

Efficacy of pharmacotherapy for MDD and PTSD from torture

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Key points of interest

- Antidepressants are the most frequently studied pharmacotherapy in the management of Post-Traumatic Stress Disorder (PTSD) and Major Depressive Disorder (MDD) in torture survivors.
- There is lack of strong evidence that antidepressants improve symptoms of any of them in torture survivors.

Abstract

Introduction: The large numbers of torture survivors suffering from Post-Traumatic Stress Disorder (PTSD) and other psychological trauma in the United States suggest that healthcare professionals should be aware of, and attentive to, the efficacy of drug therapies for this population.

Method: To this end, we systematically review the literature on pharmacotherapy for survivors of torture. Published literature assessing the use of pharmacotherapy in torture victims were sought from MEDLINE, Cochrane Library, PsychInfo and CINAHL.

Search terms “torture,” “pharmacotherapy,” “depression OR PTSD,” “refugee OR asylum seekers” and “treatment or rehabilitation” were utilized.

Results: Review of controlled and uncontrolled studies reveals that antidepressants are the most widely studied medications, particularly sertraline, a selective-serotonin reuptake inhibitor, in the torture survivor populations, expanding to refugees and asylum seekers. Anti-adrenergic medications were used as adjunctive treatment in some uncontrolled studies. In randomized controlled trials, pharmacotherapy did not differentiate from placebo in reducing symptoms. Uncontrolled trials had yielded variable outcomes from pharmacotherapy.

Discussion: There is lack of strong evidence in supporting the use of pharmacotherapy for the treatment of PTSD and Major Depressive Disorder (MDD). Heterogeneity in the study design, patient ethnicity and the social and political status at the time of the study may have contributed in the varied clinical responses to pharmacotherapy.

Keywords: torture, PTSD, MDD, antidepressant, pharmacotherapy, antiadrenergic medication.

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Table 1. Summary of all reviewed literature

Author	Type of Study	Partici- pants	Outcome Assess- ment	Intervention	Outcome
Sandahl (2020)	Prospective, randomized, controlled study	N=230 (79% torture survivors)	Pittsburgh Sleep Quality Index (PSQI), Harvard Trauma Questionnaire (HTQ), Hopkins Symptom Check List (HSCL-25)	Imagery Rehearsal Therapy and/or mianserin	No significant difference in sleep, PTSD and depressive symptoms
Buhmann et al. (2016/18)	Prospective, randomized, controlled study	N=280 (43% torture survivors)	Harvard Trauma Questionnaire's (HTQ)	Sertraline and/or psychotherapy	No significant difference in PTSD symptoms; a small reduction in depressive symptoms with sertraline (secondary outcome)
Sonne et al. (2016)	Prospective, active-controlled randomized study	N=207 (42% torture survivors)	HTQ	Venlafaxine and Sertraline	No significant symptom improvement
Smajkic et al. (2001)	Prospective, randomized study	N=32 (Bosnian refugees)	PTSD Symptoms Scale Beck Depression Inventory (BDI) Global Assessment of Functioning (GAF)	Sertraline, paroxetine and venlafaxine	Overall improvement (venlafaxine did not reach statistical significance in depressive symptoms)
Hinton et al. (2012)	Prospective study	N=56 (Cambodian refugees)	Cambodian Somatic Symptoms and Syndrome Inventory (SSI)	Paroxetine	Overall improvement in somatic and cultural symptoms
Kinzie et al. (2012)	Prospective study	N=33 (torture survivors)	Harvard Trauma Scale, Sheehan Disability Scale and WHOQOL-Bref	SSRI, Tricyclic antidepressant (TCA), bupropion, duloxetine, clonidine and prazosin	Overall improvement of Symptoms

