

Psychopharmacology for Refugee and Asylum- Seeker Patients

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The pharmacotherapy of patients with PTSD has been influenced by the greatly increased knowledge of the neurobiology of severe trauma and the increasing sophistication of drug trials for treatment of traumatic conditions. The expanded scientific knowledge will briefly be reviewed below. However, a critique of these studies will indicate a limited relevance to highly traumatized refugees. The clinical complexity of these patients, emphasizing their cultural aspects of treatment, will be reviewed. Based upon broad clinical and empirical treatments, suggested pharmacological approaches to traumatized refugees from various cultures will be given.

NEUROBIOLOGY OF PTS

Multiple neurobiological symptoms are associated with stress and some are probably involved directly in symptom formation in PTSD. The evidence for these has been summarized elsewhere (Bremner, Southwick & Charney, 1999; Friedman, 2001b). Adrenergic mechanisms, especially those mediated by norepinephrine, have shown heightened reactivity in

PTSD. The evidence is strongest when subjects are exposed to laboratory stressors or traumatic memories, where elevated heart rate, blood pressure, and skin conductance have been found (Pitman, Orr, Foa, de Jong, & Claiborn, 1987). Altered norepinephrine function is also indicated by other biological abnormalities such as response to yohimbine, depressed platelet MAO activity and MHPG response (Southwick, Bremner, Rasmusson, Morgan, & Arnsten, 1999). Abnormalities have also been detected in the hypothalamic-pituitary-adrenal (HPA) system including increased corticotrophin-releasing factor supersuppression with the glucocorticoid dexamethasone, increased density of lymphocytic receptors, and mixed results with urinary and plasma cortisol. Decreased serotonin uptake and binding has been found in platelets. In one study, PTSD patients exhibited platelet-poor plasma concentration of serotonin levels and elevated norepinephrine levels (Spivak, Vered, Graff, Blum, Mester, & Weizman, 1999). PTSD, anxiety, and flashback symptoms have been provoked with both adrenergic (e.g., yohimbine) and serotonergic (e.g., mCPP) agonists (Southwick, Krystal, Morgan, Johnson, Nagy, Nicolaou, et al., 1993). Recent studies on brain imaging indicate that PTSD is associated with both structural and functional abnormalities (Pitman et al., 2002). As we learn more about neurobiological alterations associated with PTSD, there is reason to hope that new medications might be designed to ameliorate symptoms caused by the unique pathophysiology of PTSD (Vermetten & Bremner, 2002; Friedman, 2000).

DRUG STUDIES IN PTSD

Antidepressants

There have been an increasing number of clinical trials with medications for treatment of PTSD in the past 10 years. The ones on nonrefugee populations will be summarized below. An early study on veterans indicated improvement in PTSD symptoms with the MAO inhibitor, phenelzine, and the tricyclic antidepressant imipramine in veterans (Kosten, Frank, Dan, McDougle, & Giller, 1991). A dual effect on both depression and PTSD symptoms was also found with the tricyclic antidepressant, amitriptyline (Davidson, Kudler, Saunders, Erickson, Smith, Stein, et al., 1993). The SSRI, sertraline, is the first medication to have received FDA approval for use in PTSD based on results in two large multisite trials with a total of approximately 400 subjects (Davidson, Rothbaum, van der Kolk, Sikes, & Farfel, 2001). In a longer (24-week) study with sertraline, it was shown that remission of PTSD symptoms continued over time (Lindberg, Hegel, Goldstein, Goldstein, Himmelhoch, Maddock, et al., 2001). When sertraline treatment was extended to 64 weeks, the quality of life improved for those kept on the medication, while symptoms worsened for subjects randomly switched to

