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Imagery rehearsal therapy and/or mianserin in treatment of refugees diagnosed with PTSD: Results from a randomized controlled trial

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Abstract

Sleep disturbances are frequently part of the symptomatology in refugees with post-traumatic stress disorder (PTSD). It has been suggested that targeting sleep disturbances may enhance the outcome of PTSD treatment. However, randomized studies on the effect of treatment focusing on sleep disturbances in refugees with PTSD are lacking. The aim of this study was to examine add-on treatment with imagery rehearsal therapy (IRT) and/or mianserin against treatment as usual (TAU) alone in a sample of trauma-affected refugees with PTSD at 8–12 months follow-up. In a randomized controlled trial, 219 adult refugees diagnosed with PTSD and suffering from sleep disturbances were randomized to four groups (1:1:1:1) receiving, respectively, TAU, TAU + mianserin, TAU + IRT, and TAU + IRT + mianserin. The primary outcome was subjective sleep quality (Pittsburgh Sleep Quality Index) and the secondary outcomes included PTSD and depression symptoms, level of functioning and subjective well-being. The data were analysed using mixed models. The only significant effect of IRT was on level of functioning ($p = .040$, ES 0.44), whereas there was no significant effect of mianserin on any of the measured outcomes. Low adherence to both IRT (39%) and mianserin (20%) was observed. Contrary to our hypothesis, we did not find IRT or mianserin to be superior to TAU. The low adherence may potentially cause an underestimation of the effect of IRT and mianserin and indicates a necessity to further analyse the complex factors that may impact the motivation and ability of trauma-affected refugees to participate in and profit from available treatment options.

KEYWORDS
psychopharmacology, psychotherapy, PTSD, sleep, treatment

1 | INTRODUCTION

In a previous study, 99% of trauma-affected refugees diagnosed with post-traumatic stress disorder (PTSD) reported being bothered to some degree by sleep disturbances and recurrent nightmares and 53% reported being extremely bothered by sleep disturbances (Sandahl et al., 2017). Among other trauma-affected populations, such as war veterans, around 70%–90% report sleep disturbances and recurrent nightmares (El-Solh et al., 2018; Waltman et al., 2018). Despite these high numbers, most treatments for PTSD focus primarily on daytime PTSD symptoms and do not focus directly on sleep disturbances. Studies have shown sleep disturbances prior to, and in the time following, a traumatic event to be a risk factor for development of PTSD (Gehrman et al., 2013; van Liempt, 2012; Mellman et al., 2002). This suggests that sleep disturbances are not merely a secondary symptom to PTSD, but may play a role in the development and maintenance of PTSD. A bidirectional relation between sleep disturbances and PTSD has been hypothesized, and targeting sleep disturbances in treatment of PTSD has been suggested to accelerate recovery from PTSD (El-Solh et al., 2018; Miller et al., 2020; Spoormaker & Montgomery, 2008). The high incidence of sleep disturbance associated with PTSD and the suggested bidirectional relation accentuate the need for treatment interventions targeting sleep disturbances (El-Solh et al., 2018; Miller et al., 2020). However, randomized studies on the effects of treatment focusing on sleep disturbances are scarce in general and lacking in trauma-affected refugees (Gieselmann A et al., 2019; Sandahl, Vindbjerg, et al., 2017).

Reviews and meta-analysis have found cognitive-behavioural therapy (CBT) for sleep disturbances in PTSD to be an effective treatment for sleep disturbances, PTSD and depression (Gieselmann A et al., 2019; Ho et al., 2016; Miller et al., 2020; Waltman et al., 2018). Imagery rehearsal therapy (IRT) is one such adapted CBT where the patient rehearses positive images and, guided by the therapist, writes and rehearses a new and non-disturbing script of a nightmare. The American Academy of Sleep Medicine recommends IRT as first choice psychotherapeutic treatment for PTSD-related nightmare disorders, and IRT is likewise recommended as the preferred treatment in reviews and meta-analyses (Casement & Swanson, 2012; El-Solh et al., 2018; Miller et al., 2020; Waltman et al., 2018; Yücel et al., 2020). Based on the above-mentioned recommendations and the absence of randomized controlled trials studying IRT in trauma-affected refugees (Gieselmann A et al., 2019; Sandahl, Vindbjerg, et al., 2017), it was decided to study IRT in the current trial.

There is an absence of suitable pharmacological treatment of sleep disturbances, including nightmares in PTSD (El-Solh et al., 2018; Miller et al., 2020; Sandahl, Vindbjerg, et al., 2017; Waltman et al., 2018). In a recent meta-analysis Prazosin (a selective α-1-adrenergic receptor antagonist) showed similar effect as IRT on nightmares, sleep quality and PTSD (Yücel et al., 2020). However, prazosin is not available for treatment in Denmark. Often benzodiazepines and sedating antipsychotics are chosen despite recommendations to limit the use of these drugs off-label because of serious adverse effects and unknown long-term effects (Brownlow et al., 2015; El-Solh et al., 2018). As a safer alternative to antipsychotics and benzodiazepines, sedating antidepressants may be chosen as an off-label treatment for sleep disturbances (El-Solh et al., 2018). Mianserin is one of several sedating antidepressants and has shown promising effect in treatment of sleep disturbances in trauma-affected refugees (Buhmann, 2014). Mianserin is a noradrenergic and specific serotonergic antidepressant similar in receptor profile to the more frequently prescribed antidepressant mirtazapine but with a shorter half-life. Mianserin acts as a histamine H_1- antagonist and alfa$_1$- antagonist, whereby a sedating effect, and sleep enhancing effect, may be achieved (Ferreri et al., 2008; Mayers & Baldwin, 2005).

The current study is a response to a need for randomized controlled studies comparing pharmacological and psychotherapeutic interventions in different combinations and sequences in trauma-affected populations in general (El-Solh et al., 2018; Miller et al., 2020; Waltman et al., 2018) and in refugee populations in particular (Gieselmann A et al., 2019; Sandahl, Vindbjerg, et al., 2017). Studies of the effect of sleep-enhancing treatment on daily functioning and quality of life are scarce and needed to shed light on the clinical implications of treatment focusing on sleep in PTSD (Brownlow et al., 2015; Spoormaker & Montgomery, 2008).