Table 1. Summary of all reviewed literature

Author	Type of Study	Participants	Outcome Assessment	Intervention	Outcome
Carlsson et al. (2010)	Prospective study	N=70 (45 tortured refugees)	HTQ, Hopkins Symptoms Checklist-25 (HSCL), Hamilton Depression Scale and WHOQOL-Bref	Psychotherapy, physiotherapy, medical assistance, social counseling and psychopharmacotherapy	Overall improvement of symptoms (no association found with pharmacotherapy)
Boynton et al. (2009)	Retrospective chart review	N=23 (8 torture refugees)	Clinician-administered PTSD Scale (CAPS)	Prazosin	Reduction in nightmares
Boehnlein et al. (2004)	Retrospective cohort study	N=23 (Cambodian refugees)	CAPS, Hamilton Depression Scale and Sheehan Disability Scale	SSRI, TCA along with psychotherapy	Inconclusive between good outcome and poor outcome group
Drozdek et al. (1997)	Observational study	N=120 (Bosnia-Herzegovina concentration camp survivors)	Watson Questionnaire for PTSD	TCA (amitriptyline and clomipramine) and anxiolytic (diazepam, oxazepam), psychotherapy or combination	No association between drug therapy with PTSD diagnosis
Mollica et al. (1990)	Observational Study	N=52 (Cambodian, Hmong/Laotian, Vietnamese (5 torture victims))	HSCL-25	Fluoxetine, counseling, and social work support	Improvement in specific groups

Efficacy of pharmacotherapy for MDD and PTSD from torture

Article 1 of the United Nations Convention Against Torture, signed by the United States in 1988 and ratified in 1994, defines torture as “any act by which severe pain or suffer-

ing, whether physical or mental, is intentionally inflicted on a person for such purposes as obtaining from him or a third person information or a confession, punishing him for an act he or a third person has committed or is suspected of having committed, or intimi-

dating or coercing him or a third person, or for any reason based on discrimination of any kind, when such pain or suffering is inflicted by or at the instigation of or with the consent or acquiescence of a public official or other person acting in an official capacity".(United Nations Convention against Torture, 1984)

The American Medical Association Code of Medical Ethics is more explicit about including punishment as a context for torture: "the deliberate, systematic, or wanton administration of cruel, inhuman, and degrading treatments or punishments during imprisonment or detainment"(American Medical Association, 2016).

This review focuses on the two most disabling major mental health problems faced by torture victims, Post-Traumatic Stress Disorder (PTSD) and Major Depressive Disorder (MDD) (May et al., 2014). Published records of psychopharmacological treatments in torture victims were searched in MEDLINE, Cochrane Library, PsychInfo and CINAHL. In order to maximize search results, there was no filter applied to the search. The articles that described outcomes of psychopharmacological intervention and written in English were included. The literature search was conducted using the following search terms through March 2021: "torture," "pharmacotherapy," "depression OR PTSD," "refugee OR asylum seekers" and "treatment OR rehabilitation." After abstract review, 24 documents were selected for a full-text review from the search. Following full-text review, 5 items were excluded from this review because either i) the study sought to assess benefits of psychotherapeutic interventions or ii) the case study included comorbid diagnosis of schizophrenia. Five documents were identified through other resources. Ultimately, 24 publications were included for review in this article.

Randomized controlled trials

Sandahl and colleagues conducted a prospective, randomized study assessing the effect of mianserin and psychotherapy (image rehearsal therapy) on PTSD-associated sleep disturbances in 240 refugees, of whom a significant number had torture history (Sandahl et al., 2021). The aim of this study was to examine add-on treatment with imagery rehearsal therapy (IRT). The control arm, treatment-as-usual, had a multidisciplinary approach with standard medicine, physiotherapy, psychoeducation, and cognitive-behavioral therapy components. Mianserin (average dose of 13 mg) was given in 101 subjects over a period of 8-12 months. The difference in sleep quality, post-traumatic or depressive symptoms was insignificant after the treatment. This may be due to the poor adherence to the treatment protocol, supported by a positive drug serum in only 20% of the participants.