placebo treatment (Rapaport, Endicott, & Clary, 2002). In addition to successful PTSD trials, Brady, Sonne, and Roberts (1995) found that sertraline also decreased alcohol consumption while PTSD symptoms improved. Another SSRI, paroxetine, has also received FDA approval based on three successful 12-week randomized clinical trials; it was found to improve all symptom clusters of PTSD (Tucker, Zaninelli, Yehuda, Ruggiero, Dillingham, & Pitts, 2001). Fluoxetine, a selective serotonin reuptake inhibitor (SSRI), was found to be effective in reducing PTSD in nonveteran, mostly female patients who responded better than veterans receiving treatment in a Veteran's Affairs (VA) clinic (van del Kolk, Dreyfuss, Michaels, Shera, Berkowitz, & Fisler, 1994). A recent multisite randomized clinical trial confirmed these early results and indicated that fluoxetine is a very effective treatment for PTSD that is well tolerated (Martenyi, Brown, Zhang, Prakash, & Koke, 2002). Citalopram (another SSRI) has also been found to be useful in adults and children with posttraumatic stress disorder (Seedat, Stein, & Emsley, 2000). A different antidepressant, nefazodone, which enhances serotonergic function through different mechanisms than SSRIs, has been shown to promote PTSD improvement in several open-label trials (Davidson, Weisler, Malik, & Connor, 1998; Zisook, Chentsova-Dutton, Smith-Vaniz, Kline, Ellenor, Kodosi, et al., 2000). Finally, an open trial with the antidepressant bupropion, which enhances adrenergic and dopaminergic (but not serotonergic) activity, has also been successful with PTSD subjects (Canive, Clark, Calois, Quells, & Tuason, 1998).

Antiadrenergic Agents

Because of known abnormalities in the adrenergic system in PTSD, it was thought as early as 1984 that the antiadrenergic agents such as propranolol and clonidine would be helpful (Kolb, Burris, & Griffiths, 1984). Propranolol is a postsynaptic beta-adrenergic antagonist, while clonidine is a presynaptic alpha-2 agonist that inhibits the activities of the adrenergic system by reducing the amount of norepinephrine released presynaptically. As such, it is an effective antihypertensive agent. Clonidine has been used extensively with traumatized refugees and our experience with this medication will be discussed later. A recent report from Argentina regarding emergency room patients prescribed medication immediately after trauma exposure suggests that those who received clonidine or propranolol exhibited marked improvement 6 months later, whereas those who received antidepressants (such as venlafaxine, sertraline, and citalopram) or the benzodiazepine, alprazolam, showed no improvement (Mosca & Muro, 2002). Recently, the adrenergic postsynaptic alpha-1 blocking agent and antihypertensive medication, prazosin, has been found to reduce traumatic nightmares and global PTSD symptoms in combat veterans and in civilians (Raskind, Thompson, Petrie, Dobie, Rein, Hoff, et al., 2002; Taylor & Raskind, 2002).

Benzodiazepines

Although anxiety seems to be a major component of PTSD, and PTSD is included in the anxiety disorder section of DSM-IV, benzodiazepines have not proven effective against core PTSD symptoms (Friedman, 2001a).

Antipsychotics

Although antipsychotics have not been considered the recommended treatment for PTSD (Cyr & Farrar, 2000), psychotic symptoms can be associated with PTSD (Mueser & Butler, 1987; Mueser, Goodman, Trumbetta, Rosenberg, Osher, et al., 1998). Kinzie Boehnlein (1989) discussed it as a fairly common phenomenon in traumatized refugees. It would be useful to have studies on these difficult patients, particularly with atypical antipsychotics, which affect both the dopaminergic and serotonergic systems and are fairly well tolerated. Although randomized trials have not been carried out on the efficacy of atypical antipsychotics for PTSD, preliminary data on veterans indicate that olanzapine can ameliorate SSRI-resistant PTSD (Stein, Kline, & Maltoff, 2002), and risperidone has been shown to reduce comorbid psychotic symptoms with PTSD (Hammer, Faldowski, Ulmer, Frueh, Huber, et al., 2003), and be useful for irritable aggression (Monnelly, Ciraulo, Knapp, & Keane, 2003). Theoretically, risperidone could reduce nightmares due to its strong alpha-1 and alpha-2 blockade, the highest blockade of all atypical antipsychotics (Bezchlibnyk-Butler & Jeffries, 2000, p. 80). Although it currently appears that antidepressants affecting the serotonin system SSRIs have performed better than those affecting the norepinephrine system (e.g., bupropion and desipramine), there have been too few clinical trials with adrenergic agents to support such a conclusion. Given the recent FDA approval of two SSRI medications, and the consistent success of these medications in treating all PTSD symptom clusters, these agents must be considered first-line treatment for PTSD at this time (Friedman, Davidson, Mellman, & Southwick, 2000).