In the current study, we hypothesized that treatment with IRT and/or mianserin added to treatment as usual (TAU), will improve sleep quality, reduce severity of nightmares, symptoms of PTSD and depression, and furthermore improve quality of life and level of functioning compared to TAU. Furthermore, we hypothesized that treatment with IRT and mianserin added to TAU will improve the same parameters more than each add-on treatment alone.

The aim of this study was to estimate treatment effects of IRT and/or mianserin compared to TAU in a pragmatic randomized controlled clinical trial in outpatient trauma-affected refugees with PTSD.

2 | MATERIALS AND METHODS

2.1 | Study design

The study was a randomized controlled superiority trial with an allocation ratio of 1:1:1:1 and an allocation sequence with block size unknown to the investigator. The randomization was stratified by gender.

The study was approved by The Ethics Committee of the Capital Region of Denmark (H-15014503), the Danish Medicines Agency (EudraCT: 2015-004153-40) and the Danish Data Protection Agency (2012-58-0004) and was registered at ClinicalTrials.gov ID (NCT02761161).

A study protocol has been published and can be consulted for an in-depth description of methods (Sandahl et al., 2017).

2.2 | Participants

Participants were recruited and data collected at a tertiary mental health service outpatient clinic in the Capital Region of Denmark, the Competence Centre for Transcultural Psychiatry (CTP).

2.3 | Inclusion criteria

- Adults (18 years or older)
- Refugees or persons who have been family reunified with a refugee
- PTSD according to the International Classification of Diseases, 10th edition (ICD-10) research criteria
- Prior psychological trauma experienced outside Denmark. Trauma was defined as imprisonment or detention with torture (according to the United Nations definition of torture) or acts of cruel, inhuman and degrading treatment or punishment. Trauma could also be organized violence, long-term political persecution and harassment, or war and civil war experiences.
- Sleep disturbances measured as a score > 8 on The Pittsburgh Sleep Quality Index
- Nightmares measured as a score ≥ 'a little' on the Harvard Trauma Questionnaire nightmare item
- Signed informed consent

2.4 | Exclusion criteria

- Severe psychotic disorder (defined as patients with an ICD-10 diagnosis F2x and F30.1-F31.9). Participants were excluded only if the psychotic-like experiences were assessed to be part of an independent psychotic disorder and not part of a severe PTSD and/or depression
- Current alcohol or drug use disorder (F1x.24-F1x.26)
- Known neurodegenerative disorder (Alzheimer's disease, Parkinson's disease, Lewy-Body dementia)
- Need for admission to psychiatric hospital
- Pregnant and breastfeeding women and women of reproductive age who wished to conceive during the project period.
- Allergy towards active ingredients or excipients in mianserin
- Lack of informed consent

2.5 | Pre-treatment assessment

All patients referred to the CTP were screened in a 2–3-h pre-treatment assessment with a physician. Sociodemographic factors were collected using a standardized interview form. Standardized diagnostic tools, part of Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (Wing et al., 1990), the ICD-11 diagnostic interview for PTSD, and the ICD-10 research criteria were applied in the interview. Patients received oral and written information about the study. If a patient was eligible to participate, the patient provided written informed consent for study participation at the pre-treatment assessment.

2.6 | The intervention and treatment

The study design corresponded to a 2 (mianserin versus non-mianserin) ×2 (IRT versus non-IRT) factorial design with four groups receiving the following treatment: (1) treatment as usual (TAU), (2) TAU and add-on treatment with mianserin, (3) TAU and add-on treatment with IRT, (4) TAU and add-on treatment with both IRT and mianserin.

2.7 | Treatment as usual

Treatment as usual was an interdisciplinary treatment approach, covering a period of 8–12 months, with medicine according to standard at the CTP (best clinical practice in the field), physiotherapy, psychoeducation (including sleep hygiene education and relaxation techniques) and manual-based CBT. The treatment was two-phased: phase one, 2–4 months treatment provided by physician and physiotherapist; phase two, 4–8 months of combined treatment provided by both physician and psychologist. For a detailed description of TAU, please see study protocol (Sandahl, Jennum, et al., 2017). Experienced interpreters were present in sessions, if needed, and during ratings, as required.

2.8 | Trial psychotherapy: Imagery rehearsal therapy

Imagery rehearsal therapy was integrated in six sessions of manual-based CBT administered by a psychologist. The IRT treatment consisted of three methods: (1) psychoeducation on disturbing dreams, nightmares and sleep, as well as exercises in cognitive restructuring, (2) imagery education and positive imagery exercises, and (3) imagery rescripting of the disturbing dream or nightmare and rehearsal of a new and non-disturbing dream. The manual was developed to accommodate individual differences in the participants and allowed the therapist flexibility in sequencing of methods. However, positive imagery exercises had to be performed prior to initiating imagery rescripting. The number of sessions devoted to each method was flexible and adapted to the individual participant.

All psychologists were trained and supervised in this specific method, described in detail in the IRT manual available at ctp-net.dk.

2.9 | Trial medication: mianserin

Mianserin was prescribed and delivered to the participant by the treating physician and initiated at 10 mg before bedtime. The dose could be increased gradually to a maximum dosage of 30 mg, adjusted according to effect and side effects. At each session with the

physician, the participants were asked to report whether they had taken their medication as prescribed, and the current dose of mianserin was registered. Adherence was monitored by measuring the plasma concentration of mianserin after phase one and phase two (post-treatment).

2.10 | Measures

Treatment outcomes were evaluated pre-treatment (baseline) and after phase one and phase two (post-treatment), using both self-administered rating scales and observer ratings (see Figure s1 [please see study protocol for an in-depth description of ratings; Sandahl, Jennum, et al., 2017]). The rating scales applied were translated into relevant languages.

The primary outcome was Pittsburgh Sleep Quality Index (PSQI) assessments of sleep quality and the severity of sleep disturbances. The PSQI consists of 19 items and measures seven components of sleep (Buysse et al., 1989; Insana et al., 2013).

The following self-administered rating scales were used: frequency and severity of nightmares were measured with the Disturbing Dreams and Nightmare Severity Index (DDNSI) (Krakow, 2006); severity of PTSD symptoms was measured with The Harvard Trauma Questionnaire (HTQ) (Hollifield et al., 2002); severity of anxiety (10 questions) and depression (15 questions) was measured with the Hopkins Symptom Check List (HSCL-25) (Mollica et al., 1987); quality of life was measured with WHO-5 (Timmerby et al., 2016); and functional impairment was measured with the Sheehan Disability Scale (SDS) (Sheehan & Sheehan, 2008).

