.66)</strong></td>
<td>0.04</td>
</tr>
<tr>
<td>CSS</td>
<td>Sertraline (86)</td>
<td>21.91 (8.63)</td>
<td>22.64 (7.52)</td>
<td>0.73 (7.44)</td>
<td>0.37</td>
</tr>
<tr>
<td>CSS</td>
<td>Venlafaxine (72)</td>
<td>22.28 (7.20)</td>
<td>22.33 (6.82)</td>
<td>0.05 (6.28)</td>
<td>0.95</td>
</tr>
</tbody>
</table>

WHO-5 = 0-100 (100 best score), SDS = 0-10 (0 best score), SAS-SR = 1-5 (1 best score), CSS = 1-7 (7 best)

### Observer ratings

<table>
<thead>
<tr>
<th>Rating</th>
<th>Group (n)</th>
<th>Mean baseline score (SD)</th>
<th>Mean follow-up score (SD)</th>
<th>Difference (SD)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAM-D</td>
<td>Sertraline (89)</td>
<td>23.84 (5.53)</td>
<td>22.29 (8.10)</td>
<td>-1.55 (7.49)</td>
<td>0.054</td>
</tr>
<tr>
<td>HAM-D</td>
<td>Venlafaxine (69)</td>
<td>23.61 (5.44)</td>
<td>22.52 (7.71)</td>
<td>-1.09 (6.86)</td>
<td>0.19</td>
</tr>
<tr>
<td>HAM-A</td>
<td>Sertraline (88)</td>
<td>26.84 (6.75)</td>
<td>26.31 (9.80)</td>
<td>-0.53 (9.10)</td>
<td>0.58</td>
</tr>
<tr>
<td>HAM-A</td>
<td>Venlafaxine (69)</td>
<td>27.09 (6.15)</td>
<td>26.23 (8.92)</td>
<td>-0.86 (8.28)</td>
<td>0.39</td>
</tr>
<tr>
<td>GAF-S</td>
<td>Sertraline (68)</td>
<td>47.50 (5.74)</td>
<td>51.37 (8.18)</td>
<td><strong>3.87 (6.39)</strong></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>GAF-S</td>
<td>Venlafaxine (56)</td>
<td>48.16 (5.35)</td>
<td>51.84 (7.15)</td>
<td><strong>3.68 (8.10)</strong></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>GAF-F</td>
<td>Sertraline (67)</td>
<td>48.55 (6.71)</td>
<td>50.27 (8.24)</td>
<td><strong>1.72 (6.55)</strong></td>
<td>0.04</td>
</tr>
<tr>
<td>GAF-F</td>
<td>Venlafaxine (56)</td>
<td>48.75 (5.41)</td>
<td>51.77 (7.49)</td>
<td><strong>3.02 (6.74)</strong></td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

HAM = 0-4 (0 best score), GAF = 0-100 (100 best score)

*Overview over rating scores at baseline and follow-up for the intention-to-treat sample. Numbers in brackets after group indicates the number of patients included in this analysis, which are all patients who have completed a follow-up rating.*

**Bold** = Statistically significant improvement

**Bold and Italic** = Statistically significant deterioration
Table 3: Regression coefficients for group differences at follow up
Adjusted for baseline rating scores

*Intention to treat sample (n=195)*

<table>
<thead>
<tr>
<th>Rating</th>
<th>Regression coefficient (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HTQ</td>
<td>0.07 (-0.09 – 0.22)</td>
<td>0.40</td>
</tr>
<tr>
<td>HSCL</td>
<td>0.07 (-0.1 – 0.23)</td>
<td>0.42</td>
</tr>
<tr>
<td>SCL</td>
<td>0.12 (-0.12 – 0.35)</td>
<td>0.31</td>
</tr>
<tr>
<td>SDS</td>
<td>2.31 (0.10 – 4.52)</td>
<td>0.04*</td>
</tr>
<tr>
<td>WHO-5</td>
<td>-5.79 (-12.05 – 0.46)</td>
<td>0.07</td>
</tr>
<tr>
<td>VAS-neck/back</td>
<td>0.28 (-0.49 - 1.05)</td>
<td>0.48</td>
</tr>
<tr>
<td>VAS-arms</td>
<td>0.70 (-0.13 - 1.54)</td>
<td>0.10</td>
</tr>
<tr>
<td>VAS-legs</td>
<td>0.72 (-0.01 – 1.45)</td>
<td>0.053</td>
</tr>
<tr>
<td>VAS-head</td>
<td>0.02 (-0.80 -0.85)</td>
<td>0.95</td>
</tr>
<tr>
<td>SAS-SR</td>
<td>0.10 (-0.09 – 0.29)</td>
<td>0.29</td>
</tr>
<tr>
<td>CSS</td>
<td>-0.35 (-2.18 - 1.47)</td>
<td>0.71</td>
</tr>
<tr>
<td>GAF-F</td>
<td>1.35 (-0.93 – 3.63)</td>
<td>0.25</td>
</tr>
<tr>
<td>GAF-S</td>
<td>0.06 (-2.40 - 2.52)</td>
<td>0.96</td>
</tr>
<tr>
<td>HAM-D</td>
<td>0.19 (-1.94 – 2.33)</td>
<td>0.86</td>
</tr>
<tr>
<td>HAM-A</td>
<td>-0.57 (-3.19 – 2.04)</td>
<td>0.67</td>
</tr>
</tbody>
</table>

**Bold:** In favor of Sertraline

**Italic:** In favor of Venlafaxine

**Bold and *:** Statistically significant
Psychosocial predictors of treatment outcome for trauma-affected refugees

Charlotte Sonne (corresponding author)
Competence Centre for Transcultural Psychiatry
University of Southern Denmark
Mental Health Centre Ballerup
Maglevaenget 2
2750 Ballerup
Denmark
Email: charlotte.sonne@regionh.dk
Phone: +45 3864 5178

Jessica Carlsson
Competence Centre for Transcultural Psychiatry
University of Copenhagen
Mental Health Centre Ballerup
Maglevaenget 2
2750 Ballerup
Denmark
Email: jessica.carlsson.01@regionh.dk

Per Bech
Mental Health Centre North Zealand
University of Copenhagen
Dyrehavevej 48
3400 Hillerød
Denmark
Email: per.bech@regionh.dk

Erik Vindbjerg
Competence Centre for Transcultural Psychiatry
University of Southern Denmark
Mental Health Centre Ballerup
Maglevaenget 2
2750 Ballerup
Denmark
Email: erik.vindbjerg@regionh.dk

Erik Lykke Mortensen
Institute of Public Health and Centre for Healthy Aging
University of Copenhagen
Øster Farimagsgade 5
1353 København K
Denmark
Email: elme@sund.ku.dk

Ask Elklit
University of Southern Denmark
National Center for Psychotraumatology
Campusvej 55
5230 Odense
Denmark
Email: aelklit@health.sdu.dk
Abstract

This study examined possible predictors of treatment outcome for trauma-affected refugees. The participants were 195 adult refugees with PTSD who participated in a six-to-seven month treatment programme at the Competence Centre for Transcultural Psychiatry (CTP), Denmark. The CTP predictor index used in the study included 15 different possible outcome predictors. The primary outcome measure was PTSD symptoms measured on the Harvard Trauma Questionnaire (HTQ). Other outcome measures included the Hopkins Symptom Check List-25 (HSCL-25), WHO-5 well-being index, Sheehan Disability Scale (SDS), Hamilton Depression and Anxiety scales (HAM-D+A), the somatisation items of the Symptoms Checklist-90 (SCL-90), Global Assessment of Functioning scales (GAF) and pain rated on visual analogue scales (VAS). Correlations between pre- to post-treatment score changes and total score as well as subscores of the CTP predictor index were analysed. Overall, score changes on most ratings showed a significant correlation with the total score of the predictor index, though borderline significantly for HTQ (p=0.06). While employment status was the only single item significantly correlated to HTQ changes, a number of single items from the CTP predictor index correlated significantly with changes in depression and anxiety symptoms, but the size of the correlation coefficients were modest. Consequently, there is a need for further studies focusing on identifying predictors of treatment outcome in trauma-affected refugees. Although identifying strong predictors of treatment outcomes is not easy, it is nonetheless still necessary in order to potentiate treatment outcomes and to be able to offer personalised treatment programmes, based on the resources of the individual patient.

**Keywords:** Refugee; treatment; predictor; Stress Disorders, Post-Traumatic; depression
**Introduction**

Post-traumatic stress disorder (PTSD) is a severe, and in some cases chronic, mental disorder that is estimated to be present in approximately 30% of all refugees (Steel et al., 2009). In the international classification system ICD-10, it is defined as a non-psychotic anxiety disorder resulting from an exceptionally threatening or catastrophic experience, which is likely to cause distress in almost everyone (WHO, 1993). However, for trauma-affected refugees, it is usually not a single event that leads to emotional distress, but rather a history of prolonged and repeated trauma in their countries of origin, often exacerbated by further stressful events during and after their flight (McDonnell, Robjant, & Katona, 2013; Silove, 1999). Although recent years have seen an increasing focus on providing evidence-based treatment for trauma-affected refugees, knowledge about intervention effects is still scarce. The effects of treatment in studies with trauma-affected refugees vary considerably between studies, but also between patients within the single studies, with some patients responding markedly better to treatment than others (Crumlish & O’Rourke, 2010; Nickerson, Bryant, Silove, & Steel, 2011; Palic & Elklit, 2011). However, we know little about why some patients benefit more from treatment. When it comes to pharmacological treatment, some biological factors, such as genetic differences in the enzyme cytochrome P monooxygenases (CYP), are assumed to affect treatment response (Lin, Poland, Lau, & Rubin, 1988; Noerreregaard, 2012). Nonetheless, the contribution of non-biological factors to differences in treatment response is less well understood.