Buhmann and colleagues conducted a six-month prospective, placebo-controlled randomized trial comparing psychotherapy alone, pharmacotherapy alone and pharmacotherapy combined with psychotherapy (sertraline, dose range 25-200 mg, and mianserin as needed for sleep) (Buhmann et al., 2016). Two hundred and eighty patients were randomized into one of the four groups: pharmacotherapy and psychotherapy (n=71), pharmacotherapy (n=71), psychotherapy (n=70) and waiting list as the control group (n=68). Ninety-two patients (43%) were torture survivors. After six months of treatment, no statistically significant difference was found among all groups in PTSD symptoms, yet a small reduction in depressive symptoms was associated with pharmacotherapy. Eleven percent of patients receiving sertraline discontinued treatment due to adverse effect. In a follow-up study of the original trial, 145 (67%; 69 of these patients received antidepressants) and 118 (54%;

39 of these patients received antidepressants) patients completed the follow-up interviews at 6-months and 18-months post-treatment, respectively (Buhmann et al., 2018). No significant association was found with pharmacotherapy for any of the outcome measures, including self-rated PTSD severity, self-rated and clinician-rated depression and anxiety severity, self-rated functioning, self-rated quality of life, pain scores, and self-rated somatization. A small, statistically significant reduction in symptoms were seen across all measures except for pain scores (Visual Analog Scale) independent of the intervention.

Sonne and colleagues conducted a randomized, active-controlled trial of venlafaxine combined with psychotherapy in refugee population (Sonne et al., 2016). Its active comparator was sertraline combined with psychotherapy. A total of 207 patients were randomized to the venlafaxine (n=98, 55% torture history) and sertraline groups (n=109, 42% torture history). Neither the patient nor the physician was blinded to the randomization due to patient comfort and trust; only the raters were blinded to the timing of the interview (pre-treatment vs post-treatment). Medication compliance was measured by pill count at every visit. Both medications were initiated at the low dose and subsequently titrated to the maximally tolerated dose (mean dose of venlafaxine 125.41 mg/day, mean dose of sertraline 96.21 mg/day) by the end of 8 weeks. An adjunctive antipsychotic was administered for PTSD-associated psychotic symptoms in 21% and 22% of patients in venlafaxine and sertraline groups, respectively. A total of 17 patients dropped out of the study prematurely, 10 due to adverse effects of medication. Most of the primary and secondary outcomes that assessed trauma, depression, pain, and functioning did not reach statistical significance between the groups, with the exception of the

Sheehan Disability Scale, which suggested that sertraline was superior to venlafaxine. It is noteworthy that many patients were not able to receive a higher dose of venlafaxine due to tolerability. Venlafaxine's dual antidepressant action occurs only at doses greater 225 mg/day.

Smajkic and colleagues conducted a 6-week, prospective, randomized clinical trial of 3 newer antidepressants (sertraline, paroxetine, and venlafaxine) in 32 Bosnian refugees who had been diagnosed with PTSD (Smajkic et al., 2001). Sertraline (n=15) was dosed to maximum 100 mg daily, paroxetine (n=12) 20 mg daily and venlafaxine (n=13) 75 mg twice daily. Six patients received clonazepam 0.5 mg at bedtime for sleep. Eight patients in the venlafaxine group, which included all the women of the group, dropped out due to medication adverse effect (abdominal pain, agitation, dizziness, diaphoresis, headache, nausea and palpitation). All three antidepressants resulted in statistically significant improvement in PTSD symptom severity and Global Assessment Functioning. While sertraline and paroxetine yielded statistically significant reduction in depressive symptoms, venlafaxine did not reach statistical significance. All patients still met the criteria for PTSD after 6 weeks.

Summary and discussion

Antidepressants have been studied in all randomized controlled trials of PTSD and MDD in torture survivors and refugee population. Adjunctive medications were allowed, and psychosocial interventions were employed in various forms. Though an earlier study by Smajkic showed favorable response to antidepressants, namely sertraline, paroxetine and venlafaxine, later studies failed to show a similarly robust response from antidepressants. (Buhmann et al., 2016, 2018; Smajkic et al., 2001; Sonne et al., 2016) One reason may be the difference in patient population; the study

by Smajkic and colleagues recruited Bosnian patients while studies by Sonne and Buhmann had their majority of patients from Arab countries (Buhmann et al., 2016; Smajkic et al., 2001; Sonne et al., 2016). Sertraline may be more tolerable in torture survivors as venlafaxine had overall higher rate of treatment discontinuation due to adverse effects in two studies even at low dose range (Smajkic et al., 2001; Sonne et al., 2016).

