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CLINICAL RESEARCH ARTICLE

Interpersonal psychotherapy versus sertraline for women with posttraumatic stress disorder following recent sexual assault: a randomized clinical trial

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ABSTRACT

Background: Sexual assault often triggers posttraumatic stress disorder (PTSD), a potentially chronic severe mental disorder. Most guidelines recommend selective serotonin reuptake inhibitors (SSRIs) and trauma-focused psychotherapies as treatment options. Interpersonal Psychotherapy (IPT), adapted for PTSD (IPT-PTSD), focuses on interpersonal consequences of trauma rather than confronting the trauma itself. Studies have found IPT-PTSD efficaciously reduced PTSD symptoms with limited attrition. No efficacy trials have compared IPT-PTSD and SSRI. We hypothesized IPT would reduce PTSD, anxiety, and depressive symptoms more than sertraline among women with PTSD following a recent sexual assault.

Objectives: To compare the efficacy of IPT-PTSD to SSRI sertraline in a 14-week randomized clinical trial for women with PTSD following a recent sexual assault.

Methods: Seventy-four women with PTSD who had suffered sexual assault in the last six months were randomly assigned to 14 weeks of IPT-PTSD ($n = 39$) or sertraline ($n = 35$). Instruments assessed PTSD, anxiety, and depressive symptoms. This randomized clinical trial was conducted in São Paulo, Brazil, using the Clinician-Administered PTSD Scale-5 (CAPS-5) as the primary outcome measure.

Results: Both treatments significantly reduced PTSD, anxiety, and depressive symptoms, without between-group outcome differences. CAPS-5 mean decreased from 42.5 (SD = 9.4) to 27.1 (SD = 15.9) with sertraline and from 42.6 (SD = 9.1) to 29.1 (SD = 15.5) with IPT-PTSD. Attrition was high in both arms ($p = .40$).

Conclusions: This trial showed within-group improvements without differences between IPT-PTSD and sertraline treatment of PTSD. Our findings suggest that non-exposure-based psychotherapies may benefit patients with PTSD, although we did not directly compare these treatments to an exposure therapy.

Brazilian Clinical Trials Registry RBR-3z474z.

Psicoterapia interpersonal versus sertralina para mujeres con trastorno de estres postraumatico despues de un agresion sexual reciente: un estudio clinico aleatorizado

Antecedentes: La agresión sexual con frecuencia gatilla un trastorno de estrés postraumático (TEPT), un trastorno mental severo potencialmente crónico. La mayoría de las guías clínicas recomiendan los inhibidores selectivos de la receptación de serotonina (ISRSs) y psicoterapias focalizadas en trauma como opciones de tratamiento. La Psicoterapia Interpersonal (PIP), adaptada para TEPT (PIP-TEPT), se focaliza en las consecuencias interpersonales del trauma en lugar de confrontar el trauma en sí. Los estudios han encontrado que la PIP-TEPT eficazmente redujo los síntomas de TEPT con una deserción limitada. Ningún ensayo de eficacia ha comparado PIP-TEPT e ISRS. Hipotetizamos que la PIP-TEPT puede reducir los síntomas de TEPT, ansiedad y depresión más que la sertralina entre las mujeres con TEPT después de una agresión sexual reciente.

Objetivos: Comparar la eficacia de la PIP-TEPT con sertralina, un ISRS en un ensayo clínico aleatorizado de 14 semanas para mujeres con TEPT después de una agresión sexual reciente.

Métodos: Setenta y cuatro mujeres con TEPT que habían sufrido de una agresión sexual en los últimos seis meses fueron asignadas aleatoriamente a 14 semanas de PIP-TEPT ($n = 39$) o sertralina ($n = 35$). Los instrumentos evaluaron síntomas de TEPT, ansiedad y depresión. Este ensayo clínico aleatorizado se realizó en San Pablo, Brasil, utilizando la Escala de TEPT administrada por el clínico (CAPS-5, por sus siglas en inglés) como medida de resultado primaria.

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关键词
人际关系心理治疗; 药物治疗; 性侵犯; 创伤后应激障碍; 治疗; 临床试验

HIGHLIGHTS

- Violence against women is widespread, but limited evidence on women with PTSD comes from developing countries.
- This Brazilian clinical trial compared interpersonal psychotherapy (IPT) versus sertraline to treat young women with PTSD following a recent sexual assault.
- Both interpersonal psychotherapy and sertraline lowered PTSD and depressive symptoms without significant between-group differences.

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Resultados: Ambos tratamientos redujeron significativamente los síntomas de TEPT, ansiedad y depresión, sin diferencias de resultados entre los grupos. La media del CAPS-5 se redujo de 42.5 (DE = 9.4) a 27.1 (DE = 15.9) con sertralina y de 42.6 (DE = 9.1) a 29.1 (DE = 15.5) con la PIP-TEPT. La deserción fue alta en ambos tratamientos ($p = .40$).
Conclusiones: Este ensayo mostro mejoría entre grupos sin diferencias entre la PIP-TEPT y sertralina en el tratamiento del TEPT. Nuestros hallazgos sugieren que las psicoterapias no basadas en la exposición pueden beneficiar a los pacientes con TEPT, aunque no comparamos directamente estos tratamientos con una terapia de exposición.
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近期性侵犯后患有创伤后应激障碍女性的人际心理治疗与舍曲林：一项随机临床试验