For observer ratings: global functioning was assessed with Global Assessment of Functioning – Symptoms (GAF-S) and Functioning (GAF-F) (Grootenboer et al., 2012) and the World Health Organization Disability Assessment Schedule (WHODAS 2.0) (Ustün et al., 2010); and depression and anxiety were assessed with Hamilton Depression and Anxiety scales (HAM-D and HAM-A) (Bech et al., 1986). GAF and WHODAS were rated by the responsible physician. HAM-A and HAM-D were carried out by trained medical students. The physicians and medical students participated in regular training sessions to ensure high interrater reliability.

The participants were asked about adverse events in each session with a physician and events were registered in accordance with definitions and current legislation by the Danish Medicines Agency (Medicines Agency, 2020). In addition, all discomfort in connection with psychotherapy was registered.

2.11 | Blinding

Blinding of participants and clinicians was not possible due to the different nature of the treatment interventions. However, blinded assessors performed the HAM-D and HAM-A ratings pre- and post-treatment.

2.12 | Statistics

2.12.1 | Power calculations and size of material

In previous studies, the minimal clinically important difference (MCID) on PSQI was considered 2.5 scale points. This study aimed to detect a clinically important difference between TAU and add-on treatment and not merely a statistically significant difference, and hence the MCID was set to 2.5 scale points on the PSQI and the within-groups standard deviation was set to 3 scale points (Jespersen & Vuust, 2012). With a power of 90% and alpha 0.05, we estimated a sample size for each group of 32 and a total of 128. Based on the completion rate in previous studies at the CTP, 75%–80% of the participants were estimated to complete the treatment (Buhmann, 2014; Nordbrandt, 2020). Due to the expected large dropout, a formula ($k = 1/(100\%\text{-dropout}\%)2$) calculating the increased number of participants needed in each group was used. We increased the number of participants included with a factor $k = 1/(100\%–25\%)2 = 1.78 \times 128$ and consequently estimated a total required sample size of 228 participants.

2.12.2 | Data analysis

Data were analysed using STATA/SE 14.2 for windows. The chi-squared test and one-way ANOVA were used to analyse group difference in pre-treatment characteristics and descriptive data on the content of the treatment.

The 2 (mianserin versus non-mianserin) ×2 (IRT versus non-IRT) factorial design of the study makes it possible to test the two-factor interaction between mianserin and IRT as well as the three-factor interaction between mianserin, IRT and time. Mixed models analysed the $2 \times 2 \times 2$ combinations of the two treatment factors and time (pre-treatment versus post-treatment) in models including all two-factor interactions and one three-factor interaction. The analyses showed no significant interactions between the two treatment factors, and results will be presented for models including main effects of the two treatment conditions and time as well as the interactions between each treatment factor and time. These models estimate effects of IRT by comparing IRT treatment condition (groups 3 and 4) to non-IRT treatment condition (groups 1 and 2), and effects of mianserin by comparing mianserin treatment condition (groups 2 and 4) to non-mianserin treatment condition (groups 1 and 3). As no pre-treatment group differences were expected, treatment effects are indicated by significant post-treatment treatment effects and treatment*time interactions.

Means for pre- and post-treatment ratings and the differences between pre- and post-treatment ratings were estimated using Stata's "margins" command. Stata's "contrast" command was used to test group differences in pre- and post-treatment mean scores and to test pre–post differences in ratings and group differences in these differences, corresponding to the treatment by time interactions.