STUDIES RELEVANT TO REFUGEES

The populations in the above studies, usually Vietnam veterans and Caucasian female victims of civilian traumas, are very different from refugees. Indeed, there have been few studies conducted either in war-torn countries or with refugees themselves. A report from the Indochinese Psychiatric Clinic in Boston, with Indochinese survivors of trauma, suggests that the efficacy of monoamine oxidase inhibitors for PTSD can be independent of their beneficial effects in depression (Demartino, Mollica, & Wilk, 1995). This report also raises appropriate concerns about using MAOIs with refugees, given the dietary practices of Southeast

Asians. The Intercultural Psychiatric Program in Oregon has treated refugees for 25 years and reported the successful use of clonidine and imipramine in a prospective study with 9 Cambodian patients (Kinzie & Leung, 1989). There was a marked improvement in depression and nightmares for 7 of these patients. Although there was global improvement in PTSD reexperiencing and arousal symptoms, avoidance was not affected. In an all-night polysomnographic study with 4 Cambodian patients, clonidine was extremely effective; it produced almost complete suppression of nightmares and the patients reported better sleep and less irritability (Kinzie, Sack, & Riley, 1994). This effect appears to have been restricted to PTSD improvement since depression symptoms were not affected. A report on Bosnian refugees found sertraline and paroxetine to produce statistically significant improvement in PTSD symptoms in 6 weeks (Smajkic, Weine, Djuric-Byedic, Boskaulto, Lewis, & Pavkovic, 2001). Venlafaxine produced improvement in PTSD but not depression and was associated with a high rate of side effects. All 32 patients still met PTSD diagnosis at 6 weeks.

Clinical Aspects of Refugees and Political Asylees

There are important aspects of refugees lives that greatly influence their clinical status and need to be accounted for in the management of these patients. First, the amount of trauma endured by refugees often is catastrophic and much greater in severity and duration than that reported among patients from Western countries. Cambodian survivors of the Pol Pot regime endured 4 years of concentration camp experience, starvation, forced labor, indiscriminate executions, and sometimes were forced to witness the execution of family members. Most of the Cambodian refugee patients had some family members killed and often lost their entire families, including children. After the regime fell, there was mass confusion, victimization by bandits, and they were forced to live for 3 to 5 years in a refugee camp with unsafe and unpredictable conditions. In Somalia, after the overthrow of the government in 1992, refugees were exposed to mass and indiscriminate murder by warlords; the complete lawlessness associated with fighting by rival tribe clans resulted in mass starvation. Those who made it out of the country were subjected to robbery and beatings in refugee camps and faced an unknown future. Rural farmers in Guatemala were often caught between government militia, paramilitia, and the guerrilla forces, all of whom would come at night to attack villages, kill and kidnap men, and leave the village in utter ruin. The Aethnic cleansing, with the blockade and shelling of entire towns in Bosnia, is well documented. In addition, reports of torture of Muslim men in concentration camps and the discovery of mass graves indicate the extent of the brutality inflicted on people exposed to the many wars in the former Yugoslavia.

Second, because of the trauma, refugees are confronted with massive losses, which include death of family members, loss or separation from

other families, loss of their society and culture, and loss of vocation and income because their skills are not needed in the host countries. There is a total breakdown in the social and cultural fabric of their lives. Within the family there is a disruption of the dynamics, with loss of parental authority because parents often cannot provide appropriate guidance to their children who now see them as irrelevant in a technological society. Often there is a disruption of the religious practices of the traditional Muslim and Buddhist cultures. The result is a loss of cultural continuity. Additionally, refugee families are often strapped with poverty and unable to find employment. Further, since fathers are often missing or killed, single mothers must struggle with the daunting challenge of raising children in a foreign country. Most refugees have very limited language ability in the host country so that basic activities — shopping, housing, and transportation — are often huge problems.

A special group are the asylum seekers who arrive in a country without legal status and who cannot receive services until asylum is granted. They live in an unpredictable world and have a high rate of psychiatric morbidity (Silove & Kinzie, 2001).