While a considerable number of studies have been conducted on pre- and post-migration predictors of the development of PTSD and other trauma-related disorders among refugees (Bogic et al., 2013; Levitt, Lane, & Levitt, 2005; Porter & Haslam, 2005; Teodorescu, Heir, Hauff, Wentzel-Larsen, & Lien, 2012), only a few studies have analysed predictors of treatment outcome for this population. Two studies investigated the possible predictive value of gender, torture exposure, offender status, baseline
depression and anger, as well as dissociative symptoms on treatment outcome in a study population from a randomised trial (Halvorsen, Stenmark, Neuner, & Nordahl, 2014; Stenmark, Guzey, Elbert, & Holen, 2014). They found male gender and offender status to be significant negative predictors of treatment outcome, but found no significant associations with treatment outcome for any of the remaining variables. A couple of other papers have touched upon predictors of treatment outcome when analysing study results. Van Wyk et al. studied the impact of therapeutic interventions as well as predictors of treatment outcome in a naturalistic setting (van Wyk, Schweitzer, Brough, Vromans, & Murray, 2012). They explored the possible predictive value of the total number of traumatic events, number of service contacts, score on the post-migration living difficulty scale (PMLD), and pre-intervention mental health symptoms, but found the latter to be the only significant predictor of outcome. A study from the same clinic as the present study found public financial support to be the only predictor of change in PTSD symptoms (C. Buhmann, Mortensen, Nordentoft, Ryberg, & Ekstrøm, 2015).

While the papers mentioned above studied the predictive value of sociodemographic variables, pre-migration stressors or baseline symptoms, the possible predictive value of the patient’s current social situation and psychosocial resources are equally important to study. If different aspects of psychosocial resources and their relation to treatment outcome are investigated, the resulting knowledge can guide clinicians in choosing the right treatment for the right patients. Therefore, identifying predictors of treatment outcome is a crucial first step towards offering individualised treatment on an evidence base. Consequently, the aim of the current study was to evaluate an index of 15 psychosocial potential predictors of treatment outcome in a population of trauma-affected refugees.
Methods

Participants and treatment

The patient sample comprised 195 trauma-affected refugees who constituted the intention-to-treat sample from a randomised controlled trial conducted at the Competence Centre for Transcultural Psychiatry (CTP), a specialised transcultural psychiatric outpatient clinic in Copenhagen, Denmark. The participants needed to fulfil the ICD-10 research criteria for PTSD (World Health Organisation, 2010) and have no psychotic disorders or ongoing drug/alcohol abuse. As the trial concerned pharmacological agents, pregnant or breastfeeding women were also excluded. Details of the protocol have been described in Sonne, Carlsson, Elklit, Mortensen, & Ekstrøm (2013), and the results from the trial will be published separately.

Data collection

Outcome measures

The patients were offered a six-seven month multidisciplinary treatment programme, consisting of pharmacological treatment, psychoeducation, manualised cognitive therapy and social counselling. A range of self-ratings and observer ratings were used to measure treatment outcome. For the present study, we used standard ratings during previous and on-going randomised studies at CTP (C. B. Buhmann, Nordentoft, Ekstroem, Carlsson, & Mortensen, 2015; Nordbrandt, Carlsson, Lindberg, Sandahl, & Mortensen, 2015). The primary outcome measure in the treatment effect study was self-reported PTSD symptoms assessed by Harvard Trauma Questionnaire (HTQ), part IV, which has been primarily developed for trauma-affected refugees and validated in several languages and settings (Mollica et al.,
Secondary outcome measures included self-reported depression and anxiety symptoms assessed by Hopkins Symptom Check List-25 (HSCL-25; Mollica, Wyshak, de Marneffe, Khuon, & Lavelle, 1987), and observer-rated depression and anxiety symptoms measured on the Hamilton Depression and Anxiety Ratings Scales (HAM D+A; Bech, Kastrup, & Rafaelsen, 1986). Other outcome measures included level of functioning, measured on the Sheehan Disability Scale (SDS; Sheehan, 1986), quality of life assessed using the WHO-Five Well-being Index (WHO-5; Topp, Østergaard, Søndergaard, & Bech, 2015), the somatisation items of SCL-90 (Derogatis, 1994), pain in four different body areas measured on Visual Analogue Scales (VAS), and levels of symptoms and functioning assessed using the Global Assessment of Functioning (GAF; Bastin et al., 2013). These measures are all self-reported ratings except the GAF-scores, which were completed by the medical doctor in charge of the treatment, and the HAM ratings, which were completed by blinded assessors.

HAM-ratings were completed at baseline and follow-up, while all other ratings were completed three times for the majority of the patients. For the present study, however, only the baseline and follow-up ratings were used.

The CTP predictor index

In addition to the existing rating scales mentioned above, an index of potential psychosocial predictors was developed specifically for the current study. The index was developed before data collection was initiated in order develop a tool to register and rate the psychosocial resources of the individual patients that could potentially be used to predict treatment outcome. Due to the lack of studies on treatment outcome predictors, the index was essentially based on a combination of the available literature on predictors of the development of trauma-related mental health problems (as mentioned in the introduction) among refugees and clinical experience from previous studies at CTP. All groups of
practitioners (psychiatrists, medical doctors, psychologists, and social counsellors) working at CTP contributed to the development of the index, assisted by external researchers from relevant fields.

The resulting index (hereinafter the CTP Predictor Index) consisted of 15 potential predictors: five rated by the medical doctor/psychiatrist, five rated by the psychologist, and five rated by the social counsellor. Each group of five items constituted a subscale. The items on the medical doctor subscale concerned the patient’s past (upbringing, results of previous treatment attempts), the chronicity of mental health problems and pain as well as their motivation for participating in the treatment program. The items on the psychologist subscale related to the patient’s prerequisites for engaging in psychotherapy (i.e., cognitive resources and reflectivity), while the items on the social counsellor subscale related to the patient’s current social situation (i.e. employment status and dwelling). The CTP predictor index is displayed in figure 1.

Each potential predictor was rated on a 0-4 Likert scale (4 being the best score) according to pre-defined criteria (instruction sheet available from the first author on request). The medical doctor, psychologist and social counsellor completed the index during their first session with the patient, either before the treatment programme started or at the outset of treatment. If undecided between two scores on the Likert scale, they were instructed to choose the higher of the two scores, in order not to underestimate the patient’s resources.

The item ‘employment status’ illustrates the principle of scoring: In order to reach a score of 4, patients had to be in full-time employment, while a score of 3 required a stable income, but not necessarily from employment (i.e. retirement benefit). A score of 2 required income to be stable until at least the near future, but not permanent, i.e. sick pay. To get a score of 1, the patient had to have some form of income, albeit not a stable one, e.g. being under consideration for some form of state benefit. A score of 0 meant no income at all for the entire household.
Approval

The study was approved by the local ethics committee (H-3-2012-020), The Danish Medicines Agency (2011-006228-19), and the Danish Data Protection Agency. The study was registered, prior to inclusion, at ClinicalTrials.gov (NCT01569685), and a study protocol paper (Sonne et al., 2013) was published in March 2013.

Data analyses

All analyses were performed in STATA 14. Scores of the rating scales as well as the CTP Predictor Index were recorded as missing if more than half of the single scale items were uncompleted. Pearson correlations were calculated between the overall score on the CTP Predictor Index and the pre-post difference for each outcome scale. Correlations between the individual items in the CTP Predictor Index and the symptom score changes from baseline to follow-up were analysed for the rating scales concerning PTSD, depression and anxiety symptoms: The HTQ, HSCL-25 (divided into subscales for depression and anxiety), HAM D and HAM A. Given that no significant differences between the two intervention groups were found on any of the rating scales for PTSD, depression or anxiety symptoms in the randomised study, an intervention group variable was not included in the correlation analyses. In addition, we analysed the correlations between three subscale scores: Items scored by medical doctor, items scored by psychologist and items scored by social counsellor.

Results

Out of the total intention-to-treat sample of 195 patients, the CTP Predictor Index was completed for 191 patients. The primary outcome measure, HTQ, was completed at both baseline and follow-up by 154
patients. For the remaining ratings, the number of patients completing the rating at both baseline and follow-up ranged from 123 (GAF-F) to 158 (HAM-D).

**Correlations between CTP predictor index total score and rating score changes**

Correlations between the CTP Predictor Index and the ratings used at CTP are displayed in Table 1. Overall, statistically significant correlations were found for most of the ratings, except for two of the VAS scales for pain and the GAF-functioning score. The significant correlations ranged in size from 0.18 to 0.29. For the HTQ, the correlation was borderline significant ($r = 0.15, p=0.06$).

**Correlations between single items and changes in PTSD, depression and anxiety symptoms**

The correlation between the HTQ, HSCL, Hamilton depression and anxiety score changes and the single items of the CTP Predictor are displayed in Table 2. Employment status was the only item from the index found to have a significant correlation with changes in PTSD symptoms measured on HTQ ($r = 0.18, p=0.03$). We subsequently checked if there was a similar correlation between baseline HTQ score and employment status, but no significant correlation was found.

Improvement in self-reported depression symptoms measured by HSCL-25 was negatively correlated to having previously received psychiatric treatment without effect, chronic pain, long duration of mental problems, lack of social relationships and poor integration. In respect to self-reported anxiety symptoms on the HSCL-25, improvement correlated negatively with poor acceptability of psychotherapy, limited cognitive resources, few social relationships and poor integration. Improvement in observer-rated depression symptoms on HAM-D was negatively correlated to previous unsuccessful treatment attempts, chronic pain, as well as low scores on upbringing and all psychotherapy-related items.
Observer-rated anxiety symptoms on HAM-A were also significantly correlated to all psychotherapy-related items as well as social relationships.

**Correlations among subscale scores**

The scores on the three subscales were found to correlate significantly, with correlation coefficients being of small to moderate size. The weakest correlation was between medical doctor and social counsellor subscales ($r=0.15, p= 0.04$,) while the strongest correlation was found between psychologist and social counsellor subscale scores ($r=0.35, p <0.01$).

**Discussion**

To the best of our knowledge, this is the largest and most systematic study published on predictors of treatment outcome in trauma-affected refugees. Overall, we found that the total score on the CTP Predictor Index was significantly correlated to changes on most rating scales, although only borderline significantly correlated with changes on the primary outcome measure, the HTQ. Although most correlation coefficients were modest in size, the finding of significant correlations nonetheless supports the clinical experience that patients with many psychosocial resources tend to attain a better treatment outcome than less resourceful patients.