摘要
背景：性侵犯经常引发创伤后应激障碍 (PTSD)，这是一种潜在的慢性严重精神障碍。大多数指南推荐选择性5-羟色胺再摄取抑制剂（SSRIs）和聚焦创伤的心理疗法作为治疗选择。人际心理治疗（IPT）创伤后应激障碍改编版（IPT-PTSD），专注于创伤的人际后果，而不是面对创伤本身。研究发现，IPT-PTSD 有效地减少了 PTSD 症状，且流失率有限。没有疗效试验比较 IPT-PTSD 和 SSRI。我们假设 IPT 比舍曲林更能减少近期遭受性侵犯后患有 PTSD 女性的 PTSD、焦虑和抑郁症状。
目的：在一项为期 14 周的随机临床试验中，比较 IPT-PTSD 与 SSRI 舍曲林对近期性侵犯后 PTSD 女性的疗效。
方法：74 名在过去六个月内遭受过性侵犯的 PTSD 女性被随机分配到 14 周的 IPT-PTSD组（n=39）或舍曲林组（n=35）。使用测量工具评估了 PTSD、焦虑和抑郁症状。本随机临床试验在巴西圣保罗进行，使用临床用PTSD Scale-5 (CAPS-5) 作为主要结果测量。
结果：两种治疗均显著降低了 PTSD、焦虑和抑郁症状，且无组间结果差异。 舍曲林组 CAPS-5 平均值从 42.5 (SD=9.4) 降至 27.1 (SD=15.9)，IPT-PTSD组从 42.6 (SD=9.1) 降至 29.1 (SD=15.5)。两组流失率都很高（p=.40）。
结论：本试验表明 IPT-PTSD 和舍曲林治疗 PTSD 的组内改善没有差异。我们的研究结果表明，基于非暴露的心理疗法可能会使 PTSD 患者受益，尽管我们没有直接将这些治疗与暴露疗法进行比较。
巴西临床试验登记 RBR-3z474z。

1. Introduction

Sexual violence against women violates human rights and constitutes a severe global public health problem for women's health. The World Health Organization (WHO) defines sexual violence as any sexual activity without consent in which one person uses force, threat, or takes advantage of another. Unfortunately, it is a widespread phenomenon (World Health Organization [WHO], 2014).

Among traumatic events that may challenge individuals in their lifetime, research findings suggest that interpersonal traumas have more significant impact than impersonal traumas in triggering post-traumatic stress disorder (PTSD, Kessler et al., 1995; Norris et al., 2002). Based on epidemiologic studies, sexual assault was the listed trauma with highest probability of developing PTSD (Kessler et al., 1995; Luz et al., 2016). Women who undergo sexual assault experience intense and prolonged psychological distress, and approximately half of them develop PTSD (Luz et al., 2016; Mills et al., 2006). Although the literature shows an increasing number of women receiving legal, medical, and psychological attention for sexual trauma in recent years (Baert et al., 2021; Breiding et al., 2014; Elkin, 2019), sexual assault survivors often do not receive adequate treatment for PTSD (Bach et al., 2021; Massaro et al., 2019; Olff, 2022). Difficulties in treatment access and poor adherence are well-documented (Ackerman et al., 2006; Boykins & Mynatt, 2007; Darnell et al., 2015; Holmes et al., 1998). Furthermore, attrition rates for evidence-based psychotherapies for PTSD can be high, reaching 16–18% of patients (Imel et al., 2013; Lewis et al., 2020).

Treatment guidelines recommend exposure-based, trauma-focused psychotherapies as first-line treatment to PTSD (Bisson et al., 2019; Charney et al., 2018; Cloitre et al., 2012; Forbes et al., 2007; Lee et al., 2016; National Collaborating Centre for Mental Health, 2005). As for medication, the U.S. Food and Drug Administration (FDA) has approved only two SSRIs, sertraline and paroxetine, for PTSD treatment. Usually well-tolerated, these medications have shown efficacy in reducing PTSD symptom severity and risk of relapse, with response rates ranging from 44% to 63% in peer-review published randomized clinical trials (Brady et al., 2000; Marshall et al., 2001; Martenyi et al., 2002; McRae et al., 2004; Önder et al., 2006; Panahi et al., 2011; Van der Kolk et al., 1994; Zohar et al., 2002). In a recent meta-analysis, Merz et al. found similar findings for pharmacological, psychotherapeutic, or combination treatment in adults with PTSD. The available evidence was sparse, however, indicating the need for clinical trials comparing

psychotherapy with psychopharmacology to treat PTSD (Merz et al., 2019).

Although trauma-focused psychotherapies such as prolonged exposure (PE) are considered first-line treatments for PTSD, some patients refuse exposure to the memories and reminders of traumatic events because of anxious avoidance (Hembree et al., 2003; Imel et al., 2013), and attrition is high (Lewis et al., 2020). Nor does exposure benefit all patients: there are no panaceas for PTSD (Steenkamp et al., 2015). Thus, not everyone is a candidate for this approach. Recognizing the importance of interpersonal features in developing and recovering from PTSD, interpersonal psychotherapy (IPT) is an alternative, non-exposure approach that addresses and repairs interpersonal mistrust. Moreover, as almost half of patients diagnosed with PTSD have comorbid major depression (MDD; Shalev et al., 1998), the antidepressant effect of both IPT and SSRIs could benefit these patients.

IPT is a manualized, time-limited, diagnosis-targeted psychotherapy with demonstrated efficacy for depression, anxiety, and eating disorders. Markowitz developed a manualized modification of IPT for PTSD (IPT-PTSD), focusing on how trauma has affected patients' current interpersonal functioning. Traumatized individuals isolate themselves within relationships, develop 'interpersonal hypervigilance,' and mistrust their social environment (Markowitz, 2016). The IPT focus is to help the individual understand emotions to regain safety and trust in interpersonal relationships and to mobilize social supports. In a clinical trial, Markowitz and colleagues evaluated patients diagnosed with PTSD due to different types of trauma, finding similar efficacy and lower dropout rates for IPT (15%) compared to PE (29%), especially among patients with comorbid MDD (Markowitz et al., 2015). Analyzing the subsample of sexually traumatized patients revealed better outcomes for IPT than PE or relaxation therapy. Sexual trauma moderated the treatment effect on PTSD cluster B (re-experiencing) and D (hyperarousal) symptoms, with IPT showing more significant improvement (Markowitz et al., 2017). More recently, Markowitz and colleagues found IPT improved PTSD and attachment measures in military veterans with PTSD (Milrod et al., 2020; Pickover et al., 2021).