Cultural Considerations

A major theoretical and clinical issues concern the influence of culture on symptoms following trauma, especially massive psychological trauma. Clearly, the culture of a patient, as well as his or her resilience, personality, social supports, and posttraumatic environment, will influence the expression of symptoms. Several examples from diverse non-Western cultures will demonstrate some of these factors. Traditional Buddhists, who believe in karma, often will show an acceptance of terrible events that are unacceptable to most Westerners. Islamic patients, who believe that their fate is in Allah's hands, may feel less of a need to actually strive for any relief. The animus Mien tribesmen from rural Laos subjectively feel that Western medicine is not compatible with their bodies or their yin-yang understanding of disease. Cultural factors need to be understood and often addressed if therapy is to succeed. A more comprehensive discussion of cross-cultural treatment of PTSD is beyond the scope of this chapter but can be found elsewhere (Kinzie, 2001). Based on 25 years' experience treating refugees at the Intercultural Psychiatric Program (IPP), with patients from 17 cultures and languages by one of us (JDK), we offer the following personal observations on cross-cultural issues relating to trauma.

The expression of the symptoms depends largely upon the skill, tact, empathy, and experience of the psychiatrist and the ethnic mental health counselor. The Intercultural Psychiatric Program has never used interpreters, but has trained counselors of each culture to work and provide translation both linguistically and culturally between the psychiatrist and the patients. Additionally, as counselors gain experience, they begin to serve as case managers and group leaders. The

patient's recounting of his or her symptoms, and especially the traumatic experiences, changes and is reinterpreted as trust and safety issues as the therapeutic relationship grows. Thus, the expression of symptoms and their treatment is a dynamic process involving patients, counselors, and psychiatrists.

After massive trauma, which most refugees have experienced, the core symptoms among all refugee groups are much more similar than different. All groups have described reexperiencing, particularly, nightmares and intrusive thoughts; and hyperarousal, including poor sleep, poor concentration, and irritability. Avoidance symptoms are also common, especially those involving memories and reminders of the past and violence. Numbing and social withdrawal, however, can vary depending on individual or situational differences. Many Cambodians and Somalis in the clinic setting display overt numbing, while in the nonclinical context of their own group activities and social therapy can be more overtly emotionally expressive as long as the focus is not trauma-related. Depressive symptoms seem to be universal in all the cultural groups.

Medication needs to be part of a total program in which the major therapeutic ingredients are safety and long-term continuity. In the Intercultural Psychiatric Program, the three senior psychiatrists have been associated with the program for 20 or more years each, and 10 of the 25 counselors have been with the program for 10 or more years. This stability provides confidence for the patient who receives psychotherapy with the psychiatrist and case management and counseling with the ethnic mental health counselors. Socialization and activity groups, in which about half the patients participate, reduce social isolation and provide a good forum for medication education.

For Western-trained mental health professionals who work with PTSD patients, there are several notable differences with refugees. The small number of alcohol- and substance-abusing patients is in marked contrast to U.S. veterans. Prohibited by both Buddhist and Islamic religions, substance dependence is rare but not absent in these groups. It is more prevalent in Bosnian and Latin American refugees. Suicide and suicide attempts are very uncommon. There have been about five successful attempts in the 25 years, all of which have occurred with schizophrenic patients. Personality disorder symptoms, especially cluster B, are not common. Most of the patients have had a stable childhood and their forced migration occurred during adulthood. This lack of traumatic exposure or interpersonal violation during childhood seems to have provided most refugees with a stable identity so that destructive interpersonal behaviors or frank antisocial traits are uncommon. The long-term effects of children exposed to trauma have not been extensively studied, but a 6-year follow-up of Cambodian children exposed to massive trauma showed few personality or antisocial disorders (Sack, Clarke, Him, Dickason, Goff, Lanham, et al., 1993).

This contrasts greatly with what has been reported in Americans with PTSD caused by childhood abuse. Dissociative symptoms are not

common. Most patients present in a straightforward manner, once trust is established, without the disturbances and identity problems, memory impairment, altered reality testing, or fragmented cognition, which is often present in Western patients with dissociative symptoms.

Refugee patients are both pragmatic and genuinely hopeful about Western medicine. They already have seen the obvious benefits of antibiotics, trauma surgery, good obstetrical care, cancer screening, and how effective control of blood pressure prevents cardiac death. Psychiatric medicines, providing symptom relief in the context of a relationship in which side effects are explained, are well accepted by most groups. Involving families, who often are exposed to the nightly screaming, irritability, or profound sadness of the PTSD patient, helps to ensure further compliance. If the medicine benefits the patients' perceived symptoms or needs, they will take it. A problem has been in maintaining patients on medication after symptoms have been relieved. There are similar problems getting refugees to continue to take medicine for tuberculosis treatment or for the asymptomatic treatment of hypertension.