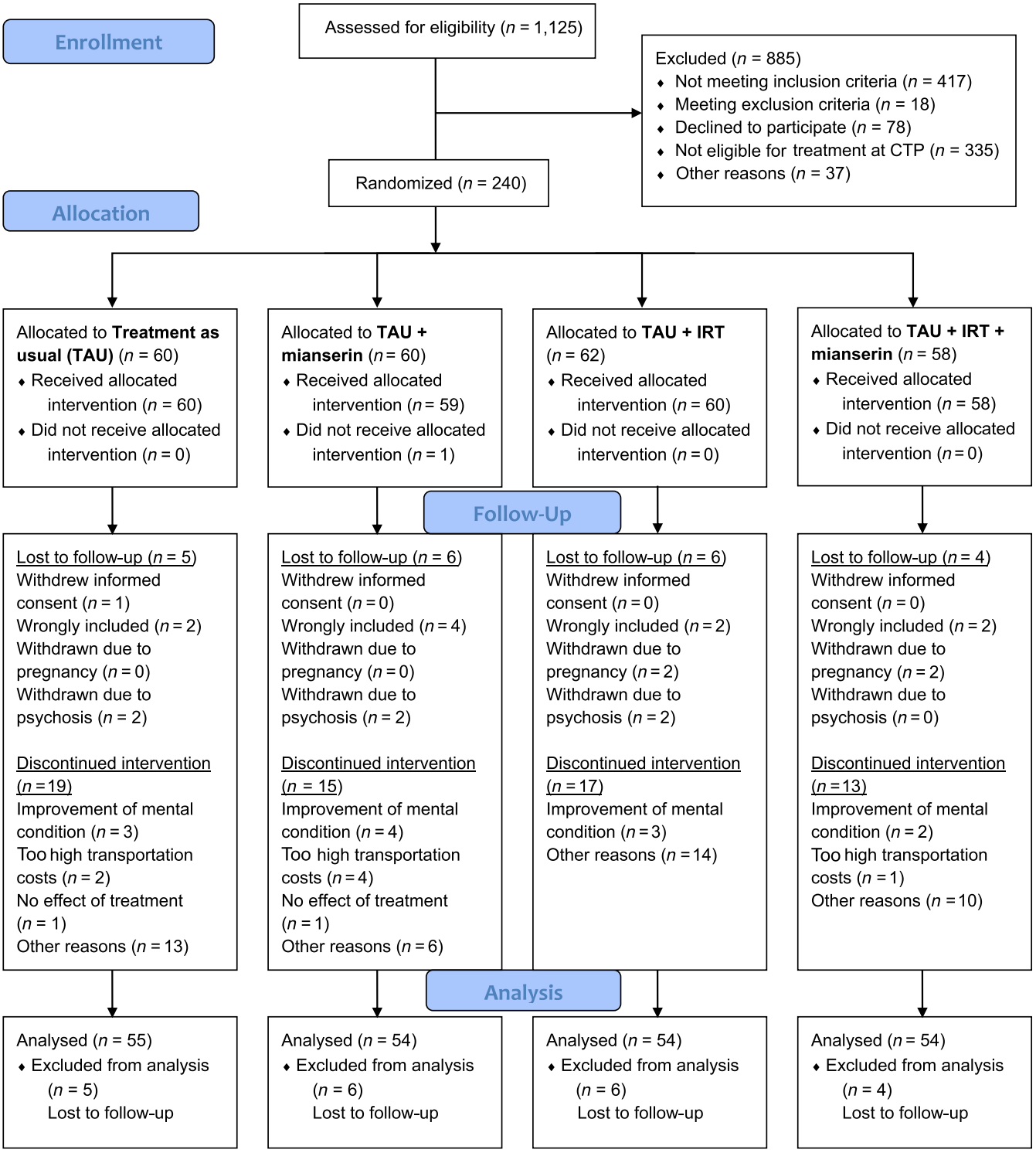

FIGURE 1 CONSORT flow diagram

Effect size was calculated by dividing the mean difference between two treatment conditions by the pooled pre-treatment standard deviation for the respective rating scale. Robust standard errors were used for conducting the mixed-model analyses. The main analyses were performed on the intention-to-treat sample, which for each outcome included all participants with pre-treatment data.

Per-protocol completers of IRT were defined as participants for whom IRT methods had been used in a minimum of four sessions. Per-protocol completers of the pharmacological treatment with mianserin were defined as participants who had a plasma level of mianserin above 0 post-treatment. The mixed-model analyses were repeated on a reduced per-protocol sample.

3 | RESULTS

In the period from March 2016 to April 2018, 1,125 patients consecutively referred to treatment at the CTP were screened for the study and 240 patients were randomized. The most frequent reasons for non-inclusion were not being eligible for treatment at the CTP or not meeting inclusion criteria, in particular that of refugee status. A total of 21 participants, equally distributed in the intervention groups, were excluded from analysis due to withdrawal of informed consent, error in eligibility assessment, or due to emergence of pregnancy or psychosis during the study. The modified intention-to-treat sample hence consisted of 219 participants. No participants were re-categorized, but included as receiving planned treatment in the intention-to-treat analyses (see flow of study illustrated in Figure 1).

3.1 | Pre-treatment characteristics of participants

The participants were comparable regarding sociodemographic variables at baseline, including age, gender, trauma history, diagnosis or previous treatments, as illustrated in Table 1.

3.2 | The treatment

In the following, the actual content of treatment will be presented. A detailed description is available in Table s1. The mean treatment length was 11.28 months, with no significant difference between groups ($p = .163$).

3.3 | IRT

A total of 110 participants were randomized to add-on treatment with IRT. There were 48 participants (44%) randomized to IRT who did not receive IRT during the study due to early dropout in phase one, because of normalized sleep or because of ongoing social stress (for instance lack of housing) or ongoing traumas (for instance family member imprisoned in Syria), participant in crisis or suffering from severe depression or cognitive deficits.

A total of 43 participants (39%) attended a minimum of four sessions of IRT and were considered IRT completers. A total of six participants (5%) reported discomfort relating to treatment with IRT.

No differences were found in pre-treatment characteristics, pre-treatment rating scores or reasons for dropout between IRT completers and non-completers.

3.4 | Mianserin

A total of 108 participants were randomized to mianserin add-on treatment. There were seven participants (6%) randomized to mianserin who did not receive mianserin during the study due to early dropout, normalized sleep or not wanting to change current medicine to mianserin.

A total of 101 participants received mianserin during the study, with a mean dose of 13.49 (6.23). After phase one, 70 out of the 81 participants who were registered to receive mianserin had levels of mianserin measured and a total of 37 participants (34%) randomized to treatment with mianserin were adherent (i.e., had a plasma level above 0).

At the end of the study (post-treatment), 46 participants out of the 51 participants who were registered to receive mianserin had levels of mianserin measured. Based on blood samples, a total of 22 participants (20%) randomized to mianserin were adherent to mianserin.

A total of 62 participants (57%) reported adverse events or reactions in response to mianserin. The most frequent reported adverse reaction to mianserin was daytime fatigue, reported by 34 participants (31%). A detailed report of adverse events and reactions in response to mianserin is available in Table S3 (Adverse events and reactions in response to mianserin).

No differences were found in pre-treatment characteristics, pre-treatment rating scores or reasons for dropout between adherent and non-adherent participants.

Due to a mistake made by the responsible physicians, four participants not randomized to mianserin received mianserin during the study.

3.5 | Adverse events

The number of serious adverse events (SAEs) did not differ between the four groups. No SAEs led to discontinuation. No serious adverse reactions (SARs) or suspected unexpected serious adverse reactions (SUSARs) were reported.

3.6 | Outcomes

The mixed model analyses on the ITT sample are illustrated in Table 2, which shows estimated means and differences in means between the add-on treatment condition and the no add-on treatment condition and between the pre- and post-treatment difference scores. The *p*-values for differences in change over time between the add-on treatment condition and the no add-on condition correspond to the interaction of each treatment with time, and if significant these differences may be interpreted to reflect significant effects of one of the two treatments. Because of the randomization and lack of pre-treatment differences, significant post-treatment differences between the add-on treatment and the no add-on treatment conditions may also reflect treatment effects. Table S2 presents mixed model estimates of means and differences in means between the four interventions groups. The *p*-values are presented for differences in changes over time between the four intervention groups.