The comparable response rates and discrepant guidelines recommendations indicate the need for clinical trials comparing psychotherapy with psychopharmacology of PTSD. The few randomized clinical trials (RCTs) comparing SSRIs to psychotherapy have yielded mixed results. Frommberger and colleagues first investigated the relative effectiveness of cognitive–behavioural therapy (CBT) and paroxetine in an underpowered sample of 21 patients with PTSD (Frommberger et al., 2004). The treatments similarly attenuated PTSD symptoms, though CBT patients exhibited a slighter longer-term symptomatic decrease at six months follow up. A pragmatic 2×2 factorial clinical trial showed no treatment effects or differences between treatments in PTSD symptom outcomes of traumatized refugees for CBT, PE, and sertraline (Buhmann et al., 2016). Popiel et al. found PE more effective than paroxetine in treating PTSD following motor vehicle accidents (Popiel et al., 2015), whereas Rauch et al. reported no difference in PTSD symptom change between PE and sertraline in combat veterans (Rauch et al., 2019).

As evidence suggested that IPT-PTSD might have greater efficacy than PE for PTSD symptoms among sexual trauma survivors (Markowitz et al., 2017), we compared IPT-PTSD versus sertraline in women who developed PTSD after a recent sexual assault. A two-arm RCT evaluated treatment outcomes. Following an intake interview to assess PTSD, depressive, and anxiety symptoms, patients were randomized to receive standardized IPT-PTSD or sertraline. This is the first RCT to compare IPT to an SSRI for PTSD, the first to compare psychotherapy to SSRI in a sample comprising women survivors of recent sexual assault with PTSD, and the first such RCT conducted in a developing country. Brazil suffers from epidemic violence, and in its largest city, São Paulo, where the present study was conducted, the estimated lifetime prevalence of PTSD among women is 14.7% (Ribeiro et al., 2013). Nevertheless, evidence on PTSD treatment for sexually assaulted women from low- and middle-income countries like Brazil is rare. Because IPT addresses interpersonal issues relevant to sexual trauma, we hypothesized that IPT-PTSD for women following sexual assault would be superior in reducing PTSD, anxiety, and depressive symptoms than sertraline, a medication FDA-approved for PTSD, anxiety, and mood.

2. Methods

2.1. Study design

2.1.1. Setting

Participants were recruited for a more extensive study of PTSD and neuroprogression following sexual assault, described elsewhere (Coimbra et al., 2020). All women were referred from Hospital Pérola Byington (HPB), a specialized women's health centre in São Paulo City, after a brief screening for sexual assault in the past six months.

2.1.2. Sample size calculation

The RCT protocol details the input parameters used to calculate sample size and other aspects of the design and interventions (Coimbra et al., 2020). Briefly, we considered a 60% response favouring sertraline for active

treatment for PTSD versus a 30% placebo group response, under a two-arm design, power of 80%, with a significance level of 5% for a bicaudal test. This yielded 42 participants per arm (Khoo et al., 2015; Lee et al., 2016). Enrolees were randomly assigned to receive 14 weeks of either IPT-PTSD or sertraline. The RCT started in January 2016 and ended in April 2019.

2.1.3. Randomization

A random allocation sequence was generated through stratified randomization using Fossaluza's et al. method to balance prognostic factors in clinical trials (Fossaluza et al., 2009). Stratification variables were Clinician-Administered PTSD Scale CAPS-5 total score, age, and educational level. Allocation followed strict procedure: when a potential participant fulfilled all inclusion criteria, the study coordinator called the statistician, who generated an allocation sequence, sequestering the assignment schedule in his computer in a building to which the clinical treatment team lacked access.

2.2. Participants

Study subject eligibility was assessed after the preliminary screening to verify inclusion criteria: (1) age 18–45; (2) sexual assault experience 1–6 months beforehand, regardless of childhood sexual abuse history; (3) current PTSD diagnosis on Mini-International Neuropsychiatric Interview (MINI); (4) CAPS-5 score >26, indicating suprathreshold PTSD; and (5) Ethics Review Board-approved signed informed consent. Exclusion criteria were: (1) ongoing psychiatric or psychotherapeutic treatment; (2) severe suicidal risk, evaluated in a clinical interview by a trained researcher; (3) pregnancy; (4) chronic corticosteroid use; (5) unstable medical condition or neurologic disease; (6) researcher-determined inability to understand the informed consent or research protocol; (7) substance dependence in remission for <6 months; (8) bipolar disorder or schizophrenia.

2.3. Procedures and assessments

Enrolees were randomly assigned to receive 14 weeks of either IPT-PTSD or sertraline. The intake interview included administration of standard instruments: the Mini-International Neuropsychiatric Interview (MINI) to make an initial PTSD diagnosis, the CAPS-5 to confirm the diagnosis and evaluate PTSD symptom severity, Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI) for those respective symptom severities, and Clinical Global Impression Scale (CGI). Sexual assault experience (1–6 months beforehand) was always considered the index trauma when assessing PTSD. All study data were stored in REDCap, a secure, web-based, widely used research application. The RCT started in January 2016 and ended in April 2019. Patients with post-randomization missing data were included in the analysis following intention-to-treat analysis paradigms.