When looking at the correlation between the total score of the CTP predictor index and changes on the different rating scales, the strongest correlations were found for the Hamilton ratings. This is not surprising given that correlations tend to be stronger between ratings of the same type and both the Hamilton ratings and the CTP predictor index are based on observer ratings (in contrast to the many self-report measures).
When analysing the single items from the CTP Predictor Index, we found employment status to be the only significant predictor of changes in PTSD symptoms measured on the HTQ. This is in line with Buhmann et al. (2015), who found public financial support to be negatively associated with treatment outcome. There are a number of possible explanations for this finding. It is likely that patients in employment have a structured daily routine with more meaningful activities, and therefore get a better treatment outcome. Additionally, we know from clinical experience that many patients find the official employment support programmes, with many meetings and aptitude tests, to be an on-going stressor, and it is therefore possible that this counteracts the treatment of their stress-related psychopathology.

Although we did not have a variable for household income, it may be that financial security, rather than employment status itself, is predicting treatment outcome. In a study of general mental health in British civil servants, income was found to be a determinant of mental health, independent of job status (Ferrie, Shipley, Stansfeld, Smith, & Marmot, 2003). It also seems likely that patients who worry more about their financial situation in the immediate future may find it difficult to fully focus on the treatment and therefore achieve a poorer treatment outcome.

Contrary to several other studies (Blair, 2000; Lie, 2002) we found no significant correlation between employment status and HTQ-score at baseline. The correlation between employment status and improvement in PTSD symptoms can therefore not be explained by differences in baseline HTQ-score.

Improvement on both HSCL-25 depression items and HAM-D was negatively correlated with chronic pain, which is in line with findings from a previous study at CTP (C. Buhmann et al., 2015). Moreover, improvement on the HSCL-25 for both depression and anxiety items was found to be negatively correlated with lack of social relationships and poor integration. Other studies have found loneliness and poor integration negatively impact upon the mental health of trauma-affected refugees (Drozdek, 1997;
Silove, Sinnerbrink, Field, Manicavasagar, & Steel, 1997) although they did not analyse social isolation as a predictor of treatment outcome.

In contrast to our hypothesis, higher levels of education showed non-significant negative correlations with changes on all PTSD and depression rating scales. High education has been found to impact negatively mental health in other studies (Hermansson, Timpka, & Thyberg, 2002; Holtz, 1998) with loss of status and identity in refugees with high educational levels being possible explanations. However, a high education also negatively correlated with treatment outcome in a study with non-refugee PTSD populations (de Kleine, Hendriks, Smits, Broekman, & van Minnen, 2014). Accordingly, factors which are not related to refugee status may additionally influence the correlation between educational level and treatment outcome.

Although a number of significant correlations were identified, the correlation coefficients were not large. The modest correlations for the individual items are, however, not that surprising as there are a wide range of different factors that can potentially influence treatment outcome and the contribution of each item to the variability in treatment outcome will accordingly be limited. Possibly, for the same reasons, correlations between treatment outcome and predictors identified in studies of other PTSD patients are not noticeably stronger (van Minnen, Arntz, & Keijsers, 2002).

We did, however, expect the total score of the index to have a stronger correlation to outcome than the individual item scores, but this was generally not the case. The modest size of the correlations between the total score of the index and treatment outcome might relate to the generally small baseline to follow-up improvement found in this patient group, which may be associated with few consistent individual differences in change. The modest correlations among the subscales also indicate that the different components of the index are not closely related. This is not surprising given that we do not measure an overall homogenous construct but rather psychosocial resources from different domains.
believed to influence the patient's ability to respond positively to the treatment. The resultant score will reflect the mean level of the individual items included in the index, but it is possible that the scores on a few items may be more critical than the overall score level.

**Methodological considerations**

In our study we primarily chose to include the possible predictors in the index based on clinical experience and without a priori evidence concerning the correlations between individual factors and treatment outcome. This hypothesis-driven approach with systematic collection of ratings in a structured format minimises the risk of random findings, but an alternative approach would have been to construct an index based on statistical analyses of potential predictors of treatment outcome. Although we decided against this approach because it would require cross-validation in another sample, given the modest correlations of CTP predictor index with treatment outcome, there is an obvious need for further analyses focusing on identifying predictors of treatment outcome in refugees.

The CTP predictor index is based on observer ratings and, since we did not determine interrater reliability, the psychometric quality of the ratings should also be further investigated. Even though rating instructions are standardised the psychologist ratings, in particular, incorporate subjective components such as ratings of cognitive resources and reflectivity. However, the standardised rating instructions are an important strength of our study because they make it easy to replicate our analyses in similar settings.

The employment status item of the CTP Predictor Index includes information related to both employment and income, making it hard to determine which of the two would be the more important predictor of treatment outcome. Although it is hard to completely separate these two variables, it could be worthwhile adding a separate item for the total household income in order to analyse the
independent effects of the two variables. Similarly, there might be other items, which could be separated into two or further specified for future use of the index.

**Perspective**

In the present study, we proposed an index of possible predictors, of which the total score is demonstrated to correlate significantly with outcomes of a number of rating scales commonly used in refugee healthcare settings. While job status was the only item which was significantly correlated to the primary outcome measure of changes in PTSD symptoms, we found a number of single items to be significantly correlated to changes in depression and anxiety symptoms. However, these correlations were modest in size, possibly due to the fact that a range of different factors influence treatment outcome.

Although it might not be easy to identify strong predictors of treatment outcomes, it is nonetheless still necessary to continue the search for predictors if we wish to be able to offer personalised treatment programmes, based on the resources of the individual patient. Personalised treatment will potentially benefit both patients with few psychosocial resources, who need more intensive social support, and patients with more resources, who are able to participate in more cognitively-demanding treatment programmes. In addition, it may lead to socioeconomic benefits for society, as the costs of treatment programmes could be reduced if clinicians become better equipped to match patient and treatment modalities in the future.
References


the American Medical Association, 302(5), 537–49. doi:10.1001/jama.2009.1132


### Figure 1: Score sheet of the CTP Predictor Index

**Medical doctor:**

<table>
<thead>
<tr>
<th></th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motivation</td>
<td>☐</td>
</tr>
<tr>
<td>Upbringing</td>
<td>☐</td>
</tr>
<tr>
<td>Previous relevant treatment carried out without measurable effect</td>
<td>☐</td>
</tr>
<tr>
<td>Chronic pain</td>
<td>☐</td>
</tr>
<tr>
<td>Chronicity of mental condition</td>
<td>☐</td>
</tr>
</tbody>
</table>

**Psychologist:**

<table>
<thead>
<tr>
<th></th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Understanding of the concept of therapy</td>
<td>☐</td>
</tr>
<tr>
<td>Receptiveness/acceptability to psychological treatment</td>
<td>☐</td>
</tr>
<tr>
<td>Reflectivity</td>
<td>☐</td>
</tr>
<tr>
<td>Motivation for active participation</td>
<td>☐</td>
</tr>
<tr>
<td>Cognitive resources</td>
<td>☐</td>
</tr>
</tbody>
</table>

**Social worker:**

<table>
<thead>
<tr>
<th></th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Social relations</td>
<td>☐</td>
</tr>
<tr>
<td>Education</td>
<td>☐</td>
</tr>
<tr>
<td>Dwelling</td>
<td>☐</td>
</tr>
<tr>
<td>Employment status</td>
<td>☐</td>
</tr>
<tr>
<td>Integration</td>
<td>☐</td>
</tr>
</tbody>
</table>
Table 1: Correlation coefficients, the CTP predictor index score

<table>
<thead>
<tr>
<th>Rating</th>
<th>Pearson’s r (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HTQ</td>
<td>0.15 (-0.01 – 0.30)</td>
<td>0.06</td>
</tr>
<tr>
<td>HSCL-25</td>
<td><strong>0.25 (0.10 – 0.40)</strong></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>WHO-5</td>
<td><strong>-0.22 (-0.37 – -0.06)</strong></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>SCL-90 (somatisation)</td>
<td><strong>0.21 (0.05 – 0.36)</strong></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>SDS</td>
<td><strong>0.19 (0.03 – 0.34)</strong></td>
<td>0.02</td>
</tr>
<tr>
<td>VAS-neck/back</td>
<td><strong>0.18 (0.02 – 0.33)</strong></td>
<td>0.03</td>
</tr>
<tr>
<td>VAS-arms</td>
<td><strong>0.26 (0.10 – 0.41)</strong></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>VAS-legs</td>
<td>-0.03 (-0.19 – 0.13)</td>
<td>0.72</td>
</tr>
<tr>
<td>VAS-head</td>
<td>0.14 (-0.02 – 0.30)</td>
<td>0.09</td>
</tr>
<tr>
<td>HAM-D</td>
<td><strong>0.29 (0.14 – 0.43)</strong></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HAM-A</td>
<td><strong>0.27 (0.12 – 0.41)</strong></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>GAF-F</td>
<td>-0.16 (-0.33 – 0.02)</td>
<td>0.08</td>
</tr>
<tr>
<td>GAF-S</td>
<td><strong>-0.23 (-0.39 – -0.05)</strong></td>
<td>0.01</td>
</tr>
</tbody>
</table>