Uncontrolled Studies

Hinton and colleagues conducted a prospective trial with antidepressant pharmacotherapy in Cambodian refugees with PTSD (Hinton et al., 2012). The authors used a culturally sensitive outcome measure that assessed somatic symptoms (e.g. dizziness, cold hands and feet, neck soreness) and cultural syndromes (e.g. excessive inner hotness, sleep paralysis, thinking too much), known as the Cambodian Somatic Symptoms and Syndrome Inventory (SSI). Fifty-six patients received treatment that included paroxetine at maximally tolerated dose, with add-on bupropion or mirtazapine as needed, and brief psychoeducation during clinic visits. A statistically significant reduction was seen in the somatic subscale and cultural syndrome subscale of the SSI, and these findings correlated with PTSD Check List scores.

Kinzie and colleagues report a result of a prospective, one-year treatment of torture survivors at a U.S.-based specialty clinic (Kinzie et al., 2012). Thirty-three patients participated in the treatment that involved multidisciplinary professions and therapies, including medications. The medication choices were made by psychiatrists, and included antidepressants, anti-adrenergics and antipsychotics. After one year, most patients (20/22) reported improvement in symptoms of post-traumatic stress and the quality of life.

In a prospective, longitudinal study, Carlsson and colleagues assessed the change of mental state and quality of life in tortured refugees after a multidisciplinary treatment that included psychotherapy, physiotherapy, medical assistance, social counseling and psychopharmacotherapy (Carlsson, Olsen, Kastrup, & Mortensen, 2010). Of the 70 patients who were enrolled in this study, 45 completed both follow-up exams at 9 and 23 months after the treatment. There was a trend toward regression of symptoms of PTSD, depression, and anxiety at the follow-up, and majority of the patients remained symptomatic. Psychopharmacotherapy was not shown to be associated with the improvement in mental health.

Boynton and colleagues conducted a retrospective chart review of prazosin for the treatment of PTSD-associated nightmares (Boynton et al., 2009) (mean dose 2.3 mg/day). Of the 23 patients who were included, eight patients had a record of torture. Of the 23 patients, 22 were concomitantly on one or more psychotropic medications (e.g. SSRI, TCA, benzodiazepine, antipsychotic, valproate, and trazodone). At the end of eight weeks, there was a decrease in reported distressing dream frequency. The overall PTSD scores based on CGI-C improved in 6 patients, “moderately improved” in 11 patients and “minimally approved” in 6 patients.

Boehnlein and his colleagues reported the therapeutic outcomes of 23 traumatized Cambodian refugees who had been in voluntary treatment for mean 13.5 years (Boehnlein et al., 2004). All patients received consistent medication therapy, including antidepressants (SSRI or a tricyclic), some combined with anti-adrenergic medication (prazosin or clonidine) for the management of nightmares. The authors divided the cohort into two groups, “good outcome (n=13)” and “poor outcome (n=10)” based on current symptoms and func-

tional disability, comparing the treatment between the groups. No significant difference was noted in the past treatment patterns of these two groups, except a slightly higher rate of TCA use in the 'good outcome' group.

Drozdek reported the result of a three-year observational study of 120 Bosnia-Herzegovina concentration camp survivors who received treatment for PTSD (either psychotherapy alone, medication alone, or a combination) versus no treatment for six months (Drozdek, 1997). For the medication group, amitriptyline or clomipramine was used along with as-needed benzodiazepine for anxiety. At the end of 6 months, 73% of those who received treatment met the criteria for PTSD, while 90% of those who did not receive treatment met the criteria for PTSD. At the three-year follow up, 83% of those who received treatment met the criteria for PTSD while 60% of those who did not receive treatment retained the diagnosis. There was no difference in the outcomes among the psychotherapy group, the medication group, and the combination group.