2.4. Interventions

2.4.1. IPT-PTSD

IPT was delivered in 14 weekly 50-min individual sessions at the Department of Psychiatry of the Federal University of São Paulo, following the IPT-PTSD manual (Markowitz, 2016). Therapists were five women psychiatry graduates, 32–46 years old, who had at least one year of experience using IPT to treat depression and were trained and supervised weekly to use IPT for PTSD. Their supervisors were a M.D., Ph.D. psychiatrist and an M.Sc. psychologist with >10 years of experience in treating patients with IPT and PTSD. Sessions were audiotaped with patient authorization to certify therapy quality.

2.4.2. Sertraline

Sertraline dosage ranged from 50 to 200mg daily, titrated to each patient's clinical presentation and tolerance. Two psychiatrists with >10 years' experience in PTSD provided pharmacotherapy. Appointments were scheduled at baseline, week 2, week 4, week 8, and week 14. Pharmacotherapy sessions lasted 15–30 min, focusing on medication benefits and side effects. Pharmacologists offered general encouragement but no formal psychotherapy. Both sertraline and IPT-PTSD patients could receive low dose quetiapine (25–50 mg), risperidone (0.5–2.0 mg), or zolpidem CR (12.5 mg) to control high-level anxiety, suspiciousness, and/or insomnia.

2.5. Instruments

Two evaluators blinded to treatment condition assessed patients, reminding them not to identify their treatment or therapist. Serial evaluations occurred at baseline and weeks 2, 4, 8, and 14 using standardized canonical instruments.

- *Sociodemographic inventory and sexual assault history:* We developed a detailed sociodemographic inventory to collect patient sociodemographic and sexual assault characteristics. (See Supplemental Materials).
- *Childhood Trauma Questionnaire (CTQ)*: This instrument was used at baseline to assess childhood trauma exposure (Grassi-Oliveira et al., 2006). Cronbach's alpha ($\alpha = 0.935$).
- *Life Events Checklist for DSM-5 (LEC-5)*: We screened potentially traumatic lifetime events at baseline with this brief, 17-item, self-report measure (Lima et al., 2016).

- *Clinician-Administered PTSD Scale for DSM-5 (CAPS-5):* This, the gold standard assessment of PTSD diagnostic status and symptom severity, is a structured, clinician-rated interview evaluating frequency and intensity of PTSD symptoms and trauma-associated variables (Weathers et al., 2018). The CAPS-5 has been validated to Brazilian Portuguese (Oliveira-Watanabe et al., 2021). Cronbach's alpha ($\alpha = 0.790$). Inter-rater reliability score was high (intraclass correlation coefficient = .994, 95% CI [.987–.997], $p < .001$) (Oliveira-Watanabe et al., 2021).
- *Mini-International Neuropsychiatric Interview (MINI):* This structured diagnostic interview, widely used internationally, provides accurate psychiatric diagnoses (Amorim, 2000; Sheehan et al., 1998).
- *Beck Depression Inventory (BDI):* This self-report surveys depressive symptoms. Each of the 21 multiple-choice questions presents four alternatives in rising levels of depressive severity. Minimal depression (<13); mild depression (14–19); moderate depression (20–28) and severe depression (>29) (Beck et al., 1996; Gomes-Oliveira et al., 2012). Cronbach's alpha ($\alpha = 0.939$).
- *Beck Anxiety Inventory (BAI):* Analogous to the BDI, this 21-item self-report queries clinical anxiety symptoms rated in severity from 0 to 3. Minimal anxiety levels (<7), mild anxiety (8–15), moderate anxiety (16–25), and severe anxiety (>26) (Beck et al., 1988; Quintão et al., 2013). Cronbach's alpha ($\alpha = 0.937$).
- *The Clinical Global Impression Scale (CGI):* This 7-point clinician-rated scale of the patient's mental condition assesses disease severity and improvement during interventions (Busner & Targum, 2007; Lima et al., 2007).

2.6. Adherence raters

Therapist IPT adherence was evaluated using the NIMH *Collaborative Study psychotherapy rating scale (CSPRS-6)* (Evans et al., 1984; Hollon, 1984). The most highly developed adherence instrument, CSPRS-6, measures therapist uses of specific and common factors therapeutic techniques during the session on an anchored 7-point scale.

Two sets of therapy sessions for adherence ratings were randomly selected for each dyad: (1) early (from sessions 2–7) and (2) late sessions (from sessions 8–14). A computer-generated program chose every seventh recording from a list of consecutively numbered available sessions.

Raters evaluated 20 recorded sessions focusing on therapist rather than patient verbalizations. Independent raters were two female psychologists and three female psychiatrists, all clinically experienced in IPT and PTSD, who participated in a CSPRS-6 training session after extensive discussion of each CSPRS-6 item, rating and discussing pilot session recordings. CSPRS-6 ratings on the IPT subscale (3.2 SD ± 0.8) were higher than ratings on alternative therapies subscales, such as CBT (2.2 SD ± 0.5) ($p < .0001$), validating therapist adherence to IPT.

2.7. Statistical analysis

2.7.1. Generalized estimating equation

Generalized Estimating Equation (GEE) (Feng et al., 2001; Hilbe & Hardin, 2008) was used to evaluate the effects of time and group random assignment (sertraline vs. IPT-PTSD) on the primary outcome, CAPS-5 severity, and three secondary outcomes: CGI, BAI, and BDI (all continuous measures). Two variables were included in the GEE within-subjects effects: the therapists and the four longitudinal assessments per subject; first-order autoregressive effect working correlation was used to address the carry-over effects of psychological symptoms across time (Shults et al., 2009). The first-order autoregressive working correlation matrix addressed the within-subject effect, expecting temporally distant measurements to be less correlated than more proximal assessments (Gueorguieva, 2017). The models used as covariates: allocation status (sertraline or IPT-PTSD), time effect (capturing temporal changes in outcomes regardless of allocation, holding allocation constant), age, income, and medication need (dichotomous variables). We tested for likely interaction between random group assignment and BDI on CAPS-5 severity score, CGI, and BAI, and mainly whether BDI changes explained the intervention outcomes.