Correlations between the CTP predictor index score and the changes between baseline and follow-up on outcome measures. **Bold** = Statistically significant correlation.
<table>
<thead>
<tr>
<th>Item</th>
<th>HTQ</th>
<th></th>
<th>HSCL-depression</th>
<th></th>
<th>HSCL-anxiety</th>
<th></th>
<th>HAM-D</th>
<th></th>
<th>HAM-A</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pearson (95% CI)</td>
<td>p</td>
<td>Pearson (95% CI)</td>
<td>p</td>
<td>Pearson (95% CI)</td>
<td>p</td>
<td>Pearson (95% CI)</td>
<td>p</td>
<td>Pearson (95% CI)</td>
<td>p</td>
</tr>
<tr>
<td>Items rated by medical doctor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motivation</td>
<td>0.03 (-0.13 - 0.19)</td>
<td>0.72</td>
<td>0.11 (-0.05 - 0.27)</td>
<td>0.18</td>
<td>0.09 (-0.07 - 0.25)</td>
<td>0.25</td>
<td>0.03 (-0.13 - 0.19)</td>
<td>0.72</td>
<td>-0.02 (-0.18 - 0.14)</td>
<td>0.78</td>
</tr>
<tr>
<td>Upbringing</td>
<td>0.02 (-0.14 - 0.18)</td>
<td>0.81</td>
<td>0.13 (-0.03 - 0.28)</td>
<td>0.12</td>
<td>-0.12 (-0.17 - 0.15)</td>
<td>0.88</td>
<td>0.17 (0.01 - 0.32)</td>
<td>0.04</td>
<td>0.07 (-0.09 - 0.22)</td>
<td>0.41</td>
</tr>
<tr>
<td>Previously treated without measurable effect</td>
<td>0.12 (-0.04 - 0.27)</td>
<td>0.14</td>
<td><strong>0.20</strong> (0.04 - 0.35)</td>
<td><strong>0.01</strong></td>
<td>0.13 (-0.03 - 0.28)</td>
<td>0.12</td>
<td><strong>0.18</strong> (0.02 - 0.32)</td>
<td>0.03</td>
<td>0.11 (-0.05 - 0.27)</td>
<td>0.16</td>
</tr>
<tr>
<td>Chronic pain</td>
<td>0.11 (0.05 - 0.27)</td>
<td>0.17</td>
<td><strong>0.25</strong> (0.09 - 0.39)</td>
<td><strong>&lt;0.01</strong></td>
<td>0.11 (-0.05 - 0.27)</td>
<td>0.17</td>
<td><strong>0.22</strong> (0.06 - 0.36)</td>
<td><strong>&lt;0.01</strong></td>
<td>0.13 (-0.03 - 0.29)</td>
<td>0.10</td>
</tr>
<tr>
<td>Chronicity of mental condition</td>
<td>0.08 (-0.08 - 0.23)</td>
<td>0.35</td>
<td><strong>0.19</strong> (0.03 - 0.34)</td>
<td><strong>0.02</strong></td>
<td>0.048 (-0.11 - 0.21)</td>
<td>0.56</td>
<td>0.12 (-0.04 - 0.27)</td>
<td>0.13</td>
<td>0.10 (-0.06 - 0.26)</td>
<td>0.20</td>
</tr>
<tr>
<td>Medical doctor subscale – total score</td>
<td>0.12 (-0.04 - 0.27)</td>
<td>0.15</td>
<td><strong>0.29</strong> (0.13 - 0.43)</td>
<td><strong>&lt;0.01</strong></td>
<td>0.12 (-0.05 - 0.27)</td>
<td>0.16</td>
<td>0.24 (0.09 - 0.39)</td>
<td><strong>&lt;0.01</strong></td>
<td>0.13 (-0.03 - 0.29)</td>
<td>0.10</td>
</tr>
<tr>
<td>Items rated by psychologist</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Understanding of the concept of therapy</td>
<td>0.10 (-0.06 - 0.25)</td>
<td>0.22</td>
<td>0.08 (-0.08 - 0.24)</td>
<td>0.32</td>
<td>0.09 (-0.07 - 0.25)</td>
<td>0.27</td>
<td>0.25 (0.10 - 0.39)</td>
<td><strong>&lt;0.01</strong></td>
<td>0.24 (0.08 - 0.38)</td>
<td><strong>&lt;0.01</strong></td>
</tr>
<tr>
<td>Receptiveness/acceptability to psychological treatment</td>
<td>0.08 (-0.08 - 0.23)</td>
<td>0.34</td>
<td>0.10 (-0.06 - 0.26)</td>
<td>0.23</td>
<td><strong>0.16</strong> (0.00 - 0.31)</td>
<td>0.05</td>
<td><strong>0.16</strong> (0.00 - 0.31)</td>
<td>0.05</td>
<td><strong>0.18</strong> (0.02 - 0.33)</td>
<td>0.02</td>
</tr>
<tr>
<td>Reflectivity</td>
<td>-0.03 (-0.19 - 0.13)</td>
<td>0.72</td>
<td>0.00 (-0.16 - 0.16)</td>
<td>0.99</td>
<td>0.05 (-0.12 - 0.20)</td>
<td>0.58</td>
<td><strong>0.19</strong> (0.04 - 0.34)</td>
<td>0.02</td>
<td><strong>0.17</strong> (0.01 - 0.32)</td>
<td>0.04</td>
</tr>
<tr>
<td>Motivation for active participation</td>
<td>0.11 (-0.05 - 0.27)</td>
<td>0.16</td>
<td>0.14 (-0.02 - 0.30)</td>
<td>0.08</td>
<td>0.13 (-0.03 - 0.28)</td>
<td>0.12</td>
<td><strong>0.21</strong> (0.06 - 0.36)</td>
<td><strong>&lt;0.01</strong></td>
<td><strong>0.18</strong> (0.03 - 0.33)</td>
<td>0.02</td>
</tr>
</tbody>
</table>
## Correlations between single items on the CTP predictor index and the changes of PTSD, depression and anxiety symptoms from baseline and follow-up.

**Bold**=Statistically significant correlation

<table>
<thead>
<tr>
<th>Item</th>
<th>HTQ Pearson (95% CI)</th>
<th>HTQ p</th>
<th>HSCL-depression Pearson (95% CI)</th>
<th>HSCL-depression p</th>
<th>HSCL-anxiety Pearson (95% CI)</th>
<th>HSCL-anxiety p</th>
<th>HAM-D Pearson (95% CI)</th>
<th>HAM-D p</th>
<th>HAM-A Pearson (95% CI)</th>
<th>HAM-A p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive resources</td>
<td>0.13 (-0.03-0.28)</td>
<td>0.12</td>
<td>0.13 (-0.04-0.28)</td>
<td>0.13</td>
<td>0.19 (0.03-0.34)</td>
<td>0.02</td>
<td>0.26 (0.10-0.40)</td>
<td>&lt;0.01</td>
<td>0.23 (0.08-0.38)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Psychologist subscale – total score</strong></td>
<td>0.10 (-0.06-0.25)</td>
<td>0.22</td>
<td>0.11 (-0.05-0.27)</td>
<td>0.17</td>
<td>0.15 (-0.01-0.30)</td>
<td>0.07</td>
<td>0.27 (0.12-0.41)</td>
<td>&lt;0.01</td>
<td>0.25 (0.10-0.39)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Items rated by social worker</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social relations</td>
<td>0.11 (-0.06-0.26)</td>
<td>0.20</td>
<td><strong>0.27</strong> (0.11-0.42)</td>
<td><strong>&lt;0.01</strong></td>
<td><strong>0.19</strong> (0.03-0.34)</td>
<td><strong>0.02</strong></td>
<td>0.16 (0.00-0.31)</td>
<td>0.051</td>
<td><strong>0.19</strong> (0.03-0.34)</td>
<td>0.02</td>
</tr>
<tr>
<td>Education</td>
<td>-0.06 (-0.22-0.11)</td>
<td>0.49</td>
<td>-0.07 (-0.23-0.09)</td>
<td>0.39</td>
<td>-0.08 (-0.24-0.08)</td>
<td>0.33</td>
<td>-0.08 (-0.24-0.08)</td>
<td>0.32</td>
<td>-0.01 (-0.17-0.15)</td>
<td>0.87</td>
</tr>
<tr>
<td>Dwelling</td>
<td>0.04 (-0.12-0.20)</td>
<td>0.63</td>
<td>0.01 (-0.16-0.17)</td>
<td>0.93</td>
<td>0.07 (-0.09-0.23)</td>
<td>0.38</td>
<td>0.05 (-0.11-0.21)</td>
<td>0.52</td>
<td>0.12 (-0.04-0.28)</td>
<td>0.14</td>
</tr>
<tr>
<td>Employment status</td>
<td><strong>0.18</strong> (0.02-0.33)</td>
<td><strong>0.03</strong></td>
<td>0.02 (-0.14-0.18)</td>
<td>0.81</td>
<td>0.06 (-0.10-0.22)</td>
<td>0.47</td>
<td>0.00 (-0.16-0.16)</td>
<td>0.96</td>
<td>0.11 (-0.05-0.27)</td>
<td>0.17</td>
</tr>
<tr>
<td>Integration</td>
<td>0.10 (-0.06-0.26)</td>
<td>0.24</td>
<td><strong>0.27</strong> (0.11-0.42)</td>
<td><strong>&lt;0.01</strong></td>
<td><strong>0.22</strong> (0.06-0.37)</td>
<td><strong>0.01</strong></td>
<td>0.11 (-0.05-0.27)</td>
<td>0.16</td>
<td>0.14 (-0.03-0.29)</td>
<td>0.10</td>
</tr>
<tr>
<td>Social counsellor subscale – total score</td>
<td>0.08 (-0.09-0.24)</td>
<td>0.35</td>
<td><strong>0.17</strong> (0.01-0.32)</td>
<td><strong>0.04</strong></td>
<td>0.14 (-0.02-0.30)</td>
<td>0.09</td>
<td>0.07 (-0.09-0.23)</td>
<td>0.37</td>
<td>0.16 (0.00-0.31)</td>
<td>0.056</td>
</tr>
</tbody>
</table>
**Table 3: Associations between HTQ changes and baseline variables**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean HTQ change (SD)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (n=92)</td>
<td>0.11 (0.45)</td>
<td>0.02</td>
</tr>
<tr>
<td>Female (n=62)</td>
<td>0.31 (0.57)</td>
<td></td>
</tr>
<tr>
<td>Torture exposure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (n=74)</td>
<td>0.16 (0.55)</td>
<td>0.49</td>
</tr>
<tr>
<td>No (n=79)</td>
<td>0.22 (0.47)</td>
<td></td>
</tr>
<tr>
<td>Refugee status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Refugee (n=113)</td>
<td>0.13 (0.48)</td>
<td>0.04</td>
</tr>
<tr>
<td>Family reunified (n=40)</td>
<td>0.32 (0.56)</td>
<td></td>
</tr>
<tr>
<td>Refugee camp</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (n=37)</td>
<td>0.13 (0.37)</td>
<td>0.47</td>
</tr>
<tr>
<td>No (n=115)</td>
<td>0.20 (0.55)</td>
<td></td>
</tr>
<tr>
<td>Asylum centre</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (n=89)</td>
<td>0.14 (0.53)</td>
<td>0.11</td>
</tr>
<tr>
<td>No (n=60)</td>
<td>0.28 (0.50)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pearson’s r</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-0.20</td>
<td>0.01</td>
</tr>
<tr>
<td>Duration of stay in Denmark</td>
<td>-0.19</td>
<td>0.02</td>
</tr>
<tr>
<td>Depression score (HAM-D) at baseline</td>
<td>-0.22</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Anxiety score (HAM-A) at baseline</td>
<td>-0.21</td>
<td>0.01</td>
</tr>
</tbody>
</table>

*Associations between baseline variables and changes in HTQ score in univariate analyses. **Bold**: Statistically significant*
Appendices

A: Psycho-education material used in PTF3
B: Flowchart from the PTF3 psychotherapy manual
C: The CTP Predictor Index - Score sheet and instructions for raters
D: Pharmacological completer analyses, PTF3
Appendix A

Psycho-education material used in PTF3

The following psycho-education handouts were used for the sertraline group in PTF3. The only difference between the psycho-education material used for the venlafaxine and sertraline groups is on the handout concerning medicine where the section about sertraline is replaced with a section about venlafaxine.
Remember!