Mollica and colleagues conducted a preliminary study with Cambodian (n=21, of whom 3 were torture victims), Hmong/Laotian (n=13, of whom 2 were torture victims) and Vietnamese (n=18) refugees (Mollica et al., 1990). Treatment included fluoxetine, counseling, and social service support. After a six-month treatment, anxious and depressive symptoms were reduced in the Cambodian and Vietnamese population, whereas the Hmong/Laotian population experienced worsening of anxious and depressive symptoms. The authors attributed the lack of response in the Hmong/Laotian population to their general reluctance to agree to Western medical care, as well as chronic substance misuse problems that were prevalent during treatment. It

was not reported whether torture victims had a different outcome or a course of treatment.

Summary and Discussion

Results from the uncontrolled studies that attempted to assess the efficacy of pharmacotherapy in torture victims and refugee population were variable. While clinical responses were seen in some, a number of studies had worsening of depressive and post-traumatic symptoms among those who took the medication (Drozdek, 1997; Mollica et al., 1990). Antidepressants remain to be the most widely studied class of medications in these uncontrolled trials, while several studies allowed patients to receive clonidine, an anti-adrenergic medication, for additional reduction in hyperadrenergic state of PTSD (Boehnlein et al., 2004; Kinzie et al., 2012).

Summary of Case Series and Reports

Experience with SSRI

Liu-Barbaro and Stein report the successful treatment of PTSD, depression, and dissociative fugue with sertraline (maximum 150 mg daily) and prazosin (maximum 4 mg daily) in a 63-year old Ethiopian refugee (Liu-Barbaro & Stein, 2015). Schwarz-Langer and colleagues described their experience of treating 13 civil war refugees with diagnoses of MDD, somatization disorder, and anxiety disorder (Schwarz-Langer et al., 2006). All patients but one were treated with SSRIs (citalopram, sertraline, or fluvoxamine), one patient with mirtazapine, six patients with as-needed benzodiazepine or zopiclone, and eight patients with concomitant antipsychotic (olanzapine and/or flupentixol). All patients reported subjective improvement in sleep with a shortened time to fall asleep and lessening of nightmares. Most patients reported reduction in intrusive symptoms and hyperarousal. Fernandez and

colleagues published a case report on the normalization of cerebral blood flow after fluoxetine treatment in a torture-survivor (Fernandez et al., 2001).

Mixed Experience with SSRI and TCA

Bouwer published a case series of 14 torture victims with PTSD and MDD (Bouwer & Stein, 1998). After eight weeks of treatment with antidepressants (nine patients with sertraline, dose range 50-200 mg daily; two with fluoxetine, dose range 20-30 mg daily; two with imipramine, dose range 125-150 mg daily; and one with clomipramine, dose 125 mg daily), statistically significant reductions in both PTSD and MDD symptoms were observed. The two patients who took imipramine had minimal improvement.

Experience with TCA and Monoamine Oxidase Inhibitor

Cheung reported positive treatment responses from doxepin in three Cambodian refugees who were diagnosed with PTSD and depression (Cheung, 1993). Basoglu and colleagues report a successful treatment outcome in a 29-year-old torture-survivor with a diagnosis of PTSD and MDD who received amitriptyline (150 mg per day) (Basoglu et al., 1992). Frances and Kroll reported a case of a 57-year-old Hmong woman who was treated with amitriptyline and had improvement in depressive symptoms (Frances, 1989). DeMartino and colleagues described five female refugees from Cambodia/Laos who were treated with monoamine oxidase inhibitors and experienced symptom improvement (DeMartino et al., 1995). Kinzie and Leung report a 1-year treatment of imipramine and adjunctive clonidine combination in nine Cambodian refugees with PTSD and MDD (Kinzie & Leung, 1989). Five patients no longer met the criteria for MDD, and two patients for PTSD. Boehnlein and his col-

leagues reported the result of a 1-year treatment of their 12 Cambodian concentration camp survivor patients with PTSD (Boehnlein et al., 1985). Patients reported medications that were most effective in reducing symptoms were imipramine (n=5), amitriptyline (n=2), doxepin (n=6), phenelzine (n=3), beta-blockers (unknown number of patients) and benzodiazepines (unknown number of patients). The authors noted much improvement in symptoms of hypervigilance and intrusive thoughts, but little improvement in avoidance symptoms of PTSD.