2.7.2. Missing data

Due to missing outcome data, which are commonly observed (and expected) in longitudinal designs, two different approaches, assuming missing at random (Fraser & Yan, 2007) were used for estimating the effects of the main covariates of interest, time, and treatment type. The first approach was the full-information maximum likelihood, the default estimator maximum likelihood in GEE analysis, accommodating missingness easily due to the *long format* of the data set and availability of at least the screening outcome measure. The second approach to missingness was multiple imputations.

Using the CONSORT-advocated intention-to-treat paradigm (ITT) requires techniques dealing with missing data (Sylvestre, 2011). Multiple imputations are one of the most flexible procedures for addressing missing data in randomized trials (Kenward & Carpenter, 2007). It replaces lost data with one or more imputed specific values to allow statistical analysis

that includes all participants, not just those having complete data (Enders, 2017; Li et al., 2015). Under multiple imputations, to model missing data, forty data sets were imputed (Rubin, 2004). The variables entered into the unrestricted model were random allocation, age, time, income, medication need, CAPS-5 severity, CGI, BAI, and BDI. Random allocation, time, and age were used only as predictors of missingness; the remaining variables were used as predictors and imputed values. The imputation method was the fully conditional specification without constraints in the range of imputed outcomes continuous values. The reported estimates are pooled estimates derived from the 40 imputed data sets. The significance level was established at 0.05, and all analyses were run in SPSS, version 24. The effects of the covariates group assignment and time were reported in non-standardized coefficient regression because standardized effects for SPSS.24 are not available under the multiple imputation routines.

3. Results

Of 149 women referred to the Federal University of São Paulo, 74 were eligible and agreed to study participation. Thirty-five ($n = 35$) were randomized to sertraline and thirty-nine ($n = 39$) to IPT-PTSD (Figure 1). Women in both treatment arms were comparable in race, civil status, income, educational level, childhood sexual abuse, and other childhood trauma exposure (Table 1). Mean time between sexual assault exposure and assessment was 1.67 months (SD ± 0.950). Only two women in each arm of the trial reported having not experienced any lifetime LEC-5 traumatic stressor other than the

Table 1. Baseline sociodemographic characteristics of each intervention group.

	Sertraline	IPT-PTSD	Total
Age avg (±SE)	24.6 (7.1)	25.2 (6.5)	24.8(6.8)
Race			
White	16	16	32
Mixed race	14	15	29
Black	5	7	12
Asian	0	1	1
Civil Status			
Single	20	30	50
Married	14	8	22
Divorced	1	1	2
Education level			
Less than High-School	21	17	38
High-School or more	14	22	36
Childhood sexual abuse (yes)	7	7	14*
CTQ* – avg score (±SE)**	38.5 (14.7)	33 (17.2)	36 (16.0)
Income (Real)**			
Avg per month (±SE)	1063 (1418)	1196 (1169)	1138 (1276)

*There was one participant with missing data.
**1 US Dollar∼5 Real.
***CTQ (Childhood Trauma Questionnaire).