Depression - anxiety – stress

Life-threatening incidents and uncertain living conditions are causes of physical and mental stress. The production of stress hormones increases in the body when one is under stress. It may be beneficial in a short term but long term stress can cause a wide range of persistent psychiatric problems such as:

- anxiety with physical reactions such as palpitations, sweating and trembling
- sleep problems perhaps with nightmares
- sadness and lack of energy
- constant re-experiences of the traumas
- increased irritability and tension
- concentration and memory difficulties
- self-blame and shame
- thoughts of death
- isolation and loneliness
- difficulty trusting and attaching oneself to other people

Good advice

- Do not be afraid that you are becoming insane. This is a normal stress reaction among people who have experienced severe traumas such as torture, war and flight.

- Anxiety symptoms are unpleasant but not dangerous - they will pass.

- One way to handle your reliving of the trauma is to deflect attention with practical tasks and physical activities.

- Find your own way of maintaining control, if you feel irritated and angry. For example, go for a walk, think of something positive, count to 100 or do something similar.

- Do not blame yourself – other people, not yourself, are to blame for you having a hard time today.

- There is a meaning to every human life - find the things in life which make the most sense to you

- Do not isolate yourself - it aggravates and worsens your symptoms.

- Do not let fear of anything that may remind you of the trauma control your everyday life. It is you who must take control of your life, not the evil spirits from the past.
Remember!

Sessions

The purpose of the sessions at the Trauma Clinic is that you should become better at handling your daily life. In other words, you need to find methods and strategies that can help you overcome the problems you face. You can actually learn to better control your behavior, the anxiety and other emotional reactions. Through the sessions you can increase your ability to see your own strengths and resources. This can help you find meaning in your everyday life and help you become more psychically active and focused than before. Periodically you might feel that the sessions will make you relive old traumas and perhaps worsen your symptoms. However, the treatment will improve your condition in the long run.

Good advice

- The precondition for a successful treatment is that you attend all the planned sessions as much as possible.
- The sessions are just as important as the medication treatment.
- It is important that you participate actively both during and in between sessions.
- The treatment is not something that we as therapists do TO you but WITH you.
- In between sessions, it is important that you work with the things we have talked about in the last session and consider which topics you would like to discuss in the next session.
- It is important to set defined and realistic goals for the treatment.
Remember!

Medicine

Sertraline is used at the Trauma Clinic in order to relieve the symptoms of stress, anxiety and depression. If side effects occur it is typically during the first weeks of the treatment. The most common side effects are usually a dry mouth, stomach problems and dizziness. Some patients experience sexual side effects as well. It usually takes several months before the medication starts to help; the effective dose is typically 100 - 200 mg daily.

Mianserin, which is also used at the clinic, improves the sleep. The most frequent side effect can be tiredness or a heavy sensation in the body in the morning. The effect of this medicine is usually felt fairly quickly; the effective dose is typically 10-30 mg daily.

Sertraline and Mianserin do not create dependency and do not change your personality. The medicine is provided free of charge in during the treatment at the Trauma Clinic and it is cheap to buy afterwards.

Good advice

- Take the medicine as prescribed by your doctor - otherwise it does not work
- Keep on taking the medicine although there are some side effects in the beginning – they often decrease or disappear after a short while.
- In case you experience some discomfort during the treatment; it can often help to change the time of the day where you take the medication.
- Talk to your doctor about the side effects before you decide to terminate the treatment.
- If you have agreed with your doctor that the medication is effective then you should continue to take it for a longer period.
- When you no longer receive treatment at the Trauma Clinic, your general practitioner or psychiatrist can provide you with prescriptions for the medicine.
The effects of Antidepressant

When suffering from depression the brain cannot store the hormones which are responsible for feelings like happiness and therefore you will lack those hormones.

The brain keeps producing them, but they run through the brain too quickly and are destroyed.

The medicine works as a plug that blocks the “hole” where the hormones disappear.

As a result the “hole” closes and slowly the good natural mood hormones are collected.

This collective process is very slowly and it takes at least 1-2 months before you will notice any effects.
Concentration and memory

Most people who have experienced severe traumas have problems with their ability to remember things in their everyday and have difficulties concentrating. You might remember all the evil you have endured in the past but forget the little things of everyday life. There are several reasons for this:

- The unpleasant thoughts and memories continue to "spin round and round in a circle" and fill one's mind. There is almost no "room" in the mind for the present.
- Poor sleep with nightmares might make one feel constantly tired.
- One feels tense and on guard when being among other people - and one finds it difficult to stay focused.
- Pain and headache weaken one’s attention.
- Memory and concentration abilities may also be weakened as part of a depression. Just as a week muscle, the brain needs to be retrained.

Good advice

- Occupy yourself with things to distract your attention away from the negative thoughts and memories of the past. To keep your attention on the present you could, for instance, count all the red objects in the room or concentrate actively on tasting some food or fruit.

- Your lifestyle in general may also influence your concentration and memory abilities. Try to be physically active and eat regularly and healthy.

- Try not to isolate yourself and spend time with the other people even though it is hard.

- Follow the advice of sleep improvement.

- Train your memory and concentration ability. Read something every day, if only for a few minutes at the time. Draw things that you have seen during the day with as many details as possible, or play a memory game with your children.

- Write things down, perhaps in a diary, a calendar, or in a "memory book". You may also use the alarm function in your telephone in order to remember your appointments.
Remember!

Socializing

Many people, who have experienced severe traumas, find it difficult to be with other people. This can be because one finds it difficult to trust other people; one easily gets irritated over small things and gets tired of speaking or just feels uncomfortable among a group of people one perhaps does not know very well.

As a human being, however, we need to be in contact with other people. A life alone in isolation increases one’s mental problems in the long run. In solitude one becomes more focused on the pain and has difficulties finding meaning in everyday life.

Studies have shown that people with a good social network are less often ill. A social network is the people you surround yourself with. It may consist of your family, friends, acquaintances, neighbors, work colleagues or professionals in the public sector.

Studies of quality of life have shown that being occupied with something meaningful during the day has great significance to people. It may be a job but also voluntary work, hobbies, family life, nature experiences and other activities can help to enhance one's quality of life.

Good advice

- Try to be more active and outgoing in your everyday life.
- Seek support in your social network.
- Empower your network, try to be welcoming and open towards other people although it may be hard for you.
- Keep an eye out for activities in your local community.
- Ask your contact person at the commune or our social adviser about activities nearby.
Remember!

Physical Exercise

Research shows that physical activity for half an hour a day can:
- improve the mood
- increase ones energy and physical and mental capacity
- regulate the appetite and improve digestion
- improve the quality of sleep
- reduce pain sensations
- prevent lifestyle diseases

When you start training, you may experience increased pain in your body at first. This reaction is called post workout soreness, and is a natural reaction of the body after a period of physical inactivity. This reaction is not dangerous or harmful and disappears after a while.

Good advice

- Consider how physical activity can become a natural part of your everyday life. It is important that you choose to do something that you like — e.g. activities that you did when you were younger.

- It is important that you choose to do something you enjoy — something you might have done when you were younger.

- Walks are the easiest — it requires no preparation and there is no cost associated with it.

- Running can be the next step — remember to buy a pair of good running shoes.

- Cycling is good as it is easier on the legs than running and you will also get around quickly in the local area. The bike can also be carried along in the train.

- Swimming is a relatively easy, cheap and relaxing way to exercise the whole body.

- Training at your local fitness center can help strengthen your back and shoulder muscles and thereby reduce back pain and headache.

- At the clinic, we have a DVD with instructions of exercises in different languages. The exercises can be done at home.
Remember!

Mind exercises

- Through simple exercises one can learn how to relax the mind and body.
- Find a quiet and calm place and make sure not to be disturbed while you are doing the exercise.
- Below are described two simple exercises, use the one which suits you best.
- Many people find that the exercises are difficult in the beginning, and therefore one has to practise many times before one learns to do them properly. Although, it may be difficult to keep one’s concentration in the beginning, it is important not to give up.

1. Exercise

1. Sit comfortably in an upright position or lie down.
2. Close your eyes and imagine that you're at the bottom of a stairway with 10 stairs.
3. Go slowly and calmly up the stairs.
4. At each step up you breathe slower and try to become more and more relaxed.
5. When you get to the top of the stairway, open your eyes slowly.

2. Exercise

1. Sit comfortably in an upright position or lie down.
2. Close your eyes and think of a pleasant place you know or one you dream about - a beach, a meadow or somewhere similar.
3. Imagine that you are at this pleasant place - listen to the sounds, smell the scents, watch the colors. It is important that you focus on the details one at a time, e.g. the warmth of the sun against your skin and the smells of the flowers.
4. Feel the tranquility and peace fill your body and soul.
5. Open your eyes slowly and stretch your body.
6. Remember that you can always return to this place when you need peace and tranquility in your body or soul.
Breathing

Stress and anxiety are linked to your breathing. The more restless, nervous and stressed you are the more rapid and shallow the breathing becomes. Such breathing may cause physical symptoms such as prickling or tingling sensations in your hands or dizziness and fear of fainting. This accelerates the stress and the anxiety and develops a vicious circle.