TABLE 1 Pre-treatment characteristics

Pre-treatment characteristics	All (*N* = 219)	1: TAU (*N* = 55)	2: TAU + mianserin (*N* = 54)	3: TAU + IRT (*N* = 56)	4: TAU + IRT + mianserin (*N* = 54)
			Mean (*SD*)		
Demographic information					
Age (*n* =219)*	44.4 (10.4)	46.3 (10.2)	41.9 (10.1)	45.8 (10.9)	43.5 (10.2)
Years since arrival in Denmark (*n* = 211)*	13.3 (9.6)	14 (9.3)	12.8 (9.7)	14.6 (9.8)	11.8 (9.3)
			N (%)		
Male gender	110 (51)	29 (53)	27 (49)	28 (50)	26 (48)
Female gender	109 (49)	26 (47)	27 (50)	28 (50)	28 (52)
Country of origin (*n* = 207)*					
Afghanistan (*n* = 26)	26 (13)	8 (16)	5 (10)	5 (9)	8 (15)
Iran (*n* = 19)	19 (9)	7 (14)	4 (8)	4 (7)	4 (8)
Iraq (*n* = 54)	54 (26)	14 (28)	15 (29)	17 (31)	8 (15)
Lebanon (*n* = 15)	15 (7)	2 (4)	6 (12)	5 (9)	2 (4)
Syria (*n* = 58)	58 (28)	14 (28)	16 (31)	10 (19)	18 (35)
Other (*n* = 35)	35 (17)	5 (10)	5 (10)	13 (24)	12 (23)
Refugee camp before arrival in DK (*n* = 166)*	42 (25)	7 (18)	10 (24)	17 (40)	8 (19)
Danish Asylum Centre (*n* = 142)*	97 (68)	24 (62)	23 (72)	23 (62)	27 (79)
Trauma history					
War (*n* = 210)*	205 (98)	53 (98)	52 (100)	50 (98)	50 (94)
Torture (*n* = 189)*	68 (36)	16 (36)	13 (27)	19 (37)	20 (43)
Imprisonment (*n* = 195)*	83 (42)	19 (41)	18 (36)	21 (40)	25 (52)
Soldier (*n* = 189)*	47 (25)	11 (23)	12 (26)	15 (31)	9 (20)
Sexual violence (*n* = 147)*	23 (16)	5 (14)	7 (18)	5 (13)	6 (19)
Violence from relatives (*n* = 164)*	60 (37)	10 (24)	20 (48)	14 (33)	16 (42)
Cranial trauma (*n* = 166)*	62 (37)	12 (29)	14 (33)	18 (41)	18 (46)
>10 years since trauma (*n* = 172)*	126 (73)	32 (76)	28 (65)	37 (77)	29 (74)
Psychosocial status					
Needing translator during medical doctor sessions (*n* = 189)*	119 (63)	30 (61)	32 (68)	28 (57)	29 (66)
Affiliation to the labour market/studying (*n* = 183)*	67 (36)	19 (42)	20 (43)	14 (29)	13 (31)
Income from labour (*n* = 196)*	13 (7)	1 (2)	7 (14)	2 (4)	3 (6)
Living alone all the time (*n* = 198)*	28 (14)	8 (16)	11 (21)	2 (4)	7 (15)
Having children of <18 years of age (*n* = 160)*	130 (80)	30 (77)	34 (89)	35 (81)	31 (78)
Education > 10 years from home country (*n* = 165)*	86 (52)	23 (58)	16 (36)	25 (57)	22 (59)
Work experience in Denmark (*n* = 197)*	96 (48)	23 (47)	23 (4)	26 (51)	24 (50)

(Continues)

TABLE 1 (Continued)

Pre-treatment characteristics	All (*N* = 219)	1: TAU (*N* = 55)	2: TAU + mianserin (*N* = 54)	3: TAU + IRT (*N* = 56)	4: TAU + IRT + mianserin (*N* = 54)
			Mean (*SD*)		
Diagnoses (ICD-10) additional to PTSD					
Depression (*n* = 219)	157 (72)	40 (73)	39 (72)	39 (70)	39 (72)
Enduring personality change after catastrophic experience (F.62.0) (*n* = 64)*	9 (14)	3 (16)	4 (21)	1 (6)	1 (9)
Other psychiatric disorder (*n* = 62)*	6 (10)	1 (6)	1 (7)	2 (11)	2 (15)
Psychiatric symptoms for ≥10 years (*n* = 179)*	100 (56)	29 (63)	23 (50)	24 (52)	24 (59)
Functional impairment for ≥10 years (*n* = 175)*	24 (14)	8 (18)	10 (21)	4 (10)	2 (5)
Previous treatment					
Previous psychotherapy (*n* = 204)*	94 (46)	26 (50)	23 (43)	26 (52)	19 (39)
Previous psychopharmacological treatment (*n* = 202)*	138 (68)	33 (65)	35 (67)	34 (68)	36 (73)
Previously admitted to psychiatric hospital (*n* = 190)*	23 (12)	6 (13)	5 (10)	6 (13)	6 (13)
Concurrent psychopharmacological treatment at baseline					
Any psychopharmacological treatment at baseline (219)	96 (44)	26 (47)	20 (37)	31 (55)	19 (35)
Antidepressants (219)	76 (35)	15 (27)	15 (28)	29 (52)	17 (31)
Antipsychotics (219)	23 (11)	9 (16)	2 (4)	5 (9)	7 (13)
Benzodiazepines or non-benzodiazepine hypnotics (219)	16 (7)	6 (11)	3 (6)	4 (7)	3 (6)
Other (194)	8 (4)	4 (8)	1 (2)	1 (2)	2 (4)

Abbreviations: *SD*, standard deviation; TAU, treatment as usual; IRT, imagery rehearsal therapy.

*Data not available for all randomized participants

Using the mixed model, the change over time measured as the difference between pre- and post-treatment PSQI scores between treatment conditions was not statistically significant for IRT versus non-IRT ($p = .561$) or for mianserin versus non-mianserin ($p = .064$). Thus, neither the IRT treatment condition nor the mianserin treatment condition affected the subjective sleep quality of the participants compared to the non-IRT treatment condition or non-mianserin treatment condition. The marginal significant difference for the mianserin treatment condition reflected a larger decrease in PSQI scores for the non-mianserin condition. Correspondingly, the post-treatment difference between the mianserin treatment condition and non-mianserin treatment condition was significant at the 5% level.

Although there were no significant differences between the treatment conditions, we found a statistically significant decrease in PSQI scores for all four treatment conditions between the pre- and post-treatment ratings. However, the changes between pre- and post-treatment ratings did not reach the minimal clinically important difference (MCID) of 2.5 scale points on the PSQI.