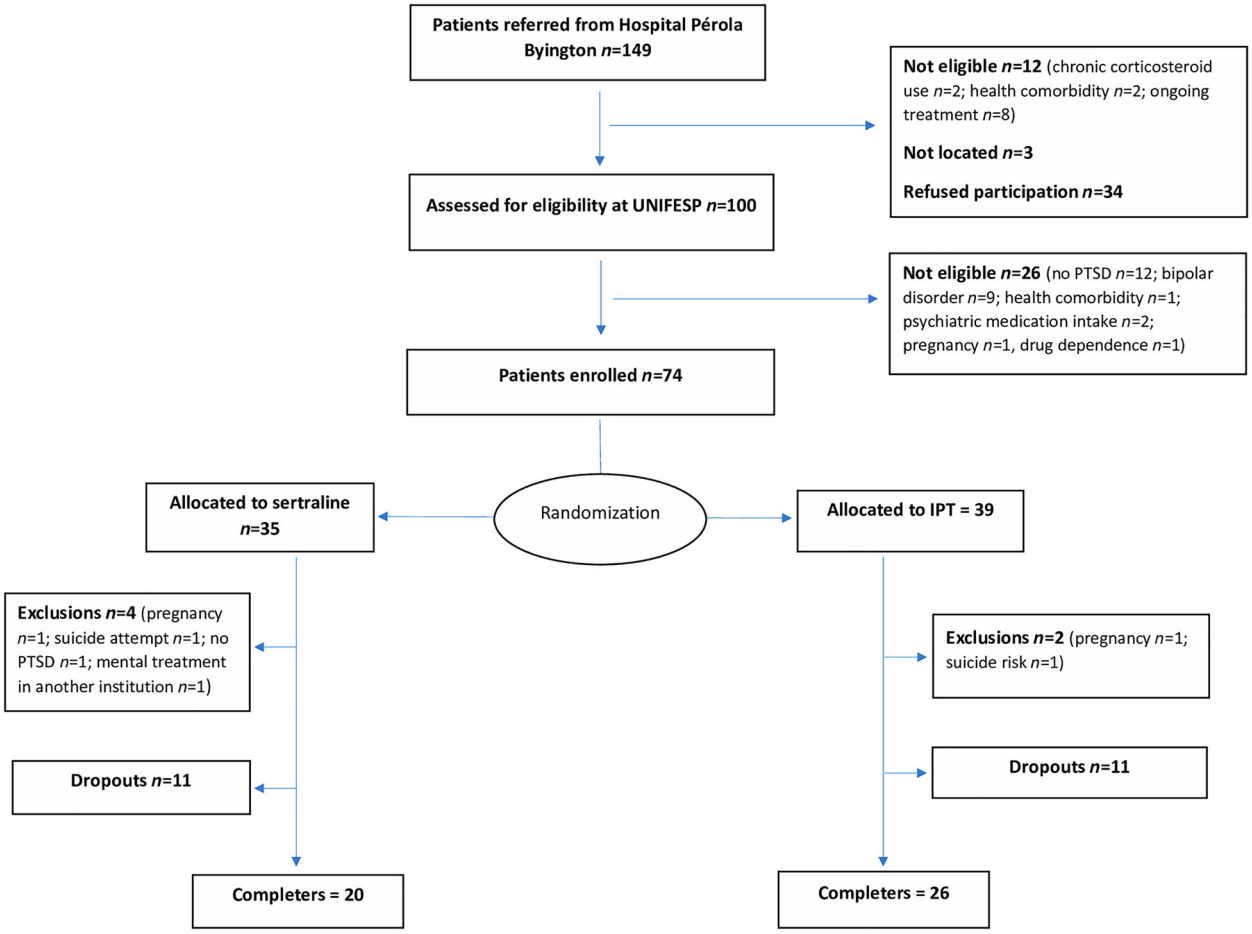

Figure 1. Clinical trial flow chart.

sexual assault, which was considered the index trauma. All the rest of women in our sample reported at least one extra lifetime LEC-5 traumatic stressor.

The mean sertraline dosage patients received was 118mg (SD = 62). Ninety-six per cent of IPT-PTSD patients and 65% of sertraline patients completing treatment received low doses of adjunctive medications (quetiapine, risperidone, or zolpidem) to control high anxiety, suspiciousness, and/or insomnia. Of the 35 women randomized to sertraline, 15 did not complete treatment: eleven dropped out and four were excluded post-randomization due to pregnancy, suicide attempt, subthreshold PTSD diagnosis, or having started concomitant treatment elsewhere. Eleven IPT patients dropped out and two were excluded: one for pregnancy and another for elevated suicidal risk at week seven. After therapist discussion with IPT supervisors, and considering the high-risk of suicidal ideation, the latter patient was referred to the emergency psychiatric unit to receive additional treatment. Despite formal study withdrawal, she continued receiving IPT combined with antidepressant, on which she showed symptomatic improvement. Attrition was thus 43% for sertraline and 33% for IPT-PTSD (n.s., $p = .40$).

Table 2 describes treatment outcomes across the four time points. Missing data and assessment score means decrease for both groups over time. CAPS-5 mean decreased from 42.5 (SD = 9.4) to 27.1 (15.9) with sertraline and from 42.6 (SD = 9.1) to 29.1 (SD = 15.5) with IPT-PTSD, while BDI means decreased from 29.15 (SD = 10.99) to 15.37 (12.51) with sertraline and from 28.31 (SD = 11.72) to 17.23 (SD = 17.21) with IPT-PTSD.

Table 3 depicts the unstandardized effects of *group* and *time* for two different GEE effects after adjusting for age, income, time, and need for adjunctive medication use over time, first without and then with multiple imputations under unconditional (on top) and conditional model (on bottom, interaction between group allocation and time). There were no statistically significant differences between treatment groups (all p-values >.05). For the effect of *time*, on average, both groups showed significant mean reductions. In other words, regardless of group assignment, by the end of the study, patients on average had lower CAPS-5, BAI, and BDI scores and showed CGI improvement across time; in other words, as the time goes by, there is an improvement in the assessed outcomes. Both approaches we used dealt with missingness; multiple imputations and full information maximum likelihood showed convergent results in terms of effect size and significance. Lack of interaction effect between time and group assignment on the four outcomes was observed (conditional model).

Women in both arms fulfilled the criteria for MDD according to MINI. Interaction effects between group assignment and BDI score on CAPS-5 severity scores ($B = 0.025$, $p = .80$), CGI ($B = -0.001$, $p = .92$), and BAI ($B = -0.002$, $p = .99$) did not find that improvement depended upon depressive symptom reduction for either intervention.

4. Discussion

This is one of the first randomized controlled studies to compare evidence-based psychotherapy to a serotonin reuptake inhibitor to treat PTSD, the first to involve IPT and do so in a developing country. The results demonstrated that both IPT-PSTD and sertraline lowered PTSD and depressive symptoms without significant between-group differences. Regardless of allocation, large within-subject effect sizes (i.e., the effect of the time on bottom part of Table 3) occurred over 14 weeks on PTSD, anxiety, and depression measures. The trial lacks evidence for the difference between treatments in treating PTSD in women victims of recent sexual assault. Nor did the treatments significantly differ in attrition rates. Our results resemble previous literature findings comparing sertraline to psychotherapy (Rauch et al., 2019).

Although we expected lower attrition in IPT-PTSD compared to attrition historically reported in PE studies (Hembree et al., 2003; Imel et al., 2013), our attrition rates were surprisingly and distressingly high in both arms, with important clinical implications. Unfortunately, as in most dropout assessments (Amsalem et al., 2022), precise understanding of the reasons for attrition was difficult. Our team tried to contact women after the trial to assess qualitative information about attrition, but we faced difficulties: some patients did not respond, other had

Table 2. Clinical outcomes across four-time points by intervention groups.