This vicious circle can be broken by taking control of the breathing. You can learn some simple techniques which help to achieve calm breathing and thus indirectly, also reduces anxiety and stress.

Exercise

- It is important that the breathing is calm and deep. You should be able to see your stomach expanding when you inhale and you should breathe in and out through your nose.

- In the beginning you listen to your body and your breathing without changing anything; you can just notice how it feels. Is it deep or shallow? Do you breathe through your nose or through your mouth? Is it fast or slow? Do you use energy or is it effortless? How does your body feel?

- Now you begin to change your breathing. Make your breathing deep and calm and breathe through the nose. If you breathe only with your chest, try to breathe down into your stomach. Each time you inhale, your stomach should expand. Put one hand on your stomach and feel it. This makes it easier in the beginning. Now breathe like this for a couple of minutes or longer.

How it should be done

- Both inhaling and exhaling should be through the nose.
- Breathe "with your stomach", i.e. breath with the diaphragm, the chest rises passively and the stomach moves out.
- Exhalation is completely passive, the diaphragm relaxes, the chest sinks and the stomach moves in.
- Exhalation may be somewhat longer than inhalation; the break is half as long.
- Over time you will find that you are getting more and more relaxed by this simple breathing exercise.
Remember!

Sleep
Most people who suffer from stress and depression have major sleep problems – difficulties with falling asleep and sleeping through the night. Poor sleep quality affects the mood and the ability to concentrate during the day. Even small things can become overwhelming and irritating.

Poor sleep at night can develop a vicious circle, where you end up turning days into nights. Common sleeping pills are addictive and lose their effect over time. This type of medicine is not used at the Trauma Clinic. Since sleep problems are some of the symptoms of stress and depression, the treatment of your disorder may also help to overcome your sleeping difficulties after a while.

Good advice

- Avoid consumption of stimulating drinks such as coca-cola, tea and coffee in the evening after dinner. Chamomile tea however, has a soothing and soporific effect.

- Alcohol and tobacco has a negative effect on the quality of sleep.

- Avoid watching disturbing news reports from war zones on TV – especially right before bedtime.

- Read a little, listen to quiet music or do one of the mind exercises before bedtime.

- Be physically active but only during the day. In the evening you should not exercise too hard but taking a walk is ok.

- Ensure a good sleep environment - fresh air and tranquility. Use earplugs, if necessary.

- Buy a bed with a comfortable mattress.

- If you cannot sleep, leave you bed and do not return to bed until you feel sleepy.

- Avoid large meals before bedtime but do not go to bed hungry either.

- Do not look at the watch at night.

- In order to sleep properly it is important that your body and mind have a fixed daily routine. Get up at about the same time each day and sleep no more than 30 minutes during the day.

- Mianserin is the medicine used at the Trauma Clinic to improve the quality of sleep. It is not addictive.
Remember!

Bodily Pain

Many people who have been exposed to traumas suffer from bodily pain. The pain may have different characters and come from various parts of the body. The pain may originate from damaged nerves or may partly be psychologically induced. If you are depressed or anxious, you will feel the pain stronger than if you are mentally balanced. The thoughts and ideas that you might have about your pain also affect the pain experience. If you are worried and are having negative thoughts about the pain, you will feel the pain more intensely than if you are not worried or do not care about the pain.

Pain can be treated with medication, but relaxation techniques and the physical exercise is just as important. It is rare that the pain disappears completely but most people can achieve a certain degree of pain relief and a better life quality despite the pain.

Good advice

- Try to stabilize your use of pain medication in cooperation with your general practitioner. Try to avoid very strong and possibly addictive drugs.

- Pain is often related to anxiety/worry/frustration which causes muscle tension. Therefore the medicine used at the Trauma Clinic also relieves the pain to a certain degree. Relaxation techniques as well can contribute to controlling stress and also to prevent and reduce muscle tension.

- Inactivity worsens the pain. You should exercise to your pain threshold even though you feel tired and/or are having muscle aches in the beginning. Physiotherapy with exercises that you can practice by yourself often helps.

- Isolation aggravates the pain - therefore try to seek contact with other people and strengthen your network. Try to strengthen your social side and thereby your defense against the pain.

- Decide actively that you will move on with your life despite the pain. You need to take control of the pain and not let the pain take control of you. You can name your pain e.g. Peter. When you experience pain, you can “discuss” with your pain: “Well, Peter, there you are again. For how long are you planning to stay around this time?” or “You think you can decide whether I am going for a walk, but I am going to do it anyway – you just have to come along, if you will not go away.”
Remember!

Diet

Many studies conclude that a healthy diet is important for both mind and health. Overall, there is no food or beverage that you cannot have – it is all about how much and how often.

- Healthy food and beverage helps to improve both your physical and mental health and your wellbeing, so that you feel less irritable and depressive, and your sleep and concentration improves.
- Healthy food – preferably combined with regular exercise – can among other things, lower your blood pressure, reduce body cholesterol and regulate your blood sugar.

Good advice

- Eat a balanced diet – then you are certain of getting enough minerals and vitamins. You can also take one vitamin tablet a day.
- When changing your diet, make sure to buy foods that you like – otherwise it can be difficult to keep your dietary changes in the long run.
- Eat light meals regularly rather than a large daily meal. Preferably you should get 3 main meals and 2-3 snacks between meals. This dietary pattern stabilizes your blood sugar and is also favourable with regard to losing weight.
- Eat primarily the kind of carbohydrates that slowly cause the blood sugar level to increase such as: rye bread, oatmeal, wholegrain pasta, brown rice and vegetables like beans, lentils and peas.
- Avoid the carbohydrates that cause a step increase in the blood sugar level such as: white bread, cornflakes and sugar. Replace sweets with nuts, figs or rice crackers. If you eat chocolate, it should be as dark as possible.
- Drink plenty of water - at least 2.5 litres a day. Avoid sugary beverages such as juice and soft drinks.
- Eat food that is rich in dietary fibre – such as coarse vegetables, fruit and whole-grain products – it helps regulate your blood sugar level and improves your digestion.
- Preferably eat fish once or twice a week - fish is rich on vitamin D and is good for the heart.
- Read the description of contents on foods and beverages. Keep informed about fat and carbohydrate content and the total amount of energy. Look for the green Keyhole label which indicates that the product has been health approved by the Danish Veterinary and Food Administration.
- Stick to the food circle: a half plateful of coarse vegetables and fruit, a quarter of a plateful of lean meat or fish, and a quarter of a plateful of products rich in carbohydrates, such as pasta, rice and potatoes.
Remember!

**Muscle tension and neck exercises**

Muscle stress and tensions are by far the most common cause of pain in back and neck. This can cause tension headaches, which is the most common type of headache.

78% of the population have experienced tension headaches and 3% have chronic tension headaches, defined as headache each or every other day around the year. That means that there are many days where you have a sore head from early morning throughout the day, and this pain is hardly affected by the doings of the day. Tension headaches can be triggered by:

- Worries and stress, lack of sleep or poor sleep.
- A large use of painkillers (such as more than 25 of e.g. panodil per week). Be careful, you can get a headache of a large usage of painkillers.
- Sitting still in the same position for a long time or having a bad sitting position, e.g. when watching television or using a computer.
- If you do not exercise, your muscles and joints become stiff, and they will ache when you try to move them – just like a rusty tap that is hard to open.

**Good advice**

The treatment consists mainly of a daily exercise programme for shoulder and neck. The exercise should be done every day, 3-4 times a day throughout a longer period (weeks-months) to have an effect:

1. **Exercise**: Stretch the chest-back: Fold your hands at the neck, pull your elbows backwards and pull your shoulder blades together.
2. **Exercise**: Lateral bend: Pull your chin in and bend your neck slowly to the side, so your ear approaches to your shoulder. Pull your other shoulder downwards and feel the stretch.
3. **Exercise**: Turning: Pull your chin in and turn your neck slowly to the side, so your nose approaches your shoulder. Turn as far as possible on both sides.
4. **Exercise**: Stretching the neck muscles: Pull your chin in and bend your neck slowly forward, so your chin approaches your chest. Place one hand at the back of your head and press gently until you feel a stretch.
5. **Exercise**: Stretch the neck: Sit up straight. Pull your chin in and make your neck long, like if someone pulls your hair towards the ceiling. You should feel your neck being straightened and it tightens at the back of your neck.
Appendix B

Flowchart from the PTF3 psychotherapy manual
The flowchart was used to determine the course of treatment

Flowchart - psychotherapy manual PTF3
If a patient has difficulties with determination of goals, resource work is conducted before moving on to the situation analysis etc.
Appendix C

The CTP Predictor Index
Score sheet and instructions for raters
### Score sheet of the CTP Predictor Index

#### Medical doctor:

<table>
<thead>
<tr>
<th>Category</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motivation</td>
<td></td>
<td></td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Upbringing</td>
<td></td>
<td></td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Previous relevant treatment carried out without measurable effect</td>
<td></td>
<td></td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Chronic pain</td>
<td></td>
<td></td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Chronicity of mental condition</td>
<td></td>
<td></td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

#### Psychologist:

<table>
<thead>
<tr>
<th>Category</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Understanding of the concept of therapy</td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Receptiveness/acceptability to psychological treatment</td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Reflectivity</td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Motivation for active participation</td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Cognitive resources</td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