On the secondary outcome measures, the only significant pre- to post-treatment difference between treatment conditions was between IRT and non-IRT on SDS scores ($p = .040$). For the remaining secondary outcome measures, there were no significant pre- to post-treatment differences between treatment conditions. Several secondary outcome measures (HTQ, HSCL-25, WHO-5, GAF-F and GAF-S) showed significant improvement in rating scores over time for the IRT treatment condition and for the non-mianserin treatment condition, whereas the mianserin treatment condition and non-IRT treatment condition only showed significant improvement on a limited number of secondary outcome measures (WHO-5, GAF-S).

The results of the per-protocol completer analyses were consistent with the intention-to-treat analyses and showed no statistically significant difference between treatment conditions on the primary or secondary outcome measures.

TABLE 2 Mixed model analyses intention-to-treat sample

Rating	Treatment condition	Mean pre-treatment score (*SE*)	Mean post-treatment score (*SE*)	Difference (*SE*)	*p*-value	Effect size
PSQI	IRT	16.50 (0.29)	14.52 (0.49)	−2.00 (0.49)	**0.000****	
	Non-IRT	16.01 (0.28)	14.41 (0.46)	−1.60 (0.46)	**0.001****	
	Difference	0.49 (0.40)	0.11 (0.66)	−0.39 (0.67)		0.13
	Difference, *p*-value	0.220	0.873	0.561		
	Mianserin	16.43 (0.29)	15.25 (0.45)	−1.17 (0.40)	**0.003***	
	Non-mianserin	16.10 (0.28)	13.66 (0.51)	−2.43 (0.55)	**0.000****	
	Difference	0.32 (0.40)	1.58 (0.67)	1.26 (0.68)		0.42
	Difference, *p*-value	0.422	**0.019***	0.064		
HTQ	IRT	3.12 (0.04)	2.87 (0.07)	−0.24 (0.07)	**0.000****	
	Non-IRT	3.11 (0.04)	3.00 (0.06)	−0.11 (0.06)	0.086	
	Difference	0.01 (0.06)	−0.13 (0.09)	−0.14 (0.09)		0.33
	Difference, *p*-value	0.865	0.181	0.137		
	Mianserin	3.13 (0.04)	3.02 (0.06)	−0.11 (0.06)	0.090	
	Non-mianserin	3.10 (0.04)	2.85 (0.07)	−0.24 (0.07)	**0.000***	
	Difference	0.03 (0.06)	0.17 (0.10)	0.14 (0.09)		0.33
	Difference, *p*-value	0.615	0.080	0.135		
HSCL-25	IRT	3.02 (0.04)	2.77 (0.08)	−0.25 (0.07)	**0.000****	
	Non-IRT	2.95 (0.05)	2.86 (0.07)	−0.09 (0.07)	0.205	
	Difference	0.07 (0.07)	−0.10 (0.10)	−0.17 (0.10)		0.36
	Difference, *p*-value	0.297	0.360	0.091		
	Mianserin	3.00 (0.05)	2.89 (0.07)	−0.10 (0.06)	0.090	
	Non-mianserin	2.98 (0.05)	2.73 (0.08)	−0.24 (0.08)	**0.002***	
	Difference	0.02 (0.07)	0.16 (0.11)	0.14 (0.10)		0.28
	Difference, *p*-value	0.765	0.135	0.165		
WHO-5	IRT	16.09 (1.48)	26.68 (2.69)	10.59 (2.44)	**0.000****	
	Non-IRT	18.58 (1.61)	23.46 (2.37)	4.87 (2.47)	**0.048***	
	Difference	−2.49 (2.18)	3.22 (3.58)	5.71 (3.46)		0.36
	Difference, *p*-value	0.253	0.369	0.099		
	Mianserin	17.22 (1.62)	25.29 (2.52)	7.95 (2.29)	**0.001****	
	Non-mianserin	17.34 (1.45)	24.98 (2.60)	7.51 (2.63)	**0.004***	
	Difference	−0.12 (2.18)	0.31 (3.64)	0.43 (3.50)		0.03
	Difference, *p*-value	0.956	0.932	0.902		
DDNSI	IRT	17.13 (0.70)	16.30 (0.76)	−0.83 (0.90)	0.358	
	Non-IRT	16.14 (0.74)	16.76 (0.83)	0.63 (0.99)	0.526	
	Difference	0.99 (1.02)	−0.46 (1.12)	−1.45 (1.33)		0.21
	Difference, *p*-value	0.329	0.682	0.276		
	Mianserin	16.22 (0.69)	16.66 (0.73)	0.46 (0.97)	0.634	
	Non-mianserin	17.08 (0.74)	16.39 (0.85)	−0.66 (0.91)	0.469	
	Difference	−0.85 (1.01)	0.27 (1.12)	1.13 (1.33)		0.16
	Difference, *p*-value	0.398	0.811	0.397		

(Continues)

TABLE 2 (Continued)