Time-point		Baseline		4-week		8-week		14-week	
Treatment	Scale	*N*	Mean (SD)	*N*	Mean (SD)	*N*	Mean (SD)	*N*	Mean (SD)
Sertraline	CAPS	35	42.49 (9.36)	23	36.17 (13.46)	21	32.71 (14.3)	19	27.11 (15.85)
	CGI	33	4.91 (0.8)	22	4.41 (1.14)	22	3.77 (1.31)	17	3.59 (1.37)
	BDI	34	29.15 (10.99)	23	21.61 (11.87)	24	16.63 (9.85)	19	15.37 (12.51)
	BAI	34	27.44 (10.88)	23	23.35 (15.09)	24	22.67 (13.85)	18	19.94 (15.09)
IPT	CAPS	39	42.59 (9.08)	25	42.6 (10.9)	24	32.29 (13.58)	26	29.12 (15.46)
	CGI	38	4.89 (0.8)	24	4.33 (0.76)	21	3.76 (1.22)	26	3.69 (1.01)
	BDI	39	28.31 (11.72)	26	24.12 (9.42)	25	17 (11.51)	26	17.23 (17.21)
	BAI	39	29.33 (11.72)	25	27.56 (14.1)	25	23.64 (17.17)	26	21.15 (12.9)

Table 3. Unstandardized effects of group and time for two different GEEs effects after adjusting for age, therapists and supplemental medication use across the four time points.

		Outcome	Group difference	95% CI		*p*-value	Time	95% CI		*p*-value	Group *Time interaction	95% CI		*p*-value
Unconditional Model	**GEE-FIML**	CAPS-5	1.73	2.80	6.26	.453	−7.55	−9.51	−5.59	.001				
	Full-information Maximum Likelihood	CGI	0.19	0.23	0.62	.37	−0.52	−0.73	−0.32	<.001				
		BDI	0.96	4.09	6.01	.71	−5.98	−7.59	−4.37	<.001				
		BAI	−0.23	5.78	5.32	.93	−4.25	−6.00	−2.49	<.001				
	GEE-MI	CAPS-5	0.76	4.14	4.29	.97	−7.43	−9.29	−5.57	<.001				
		CGI	0.08	0.27	0.44	.66	−0.48	−0.66	−0.30	<.001				
		BDI	−0.35	4.71	4.02	.88	−5.06	−6.79	−3.33	<.001				
		BAI	−1.44	6.32	3.44	.56	−4.10	−6.35	−1.86	<.001				
Conditional Model	**GEE-FIML**	CAPS-5	0.01	5.28	5.30	1.00	−7.94	−10.60	−5.29	<.001	0.78	2.015	3.575	.584
	Full-information Maximum Likelihood	CGI	0.13	4.26	0.68	.66	−0.54	−0.79	−0.29	<.001	0.03	−0.27	0.34	.84
		BDI	2.80	3.73	9.33	.40	−5.56	−7.76	−3.36	<.001	−0.83	−3.25	1.60	.50
		BAI	−0.44	7.28	6.41	.90	−4.29	−6.63	−1.95	<.001	0.09	−2.74	2.92	.95
	GEE-MI	CAPS-5	0.91	4.97	6.78	.76	−7.27	−9.63	−4.90	<.001	−0.34	−2.98	2.30	.80
		CGI	0.16	0.46	0.71	.59	−0.46	−0.67	−0.26	<.001	−0.03	0.13	−0.28	.81
		BDI	2.56	4.33	9.46	.47	−4.48	−6.54	−2.43	<.001	−1.18	−3.66	1.29	.35
		BAI	−0.67	8.04	6.70	.86	−3.95	−6.53	−1.37	.003	−0.32	−3.10	2.47	.82

Note: CI = confidence interval; CGI = Clinical Global Impression; BDI = Beck Depression Inventory; BAI = Beck Anxiety Inventory; MI = multiple imputation.

changed phone numbers. In general, patient explanations of dropout are hard to interpret. Nonetheless, the qualitative data we collected from patients who did not complete IPT-PTSD led us to theorize that a possibly important factor relating to the high attrition rate was difficulty in accommodating treatment to daily life activities and work, including the lengthy commute to treatment and consequent loss of uncompensated work income and PTSD symptomatology itself (Proença et al., 2019).

Proença et al. hypothesized that the high IPT-PTSD dropout rate in this RCT could be partially explained by the performance of one IPT therapist, who treated 60% of all IPT dropouts and had only one of four patients complete the trial. Other study therapists had at least a 75% completion rate (Proença et al., 2019). Another *post hoc* hypothesis is that socioeconomic status affected attrition: most women had low incomes, lived in distant, dangerous neighbourhoods, and relied on slow-moving public transportation to reach the treatment unit with 1–2 hourlong commutes in each direction. Long distances and crowded transportation may have been highly stressful for sexually traumatized women.

To our knowledge, this is not only the first study comparing IPT to pharmacotherapy for PTSD but also the first RCT using either IPT or an SSRI to treat PTSD in women precisely due to recent sexual trauma. For this hard-to-treat trauma in a patient sample from a particularly overwhelmed population, IPT was chosen as an alternative to trauma-focused psychotherapies. It focuses on the interpersonal consequences of the traumatic experience rather than on the trauma itself to improve social support and interpersonal functioning. As young women are at risk for sexual assault, and sexual trauma is a significant instigator of PTSD, treating this specific group is warranted to develop other interventional strategies. Our RCT focused on enrolling a sample of women in the acute stages of PTSD, and the homogeneity of our sample is one of its strengths.