#### Social worker:

<table>
<thead>
<tr>
<th>Category</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Social relations</td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Dwelling</td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Employment status</td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Integration</td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Motivation</td>
<td>The patient clearly expresses no interest in treatment or feels compelled to seek treatment e.g. by public bodies.</td>
<td>The patient expresses great doubt regarding treatment efficacy or concerns about practical issues such as transport, and therefore has limited motivation for starting treatment.</td>
<td>The clinician and/or the patient doubts whether treatment has interest. Perhaps the patient expresses motivation for trying out treatment, but doubts that it will help.</td>
<td>The patient clearly expresses a desire for change and hope regarding treatment with certain reservations, e.g. a bit of scepticism about some parts of the treatment.</td>
<td></td>
</tr>
<tr>
<td>Upbringing</td>
<td>Has throughout childhood lived under heavily disadvantaged conditions, e.g. suffering from war-like conditions in a refugee camp, being orphaned, hunger, violence or abuse.</td>
<td>Has throughout most of childhood lived under stressful conditions but with some reassuring factors, such as having a primary carer most of the time.</td>
<td>Raised under relatively safe conditions but with some deprivation, e.g. with a strained single provider, lack of care/interest from parents, poverty or the like.</td>
<td>Has throughout childhood lived under fully safe conditions with parents, adequate care and security as well as finances to meet material needs.</td>
<td></td>
</tr>
<tr>
<td>Previous relevant treatment carried out without measurable effect</td>
<td>Has previously completed a full interdisciplinary treatment programme with appropriate dosage of antidepressants &gt; 6 months + psychotherapy &gt; 8 sessions.</td>
<td>Has previously completed a full mono-disciplinary treatment programme, e.g. appropriate dosage of antidepressants &gt; 6 months OR psychotherapy &gt; 8 sessions.</td>
<td>Treatment has been partly attempted e.g. suboptimal dosage or few months of antidepressants, and if psychotherapy then &lt; 8 sessions.</td>
<td>Has discussed mental health issues with GP but not received antidepressants nor psychotherapy.</td>
<td></td>
</tr>
<tr>
<td>Chronic pain</td>
<td>Has &gt; 2 years suffered such severe pain that it constitutes a significant interference with daily life, preventing the patient from coping with shopping, cooking, etc.</td>
<td>Has &gt; 2 years had constant pain in many parts of the body and/or constant severe headache, but yet still cope with activities of daily living.</td>
<td>Is moderately bothered by pain but the duration or scope is less than 0 and 1.</td>
<td>Has only limited pain problems in a single area of the body, such as a knee or hip, and no significant reduction of functional capacity.</td>
<td></td>
</tr>
<tr>
<td>Chronicity of mental condition</td>
<td>Current symptoms, with the same severity and impact on functional capacity, have lasted &gt; 10 years.</td>
<td>Current symptoms, with the same severity and impact on functional capacity, have lasted 2-10 years.</td>
<td>Current symptoms, with the same severity and impact on functional capacity, have lasted 1-2 years.</td>
<td>Current symptoms, with the same severity and impact on functional capacity, have lasted &lt; 1 year.</td>
<td></td>
</tr>
</tbody>
</table>

Chronicity of mental condition

<p>| Motivation | The patient clearly expresses no interest in treatment or feels compelled to seek treatment e.g. by public bodies. | The patient expresses great doubt regarding treatment efficacy or concerns about practical issues such as transport, and therefore has limited motivation for starting treatment. | The clinician and/or the patient doubts whether treatment has interest. Perhaps the patient expresses motivation for trying out treatment, but doubts that it will help. | The patient clearly expresses a desire for change and hope regarding treatment with certain reservations, e.g. a bit of scepticism about some parts of the treatment. |
| Upbringing | Has throughout childhood lived under heavily disadvantaged conditions, e.g. suffering from war-like conditions in a refugee camp, being orphaned, hunger, violence or abuse. | Has throughout most of childhood lived under stressful conditions but with some reassuring factors, such as having a primary carer most of the time. | Raised under relatively safe conditions but with some deprivation, e.g. with a strained single provider, lack of care/interest from parents, poverty or the like. | Has throughout childhood lived under fully safe conditions with parents, adequate care and security as well as finances to meet material needs. |
| Previous relevant treatment carried out without measurable effect | Has previously completed a full interdisciplinary treatment programme with appropriate dosage of antidepressants &gt; 6 months + psychotherapy &gt; 8 sessions. | Has previously completed a full mono-disciplinary treatment programme, e.g. appropriate dosage of antidepressants &gt; 6 months OR psychotherapy &gt; 8 sessions. | Treatment has been partly attempted e.g. suboptimal dosage or few months of antidepressants, and if psychotherapy then &lt; 8 sessions. | Has discussed mental health issues with GP but not received antidepressants nor psychotherapy. |
| Chronic pain | Has &gt; 2 years suffered such severe pain that it constitutes a significant interference with daily life, preventing the patient from coping with shopping, cooking, etc. | Has &gt; 2 years had constant pain in many parts of the body and/or constant severe headache, but yet still cope with activities of daily living. | Is moderately bothered by pain but the duration or scope is less than 0 and 1. | Has only limited pain problems in a single area of the body, such as a knee or hip, and no significant reduction of functional capacity. |
| Chronicity of mental condition | Current symptoms, with the same severity and impact on functional capacity, have lasted &gt; 10 years. | Current symptoms, with the same severity and impact on functional capacity, have lasted 2-10 years. | Current symptoms, with the same severity and impact on functional capacity, have lasted 1-2 years. | Current symptoms, with the same severity and impact on functional capacity, have lasted &lt; 1 year. |</p>
<table>
<thead>
<tr>
<th>Understanding of the concept of therapy</th>
<th>Expresses absolutely no understanding of the concept of therapy.</th>
<th>Expresses limited understanding of the concept of therapy.</th>
<th>Expresses some understanding of the concept of therapy.</th>
<th>Expresses good understanding of the concept of therapy.</th>
<th>Expresses full understanding of the concept of therapy, has perhaps tried it previously with good effect.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Receptiveness/acceptability to psychological treatment</td>
<td>Is by no means convinced that psychological treatment can help or finds it culturally completely unacceptable to see a psychologist.</td>
<td>Expresses substantial scepticism about psychological treatment, and strongly doubts the benefit of the treatment.</td>
<td>Is reasonably open towards giving psychological treatment a chance, expresses perhaps some scepticism about results.</td>
<td>Is generally agreeable towards starting psychological treatment, has perhaps heard good things about it from others.</td>
<td>Has had a desire to see a psychologist, thinks that psychological treatment is an essential part of the treatment programme, and has perhaps had good experiences from previous programmes.</td>
</tr>
<tr>
<td>Reflectivity</td>
<td>Has no self-knowledge and reflectivity, completely black and white simplistic image of oneself and the surroundings.</td>
<td>Has rather limited self-knowledge and reflectivity.</td>
<td>Has some self-knowledge, but appears to lack a fully realistic view of own situation and resources, which, for example, are seen in an overly positive or negative light.</td>
<td>Has good self-knowledge and reflectivity with only few exceptions, e.g. in relation to certain individuals or situations.</td>
<td>Has excellent self-knowledge and demonstrates good abilities to reflect on own situation, resources, and limitations.</td>
</tr>
<tr>
<td>Motivation for active participation</td>
<td>Appears completely passive and entirely dismissive towards actively participating, e.g. doing homework.</td>
<td>Contributes only to a lesser extent actively, and appears mostly passive and appellant.</td>
<td>Expresses an interest in trying to participate actively, but the clinician doubts the patient’s actual motivation/ability to contribute actively.</td>
<td>Expresses a wish to participate actively, but has few reservations, e.g. concerns about own abilities to master the given assignments.</td>
<td>Clearly expresses understanding of the necessity of active participation and willingness to work actively for improvement, both during and between sessions, e.g. through homework.</td>
</tr>
<tr>
<td>Cognitive resources (memory, concentration + ability to stay focused)</td>
<td>Has no ability to remember or understand even basic information/need to be repeated many times, and the patient seems absent and is unable to follow the conversation.</td>
<td>Memory is clearly impaired, manages only to stay focused for a short while at a time.</td>
<td>Memory or ability to concentrate is undoubtedly somewhat reduced, but the patient manages to stay focused and follow the conversation most of the time.</td>
<td>Has only minor difficulty staying focused, e.g. towards the end of the session.</td>
<td>Has no problems with memory or concentration, manages with ease to follow the conversation and asks relevant questions.</td>
</tr>
<tr>
<td>Social relations</td>
<td>Has none or less than weekly contact with others (friends/family).</td>
<td>Has virtually no friends, and barely has sufficient contact with immediate family (spouse, children).</td>
<td>Has sufficient contact with immediate family (spouse, children), but sees few people beyond that.</td>
<td>Has sufficient contact with both immediate and more distant family, and also has a few friends.</td>
<td>Has good contact with family (if family is in Denmark), sees several friends, and actively seeks social contexts in day-to-day life.</td>
</tr>
<tr>
<td>-------------------</td>
<td>-----------------------------------------------</td>
<td>-------------------------------------------------</td>
<td>-------------------------------------------------</td>
<td>-------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Education</td>
<td>Has no or few years of education, is illiterate or write/read only a few words.</td>
<td>Has either fully or partly completed primary school education.</td>
<td>Has completed secondary school education or equivalent.</td>
<td>Has completed higher education (medium-length) or equivalent.</td>
<td>Has completed university education or equivalent.</td>
</tr>
<tr>
<td>Dwelling</td>
<td>Homeless</td>
<td>Uncertain housing situation / only temporary accommodation.</td>
<td>Has dwelling but insufficient space or issues with its location.</td>
<td>Seemingly sufficient housing conditions in relation to needs, but the patient is still unsatisfied, e.g. with the costs or size of the place.</td>
<td>Lives under fully satisfying conditions.</td>
</tr>
<tr>
<td>Employmen atus</td>
<td>Is unemployed with no household income, gets by e.g. through loans from family.</td>
<td>Has an unclear employment status, e.g. is presently under consideration for subsidised job or early retirement benefit, or will become so in immediate continuation of the treatment programme.</td>
<td>Is temporarily in receipt of benefits, e.g. integration benefit, social security benefits or sick pay, but the patient is temporarily exempt from e.g. the job activation programme while receiving psychiatric treatment.</td>
<td>Has a fairly certain employment status, but does not manage a full-time job, e.g. employed part-time, subsidised job or receives (early) retirement benefit.</td>
<td>Has a full-time job.</td>
</tr>
<tr>
<td>Integration</td>
<td>Lives as if completely left out of the community, does not speak Danish, and has no contact with anyone outside own ethnic group.</td>
<td>Feels poorly integrated and excluded from the community. Hopes to / dreams of eventually returning to home country. Does, however, manage necessary contact with the surrounding community.</td>
<td>Has some contact with the surrounding community, but feels in other ways excluded, e.g. through language problems or negative experiences with discrimination or the like.</td>
<td>Feels well-integrated, speaks Danish well enough to get by in everyday life, and has contact with people outside own ethnic group.</td>
<td>See oneself as a Dane and speaks Danish fluently. Sees Denmark as home country, and is not keen on returning to country of origin.</td>
</tr>
</tbody>
</table>