Other Medications

Rijnders and colleagues report on the use of cyproheptadine for PTSD-associated nightmares in a 29-year-old asylum seeker who failed to respond to psychotherapy (Rijnders et al., 2000). Polysomnography affirmed near normalization of sleep architecture after cyproheptadine was started. Kinzie and his colleagues reported on four Cambodian women with subjective feeling of better sleep, less daytime irritability and fewer nightmares after clonidine treatment (clonidine dose 0.3 mg divided morning and bedtime) (Kinzie et al., 1994).

Summary and Discussion

A number of the case reports and series are dated in the era where non-SSRI antidepressants were readily available. Fluoxetine, the first SSRI to be introduced to US market, was available in 1988 (Hillhouse, Porter, Clin, & Author, 2015). TCA and monoamine oxidase inhibitors were widely used as first-line medications preceding this date. It is interesting to note that when SSRI and TCA were used alongside each other, the efficacy of TCA compared to SSRIs was variable (Boehnlein et al., 2004; Bouwer & Stein, 1998). A head-to-head study would be extremely informative to as-

certain the relative efficacy of TCA and SSRI. Review of case reports and series also suggests that avoidance cluster of symptoms of PTSD may be more resistant to antidepressants than other clusters of symptoms (Boehnlein et al., 1985; Kinzie & Leung, 1989).

Discussion

Presently, the US Food and Drug Administration has approved sertraline and paroxetine for the management of PTSD. Not surprisingly, sertraline is the most frequently studied SSRI for the reviewed studies here. One head-to-head trial comparing sertraline and venlafaxine, a serotonin-norepinephrine reuptake inhibitor, showed that venlafaxine may have a poorer tolerability than sertraline, often prohibiting dose titration. (Sonne et al., 2016) TCAs were reported in a number of older case reports with clinically significant improvement in symptoms (Basoglu et al., 1992; Boehnlein et al., 1985; Frances, 1989; Kinzie & Leung, 1989). TCAs and venlafaxine have the same pharmacological mechanism, namely serotonin-norepinephrine reuptake inhibition, differing only slightly in their affinity to serotonin transporter (O'Donnell et al., 2017). Controlled studies conducted to date have not yielded sufficient evidence to recommend pharmacotherapy, specifically antidepressants, for the treatment of PTSD and MDD in torture survivors. In clinical practice, antidepressants are often utilized for symptom management in this population.

Use of anti-adrenergic medication was seen in combination with SSRI. As a note, in combat-related PTSD, anti-adrenergic agent prazosin has superior efficacy over SSRIs (VA/DOD, 2017). In torture victims, however, the evidence for use of anti-adrenergic medication is weak due to lack of placebo-controlled trial or a head-to-head comparison with an antidepressant.

Limitations

This review of literature concerning the evidence of pharmacotherapy in the treatment of PTSD and MDD in torture victims has several limitations. First, because of the paucity of studies that recruited torture victims exclusively, the search was broadened to include refugees and asylum seeker population. Though a large percentage of refugees and asylum seekers often had trauma experience and have fled from violent environments, torture victims may experience possibly more intense symptoms of psychiatric sequelae due to the nature of their trauma. Another limitation is the lack of control group in many of the reviewed studies. Control groups are often eliminated from the study design for ethical reasons, though some authors were able to recruit a control group by getting consent from patients who were either waiting for treatment or refusing treatment (Buhmann et al., 2018). Great heterogeneity is evident in the study design, patient ethnicity and the type of outcome measures. The political and social status at the time of study may also impact the patients' symptoms, potentially altering the clinical response to treatment. Furthermore, traumatic events will impact each individual differently, resulting in variable triggers, symptoms, and behavioral responses.

Conclusion and Future Direction

Efficacy of pharmacotherapy for the treatment of PTSD and MDD in torture survivors is inconclusive based on this review. With the increase in traumatic events occurring worldwide in recent years, the incidence of PTSD is increasing and becoming a significant public health concern. It is imperative to identify an effective treatment to help the growing number of torture survivors.

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