Rating	Treatment condition	Mean pre-treatment score (*SE*)	Mean post-treatment score (*SE*)	Difference (*SE*)	*p*-value	Effect size
SDS	IRT	22.87 (0.56)	20.95 (0.91)	−1.93 (0.97)	**0.046***	
	Non-IRT	21.04 (0.63)	21.79 (0.74)	0.74 (0.85)	0.385	
	Difference	−1.83 (0.84)	−0.84 (1.18)	−2.67 (1.30)		0.44
	Difference, *p*-value	**0.030***	0.475	**0.040***		
	Mianserin	22.53 (0.61)	22.06 (0.83)	−0.40 (0.95)	0.676	
	Non-mianserin	21.43 (0.58)	20.56 (0.86)	−0.79 (0.88)	0.369	
	Difference	1.10 (0.84)	1.50 (1.21)	0.39 (1.31)		0.06
	Difference, *p*-value	0.191	0.215	0.765		
HAM-D	IRT	21.77 (0.55)	21.06 (0.85)	−0.71 (0.79)	0.369	
	Non-IRT	22.42 (0.55)	22.47 (0.93)	0.04 (0.97)	0.966	
	Difference	−0.65 (0.77)	−1.40 (1.26)	−0.75 (1.25)		0.14
	Difference, *p*-value	0.401	0.267	0.547		
	Mianserin	22.53 (0.59)	22.88 (0.85)	0.36 (0.83)	0.663	
	Non-mianserin	21.65 (0.51)	20.61 (0.93)	−1.03 (0.94)	0.272	
	Difference	0.88 (0.77)	2.27 (1.26)	1.39 (1.25)		0.25
	Difference, *p*-value	0.255	0.072	0.264		
HAM-A	IRT	26.35 (0.71)	26.59 (0.96)	0.23 (0.93)	0.801	
	Non-IRT	26.06 (0.75)	26.62 (1.10)	0.55 (1.18)	0.640	
	Difference	0.29 (1.03)	−0.04 (1.46)	−0.32 (1.50)		0.04
	Difference, *p*-value	0.781	0.981	0.830		
	Mianserin	26.62 (0.75)	27.81 (0.91)	1.19 (0.88)	0.176	
	Non-mianserin	25.79 (0.70)	25.38 (1.13)	−0.40 (1.22)	0.740	
	Difference	0.84 (1.03)	2.43 (1.46)	1.59 (1.50)		0.22
	Difference, *p*-value	0.417	0.095	0.286		
GAF-F	IRT	51.59 (0.80)	55.37 (1.32)	3.79 (1.28)	**0.003***	
	Non-IRT	51.60 (0.74)	53.66 (1.19)	2.07 (1.18)	0.080	
	Difference	−0.01 (1.09)	1.71 (1.78)	1.72 (1.74)		0.19
	Difference, *p*-value	0.994	0.338	0.326		
	Mianserin	51.87 (0.76)	54.09 (1.29)	2.20 (1.19)	0.065	
	Non-mianserin	51.31 (0.78)	54.98 (1.23)	3.66 (1.28)	**0.004***	
	Difference	0.57 (1.08)	−0.89 (1.79)	−1.45 (1.75)		0.18
	Difference, *p*-value	0.603	0.619	0.407		
GAF-S	IRT	50.58 (0.57)	54.84 (1.15)	4.27 (1.13)	**0.000****	
	Non-IRT	51.43 (0.51)	53.38 (1.07)	1.96 (1.06)	0.065	
	Difference	−0.85 (0.77)	1.46 (1.57)	2.31 (1.54)		0.41
	Difference, *p*-value	0.270	0.352	0.134		
	Mianserin	50.88 (0.52)	53.93 (1.09)	3.03 (1.01)	**0.003***	
	Non-mianserin	51.11 (0.57)	54.33 (1.14)	3.19 (1.19)	**0.007***	
	Difference	−0.24 (0.77)	−0.41 (1.59)	−0.16 (1.56)		0.03
	Difference, *p*-value	0.749	0.798	0.918		

(Continues)

TABLE 2 (Continued)

Rating	Treatment condition	Mean pre-treatment score (*SE*)	Mean post-treatment score (*SE*)	Difference (*SE*)	*p*-value	Effect size
WHODAS	IRT	25.68 (0.86)	25.18 (1.59)	−0.50 (1.47)	0.731	
	Non-IRT	26.17 (0.82)	24.21 (1.63)	−1.97 (1.81)	0.276	
	Difference	−0.50 (1.19)	0.96 (2.28)	1.46 (2.32)		0.18
	Difference, *p*-value	0.676	0.672	0.529		
	Mianserin	25.41 (0.85)	24.74 (1.55)	−0.70 (1.53)	0.648	
	Non-mianserin	26.43 (0.83)	24.69 (1.66)	−1.77 (1.75)	0.311	
	Difference	−1.02 (1.19)	0.05 (2.29)	1.07 (2.31)		0.13
	Difference, *p*-value	0.390	0.982	0.642		

PSQI, 1–21 (1 best score); HTQ, 1–4 (1 best score); HSCL-25 ,1–4 (1 best score); WHO-5, 0–100 (100 best score); DDNSI, 1–37 (1 best score); SDS, 0–10 (0 best score); HAM-D, 0–52 (0 best score); HAM-A, 0–56 (0 best score); GAF-F, 0–100 (100 best score); WHODAS, 1–48 (0 best score).

Abbreviations: IRT, imagery rehearsal therapy; SE, standard error; PSQI, Pittsburgh Sleep Quality Index; HTQ, Harvard Trauma Questionnaire; HSCL-25, Hopkins Symptom Checklist-25; WHO-5, Well Being Index; DDNSI, Disturbing Dreams and Nightmare Severity Index; SDS, Sheehan Disability Scale; HAM-D/-A, Hamilton Depression and Anxiety scales; GAF-F/-S, Global Assessment of Functioning (function/symptoms); WHODAS, The World Health Organization Disability Assessment Schedule.

The table presents mixed-model estimates of means, *SE*, *p*-values and effect size. The *p*-values are presented for differences in pre-treatment and post-treatment scores and changes over time between the add-on treatment condition and the no add-on condition corresponding to the interaction of each treatment with time.

*$p \leq .05$.

**$p \leq .001$.

4 | DISCUSSION

This randomized controlled trial is the first large-scale trial to study the effectiveness of add-on psychotherapeutic and psychopharmacological treatment of sleep disturbances in trauma-affected refugees. Contrary to our hypothesis, we did not find treatment with IRT or mianserin added to TAU to be superior to TAU alone on the primary or secondary outcome measures except for level of functioning, where add-on treatment with IRT was shown to be superior. Adherence rates were low for both IRT and mianserin.

We found no interaction between IRT and mianserin. The effectiveness of IRT and mianserin will be discussed separately below, as will the limitations and strengths of the study and its clinical implications.

4.1 | Imagery rehearsal therapy

Add-on treatment with IRT had no significant effect on sleep quality ($p = .561$), severity of nightmares, symptoms of PTSD and depression, or quality of life compared to the non-IRT treatment condition. Add-on treatment with IRT had a significant effect on level of functioning measured on the SDS compared to the non-IRT treatment condition ($p = .040$). The IRT treatment condition had a statistically non-significant numerical advantage over the non-IRT treatment condition for most outcomes (PSQI, HTQ, HSCL-25, WHO-5, DDNSI, HAM-A, HAM-D, GAF-F, GAF-S). When looking at participants completing IRT per protocol the results were similar.

Several previous studies have reported large effect sizes for IRT. However, these studies compared IRT to a waiting list control condition (Casement & Swanson, 2012; Yücel et al., 2020), whereas the current study compared add-on IRT with an active control condition. The results of the current study are in line with two previous studies comparing IRT with an active psychotherapy control condition that reported a non-significant change of sleep quality, nightmare frequency and PTSD symptoms (Belleville et al., 2018; Cook et al., 2010). The failure of the IRT treatment condition to reach superiority over the non-IRT treatment condition in this study may thus partly be attributable to an effect of TAU, where elements of sleep-enhancing treatment are part of the treatment sessions with the physician, psychologist and physiotherapist.