All scores are added together. Total score range from 0-60.
Appendix D
Pharmacological completer analyses, PTF3
## 1: Baseline and follow up differences

### Symptom self-ratings

<table>
<thead>
<tr>
<th>Rating</th>
<th>Group</th>
<th>Mean baseline score (SD)</th>
<th>Mean follow-up score (SD)</th>
<th>Difference (SD)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HTQ</td>
<td>Sertraline</td>
<td>3.25 (0.37)</td>
<td>3.01 (0.53)</td>
<td>-0.24 (0.54)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HTQ</td>
<td>Venlafaxine</td>
<td>3.22 (0.41)</td>
<td>3.00 (0.57)</td>
<td>-0.22 (0.45)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HSCL-25</td>
<td>Sertraline</td>
<td>3.05 (0.43)</td>
<td>2.84 (0.63)</td>
<td>-0.21 (0.61)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HSCL-25</td>
<td>Venlafaxine</td>
<td>3.06 (0.44)</td>
<td>2.91 (0.59)</td>
<td>-0.15 (0.43)</td>
<td>0.01</td>
</tr>
<tr>
<td>SCL-90</td>
<td>Sertraline</td>
<td>2.46 (0.82)</td>
<td>2.38 (0.89)</td>
<td>-0.08 (0.94)</td>
<td>0.46</td>
</tr>
<tr>
<td>SCL-90</td>
<td>Venlafaxine</td>
<td>2.57 (0.84)</td>
<td>2.52 (0.81)</td>
<td>-0.05 (0.63)</td>
<td>0.60</td>
</tr>
<tr>
<td>VAS-Back</td>
<td>Sertraline</td>
<td>6.55 (2.95)</td>
<td>6.66 (2.82)</td>
<td>-0.11 (3.99)</td>
<td>0.78</td>
</tr>
<tr>
<td>VAS-Back</td>
<td>Venlafaxine</td>
<td>7.28 (2.40)</td>
<td>7.00 (2.32)</td>
<td>-0.28 (2.10)</td>
<td>0.33</td>
</tr>
<tr>
<td>VAS-Arm</td>
<td>Sertraline</td>
<td>5.78 (3.39)</td>
<td>5.59 (3.44)</td>
<td>-0.19 (3.20)</td>
<td>0.60</td>
</tr>
<tr>
<td>VAS-Arm</td>
<td>Venlafaxine</td>
<td>5.56 (3.39)</td>
<td>6.21 (2.76)</td>
<td>0.65 (2.85)</td>
<td>0.11</td>
</tr>
<tr>
<td>VAS-Leg</td>
<td>Sertraline</td>
<td>6.58 (3.13)</td>
<td>6.09 (3.20)</td>
<td>-0.49 (2.62)</td>
<td>0.11</td>
</tr>
<tr>
<td>VAS-Leg</td>
<td>Venlafaxine</td>
<td>6.89 (3.10)</td>
<td>7.10 (2.49)</td>
<td>0.21 (2.63)</td>
<td>0.57</td>
</tr>
<tr>
<td>VAS-Head</td>
<td>Sertraline</td>
<td>7.03 (2.44)</td>
<td>6.37 (3.05)</td>
<td>-0.66 (3.26)</td>
<td>0.09</td>
</tr>
<tr>
<td>VAS-Head</td>
<td>Venlafaxine</td>
<td>7.16 (2.70)</td>
<td>6.25 (2.78)</td>
<td>-0.91 (2.61)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

HTQ, HSCL-25, SCL = 1-4 (1 best score), VAS = 0-10 (0 best score)

### Life quality/level of functioning self-ratings

<table>
<thead>
<tr>
<th>Rating</th>
<th>Group</th>
<th>Mean baseline score (SD)</th>
<th>Mean follow-up score (SD)</th>
<th>Difference (SD)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO-5</td>
<td>Sertraline</td>
<td>12.74 (13.38)</td>
<td>23.43 (24.77)</td>
<td>10.5 (23.17)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>WHO-5</td>
<td>Venlafaxine</td>
<td>15.35 (15.90)</td>
<td>20.22 (20.26)</td>
<td>4.87 (18.69)</td>
<td>0.058</td>
</tr>
<tr>
<td>SDS</td>
<td>Sertraline</td>
<td>24.77 (5.14)</td>
<td>21.77 (8.11)</td>
<td>-3.00 (8.13)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>SDS</td>
<td>Venlafaxine</td>
<td>22.65 (6.10)</td>
<td>22.68 (7.01)</td>
<td>0.03 (7.47)</td>
<td>0.98</td>
</tr>
<tr>
<td>SAS-SR</td>
<td>Sertraline</td>
<td>2.98 (0.75)</td>
<td>2.72 (0.77)</td>
<td>-0.26 (0.69)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>SAS-SR</td>
<td>Venlafaxine</td>
<td>3.01 (0.71)</td>
<td>2.86 (0.69)</td>
<td>-0.15 (0.69)</td>
<td>0.11</td>
</tr>
<tr>
<td>CSS</td>
<td>Sertraline</td>
<td>23.64 (7.45)</td>
<td>24.41 (7.51)</td>
<td>0.77 (7.99)</td>
<td>0.41</td>
</tr>
<tr>
<td>CSS</td>
<td>Venlafaxine</td>
<td>24.02 (6.96)</td>
<td>24.62 (6.97)</td>
<td>0.60 (6.70)</td>
<td>0.50</td>
</tr>
</tbody>
</table>

WHO-5 = 0-100 (100 best score), SDS = 0-10 (0 best score), SAS-SR = 1-5 (1 best score), CSS = 1-7 (7 best)
### Observer ratings

<table>
<thead>
<tr>
<th>Rating</th>
<th>Group</th>
<th>Mean baseline score (SD)</th>
<th>Mean follow-up score (SD)</th>
<th>Difference (SD)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAM-D</td>
<td>Sertraline</td>
<td>23.78 (5.51)</td>
<td>22.13 (8.10)</td>
<td>-1.65 (7.52)</td>
<td>0.053</td>
</tr>
<tr>
<td>HAM-D</td>
<td>Venlafaxine</td>
<td>23.78 (5.38)</td>
<td>22.34 (8.11)</td>
<td>-1.44 (7.10)</td>
<td>0.12</td>
</tr>
<tr>
<td>HAM-A</td>
<td>Sertraline</td>
<td>26.80 (6.74)</td>
<td>26.25 (9.29)</td>
<td>-0.54 (9.07)</td>
<td>0.60</td>
</tr>
<tr>
<td>HAM-A</td>
<td>Venlafaxine</td>
<td>26.80 (6.38)</td>
<td>25.66 (9.45)</td>
<td>-1.14 (8.77)</td>
<td>0.32</td>
</tr>
<tr>
<td>GAF-F</td>
<td>Sertraline</td>
<td>48.44 (6.63)</td>
<td>50.28 (8.29)</td>
<td>1.84 (6.79)</td>
<td>0.04</td>
</tr>
<tr>
<td>GAF-F</td>
<td>Venlafaxine</td>
<td>48.48 (5.25)</td>
<td>52.50 (7.23)</td>
<td>4.02 (6.62)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>GAF-S</td>
<td>Sertraline</td>
<td>47.44 (5.90)</td>
<td>51.32 (8.34)</td>
<td>3.88 (6.61)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>GAF-S</td>
<td>Venlafaxine</td>
<td>47.89 (5.67)</td>
<td>52.30 (7.12)</td>
<td>4.41 (8.28)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

HAM = 0-4 (0 best score), GAF = 0-100 (100 best score)

**Blue = Improvement**  
**Red = Deterioration**  
**Green = Statistically significant change**

### 2: Regression coefficients for group differences at follow up adjusted for baseline scores

**Total completer sample (n=156)**

<table>
<thead>
<tr>
<th>Rating</th>
<th>Regression coefficient (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HTQ</td>
<td>0.00 (-0.16 to 0.17)</td>
<td>0.96</td>
</tr>
<tr>
<td>HSCL</td>
<td>0.05 (-0.12 to 0.23)</td>
<td>0.54</td>
</tr>
<tr>
<td>SCL</td>
<td>0.09 (-0.15 to 0.34)</td>
<td>0.47</td>
</tr>
<tr>
<td>SDS</td>
<td>0.59 (-0.23 to 1.42)</td>
<td>0.16</td>
</tr>
<tr>
<td>WHO-5</td>
<td>-4.76 (-11.86 to 2.34)</td>
<td>0.19</td>
</tr>
<tr>
<td>VAS-neck/back</td>
<td>0.05 (-0.80 to 0.89)</td>
<td>0.91</td>
</tr>
<tr>
<td>VAS-arms</td>
<td>0.75 (-0.14 to 1.64)</td>
<td>0.10</td>
</tr>
<tr>
<td>VAS-legs</td>
<td>0.83 (0.04 to 1.63)</td>
<td>0.04</td>
</tr>
<tr>
<td>VAS-head</td>
<td>-0.18 (-1.11 to 0.74)</td>
<td>0.70</td>
</tr>
<tr>
<td>SAS-SR</td>
<td>0.11 (-0.10 to 0.32)</td>
<td>0.30</td>
</tr>
<tr>
<td>CSS</td>
<td>0.24 (-1.93 to 2.40)</td>
<td>0.83</td>
</tr>
<tr>
<td>GAF-F</td>
<td>2.20 (-0.30 to 4.69)</td>
<td>0.09</td>
</tr>
<tr>
<td>GAF-S</td>
<td>0.70 (-2.04 to 3.43)</td>
<td>0.50</td>
</tr>
<tr>
<td>HAM-D</td>
<td>0.23 (-2.13 to 2.59)</td>
<td>0.85</td>
</tr>
<tr>
<td>HAM-A</td>
<td>-0.54 (-3.37 to 2.30)</td>
<td>0.71</td>
</tr>
</tbody>
</table>

**Blue: In favor of sertraline**  
**Red: In favor of venlafaxine**  
**Green: Statistically significant**