When the present study was designed in 2014, insufficient data had been published comparing psychotherapy to pharmacotherapy for PTSD. Since then, more evidence has emerged supporting trauma-focused psychotherapy as a first-line treatment (Bisson et al., 2019; Courtois et al., 2017; Forbes et al., 2007). Nonetheless, robust evidence supports the efficacy of sertraline for PTSD (Courtois et al., 2019; Cusack et al., 2016; Davidson et al., 2001; Lee et al., 2016), so pharmacotherapy should be considered a treatment option, mainly when evidence-based psychotherapies are scarce.

Unfortunately, this scarcity is very much the case in Brazil, where lack of access to psychotherapy is pervasive, as the overcrowded public health system precludes readily available weekly evidence-based

psychotherapy. Although most guidelines recommend psychotherapy as first-line treatment and antidepressants as second-line or adjuvant for PTSD (Cusack et al., 2016; Forbes et al., 2007), in this trial, both pharmacotherapy and psychotherapy reduced symptoms, suggesting each should be considered a treatment alternative depending on treatment availability and patient preference.

Our findings support other research indicating that non-exposure-based psychotherapies may benefit patients with PTSD (Campanini et al., 2010; Krupnick et al., 2008; Markowitz et al., 2015; Pickover et al., 2021). IPT-PTSD thus offers another clinical alternative, increasing the range of effective therapies for PTSD, especially for patients who may not tolerate treatment via reliving their trauma narrative and direct exposure to trauma reminders. Based on the above evidence, which this study reinforces, IPT is now included in the US Veterans Administration/ Department of Defense treatment guidelines as a treatment for PTSD (US Department of Veteran Affairs, 2017).

Although Cusack and colleagues did not find sufficient evidence in their systematic review to determine differential treatment effectiveness for victims of particular trauma types (Cusack et al., 2016), Markowitz et al. found IPT showed more significant benefit for sexually traumatized patients than PE or relaxation therapy (Markowitz et al., 2017). As studies have demonstrated that PTSD tends to persist unless treated (Bradley et al., 2005; Perkonigg et al., 2005; Wang et al., 2005), our findings reinforce the importance of early PTSD treatment alternatives to counter its potential long-delay-to-treatment (Pupo et al., 2015; Wang et al., 2005).

Some study limitations must be addressed. First, we did not reach the intended sample size and attrition was high, so our findings may not generalize to the broader population. We had intended to enrol at least 84 patients to achieve optimal statistical power, but a considerable number of eligible women (n = 34) declined participation. This raises the Type II question of whether lack of statistical power explains the lack of statistical difference between IPT and sertraline outcomes.

This limitation may reflect the context in which this research took place: São Paulo is South America's largest metropolis, with over 21 million inhabitants. In Brazil, people who seek consultations in the public health system usually have low incomes and live in peripheral neighbourhoods. All evaluations and appointments took place in a single health centre, in a central neighbourhood, far from most patients' residences. This typically required a 1–2 hour commute on public transportation. Furthermore, outdoor rape victimization in Brazil occurs disproportionately near bus stops compared to other public spaces, which may elevate women's threat perception (Felson et al., 2021). This may have affected patient recruitment and treatment adherence, shrinking our sample and limiting our analyses. As traumatized sexually assaulted women often struggle to complete psychological treatment and attend medical appointments (Darnell et al., 2015; Holmes et al., 1998; Keefe et al., 2018), our study suggests that enrolling and retaining low socioeconomic status women for PTSD treatment following sexual assault may be particularly challenging in Brazil. Research suggests that in Brazil, sexually assaulted women are discouraged from reporting rape and seeking support from formal service providers (Barros et al., 2015; Cerqueira et al., 2018) Besides fear of perpetrators and lack of faith in law enforcement, there may be pervasive sociocultural aspects of machismo and patriarchalism in Brazil that undermine women's efforts to commit to treatment (Cerqueira et al., 2014).

An additional limitation was that all patients were referred from a single public gynecological centre, potentially reducing variability in sample sociodemographic characteristics. Moreover, this trial did not compare interventions with trauma-focused psychotherapy, the first line researched treatment for PTSD. Despite the study's limitations, we found PTSD, anxiety and depressive symptoms significantly improved in both arms, suggesting IPT-PTSD and sertraline should be more studied, especially in contexts where trauma-focused psychotherapy is not available. Unfortunately, we did not have follow-up data at this point to see the longitudinal impact of these treatments after the end of the clinical trial.

Further research is needed to improve retention rates in PTSD treatment among sexually assaulted women. Sexual assault occurs in a social context, and there is a need to identify both patient and environmental characteristics that may predict risk of attrition, both in absolute terms and differentially by PTSD treatment type. This may provide clinicians with better tools to select a clinical approach while minimizing dropout and to assertively address difficulties in adherence at an early stage of treatment. Lastly, as sluggish transportation to health centres in metropolises like São Paulo may discourage women from attending appointments, future work might look at feasibility and efficacy of modifications to make treatment more accessible, for example comparing in-person psychotherapies with tele-psychotherapies, although low income may still present barriers to access, such as lack of broadband Wi-fi or costly smartphone minutes (Markowitz et al., 2020).

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Disclosure statement

JCM declares a minor conflict of interest regarding book royalties on IPT. The other authors declare no conflict of interest.

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Ethics statement

The Institutional Review Board of the Universidade Federal de São Paulo (UNIFESP) approved the study protocol. Written informed consent was obtained, following a statement of compliance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and the standards of the Review Board, and granting agency.

Trial registration

The clinical trial of this study was registered at Brazilian Clinical Trials, number RBR-3z474z (trial url: http://www.ensaiosclinicos.gov.br/rg/RBR-3z474z/). Registration Date: 24 March 2015.

Data availability statement

The data that support the findings of this study are openly available in Mendeley Data at https://data.mendeley.com/v1/datasets/nfw294mnn3/draft?preview=1.

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