A total of 44% of participants randomized to IRT did not receive IRT during the study and 39% of participants completed IRT, defined as a minimum of four sessions of IRT. Several factors may impact the participants' ability to participate in and profit from IRT. We found a high baseline score for the PSQI (16.25 *SD* 2.99), a high HTQ score and a high HSCL/HAMD score, reflecting severity of sleep disturbances, symptoms of PTSD and depression. Furthermore, 56% of participants had been suffering from symptoms of PTSD for more than 10 years, reflecting chronicity of symptoms. Chronicity and severity of PTSD and comorbidity of other disorders have been argued to limit treatment responsiveness to IRT (Cook et al., 2010) and chronicity of PTSD has been found to be a negative predictor for treatment outcome in a previous study on treatment of PTSD in trauma-affected refugees (Nordbrandt, 2020).

Post-migration stressors, such as difficult living conditions, unsecure visa status or ongoing trauma, may be barriers to participation in or profit from psychotherapy (Li et al., 2016), and post-migration stressors may have impacted the ability to participate in and respond to IRT.

Patients for whom sleep disturbances cause distress and dysfunction may potentially be more motivated to participate in treatment focusing on sleep-related PTSD symptoms than patients for whom sleep disturbances are experienced less prominently (Miller et al., 2019). Furthermore, it has been reported that other factors associated with the multifaceted concept of motivation, for instance illness beliefs, may impact psychotherapy outcome (Reich et al., 2015).

Chronicity and severity of symptoms, post-migration stressors and aspects related to motivation for treatment may be factors behind the observed high non-initiation rate and low completer rate, all possibly contributing to the modest effect of IRT in this study.

4.2 | Mianserin

Add-on treatment with mianserin had no significant effect on sleep quality ($p = .064$), severity of nightmares, symptoms of PTSD and depression, or quality of life and level of functioning compared to non-mianserin. The non-mianserin treatment condition had a statistically non-significant numerical advantage over the mianserin treatment condition for most outcomes (PSQI, HTQ, HSCL-25, WHO-5, SDS, DDNSI, HAM-A, HAM-D, GAF-F, GAF-S, WHODAS). The marginally significant difference on the PSQI between the mianserin treatment condition and non-mianserin treatment condition reflected a larger decrease in PSQI scores for the non-mianserin treatment condition. However, the difference was no longer marginally significant when removing the PSQI domain addressing treatment of sleep disturbances with medication, and the non-mianserin treatment condition was no longer superior. When looking at participants completing mianserin per protocol the results were similar.

These findings are contrary to those of a previous study which indicated that mirtazapine, which is similar to mianserin in receptor profile, plus sertraline showed a non-significant, although numerical, advantage over sertraline plus placebo on sleep disturbances and PTSD symptoms (effect size −0.46) (Schneier et al., 2015).

A total of only 22 participants (20%) were adherent to treatment with mianserin at the end of the study. The main explanation for the low adherence is most likely found in an unfavourable ratio between perceived improvement of sleep and experienced side effects. Contrary to our expectations, a total of 62 participants (57%) randomized to mianserin reported adverse reactions, and adverse reactions were reported to have negatively influenced their adherence to the trial medication. Although some barriers to adherence were eliminated in the study, factors related to motivation for pharmacotherapy (Balán et al., 2013), differences between participants and physicians regarding explanatory models and understanding of mental disorders and psychopharmacological treatment may have contributed to the low adherence rate (Wallach-Kildemoes et al., 2014).

4.3 | Strengths and limitations

The main strengths of this study are the randomized design with an active control condition, the large sample size, and the pragmatic design and analysis of the intention-to-treat sample, which prevent an overestimation of treatment response, which might be found if samples were selected and analyses performed merely on a completer basis and compared to a non-active control condition.

The pragmatic design contains some methodological challenges. Due to the pragmatic design and the full integration of the study in a clinical setting, the study design was not placebo controlled and neither patients nor clinicians were blinded to treatment intervention due to the non-comparable content of the two add-on interventions. The broad inclusion of participants reporting any level of sleep disturbances and nightmares may have included patients for whom sleep disturbances were just one of several symptoms and perhaps not the most prominent, and of minor importance for the participant. This may have contributed to the low adherence rates.

The treatment non-initiation rate for the IRT treatment condition was high (44%) and the treatment completer rate for the IRT treatment condition was low (39%), and factors related to treatment non-initiation and treatment completion may have contributed to the non-significant effect of IRT.

A total of only 22 participants (20%) were adherent to treatment with mianserin at the end of the study and factors related to adherence may have contributed to the non-significant effect of mianserin.

Despite the large original sample size of the study, the final relatively small completer sample for both IRT and mianserin may potentially cause an underestimation of the effect of the two treatment conditions.

4.4 | Research implications

The low level of adherence to IRT and mianserin indicates a need for further analysis of the complex factors that impact the motivation and ability of trauma-affected refugees to participate in and benefit from psychotherapy and psychopharmacological treatment and are crucial for development of effective treatment interventions. Possible predictors of treatment initiation, treatment dropout and treatment outcome regarding IRT and mianserin need further examination, as does the timing of sleep-enhancing treatment in PTSD treatment interventions. We propose further research regarding patient-centred care and a flexible modular approach to treatment (Karatzias & Cloitre, 2019), which can be guided by thorough and continuous assessments of symptoms that the patient experiences as relevant, and which will allow several different and differently sequenced validated interventions in the course of a patient's treatment.

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CONFLICT OF INTEREST

The authors declare that they have no financial or other competing interests.

AUTHOR CONTRIBUTIONS

Hinuga Sandahl, Poul Jennum, Lone Baandrup and Jessica Carlsson conceived and designed the study. Hinuga Sandahl and Jessica Carlsson conducted the study. Hinuga Sandahl performed the data analysis. Erik Lykke Mortensen advised on methodological and statistical issues. Hinuga Sandahl, Poul Jennum, Lone Baandrup, Erik Lykke Mortensen and Jessica Carlsson drafted the manuscript. All authors have read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy and ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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