CLINICAL CONSIDERATIONS

Ethnopsychopharmacology

Although transcultural psychiatrists have felt clinically that different ethnic groups respond to psychiatric agents differently, it was only in the 1990s that ethnic differences in psychobiology were scientifically studied, led by Keh-Ming Lin (Lin, Poland, & Nakasaki, 1993). Since that time, a number of authors have raised issues regarding the different effects of the same medications when administered to different ethnic groups (Jaime & Maharaja, 2000; Lin, Smith, & Ortiz, 2001; Pi, 1998; Ramirez, 1996; Sramek & Pi, 1996). It is now recognized that there are substantial differences in the metabolic capacity of different ethnic groups. For example, the frequency of mephenytoin poor metabolizes in different populations has been found as follows (Kinzie & Ediri, 1998b):

African Americans	1.7%
African Caucasians	2.6%
Chinese	14.6%
Japanese	22.6%
Vietnamese	22.0%

The clinical significance of this information is difficult to evaluate since there are many factors (individual genetic enzyme pathways, diet, smoking, and presence of other medicines) that also contribute to these differences in psychotropic drug response.

Compliance

One of the largest problems in evaluating medicine effectiveness is the high noncompliance rate among psychiatric patients. This seems especially true for refugees who have little understanding of the reasons why they should take medicines or little tolerance of side effects. In an early study on compliance with tricyclic antidepressants, marked noncompliance was found among Asian patients (see Table 21.1) (Kinzie, Leung, Boehnlein, & Flick, 1987).

Overall, no blood tricyclic levels were detected in 61% of patients, with the highest noncompliance observed among Vietnamese and Mien patients. After discussing this matter with these patients, the total noncompliance (e.g., zero blood levels) dropped to 22% and 27% among Cambodian and Vietnamese, respectively. However, the Mien were not influenced by this intervention since their noncompliance remained high at 67%. After a more thorough patient evaluation there was a further increase in compliance among Vietnamese and Cambodians, but little improvement occurred among the Mien, a hill tribe people from Laos. Clearly, the issue of medication compliance and the related issue of patient acceptability of pharmacotherapy must be considered when evaluating the effectiveness of medicines among refugees.

DIFFICULTY IN DIAGNOSIS IN REFUGEES

Among refugees from some countries, such as Cambodia, where the severe trauma is documented, making the PTSD diagnosis seems straightforward. For other refugee groups, it might be more difficult to elicit a history of trauma because of factors such as shame, amnesia, and poor interviewing or interpreting skills by clinicians. In addition, an accurate history of pretraumatic mental illness might be overlooked because of the dramatic presentation of the brutal events. Even in the Intercultural Psychiatric Program, a diagnosis of PTSD was sometimes missed during the initial evaluation and was only determined subsequently after structured reinterviewing (Kinzie, Boehnlein, Leung Moore, Riley, & Smith, 1990). Equally important is consideration of other psychiatric disorders that exist with PTSD among refugees

TABLE 21.1 Routine Check of 41 Asian Patients for TCA Blood Levels (N = %)

	None	Subtherapeutic 25-180 µg/ml	Therapeutic > 180 µg/ml
Cambodian	7 (39)	7 (39)	4 (22)
Vietnamese	9 (81)	1 (9)	1 (9)
Mien	9 (75)	2 (17)	1 (8)
Total	25 (61)	10 (24)	6 (15)

exposed to massive trauma. Below is a review of psychiatric diagnoses among 199 refugees from major war zones in Cambodia, Bosnia, and Somalia seen in the Intercultural Clinic during August 2002 (see Table 21.2).

Clearly, PTSD rarely exists alone; in only three people out of 199 was PTSD the sole diagnosis. PTSD was comorbid with depression in 57% to 79% of the cases. It was comorbid with psychotic symptoms in 5% and 13% of Bosnians and Somalis, respectively. Schizophrenia, with its long-term deterioration in function, was associated with PTSD in all groups. In contrast to U.S. veterans, Buddhist and Muslim refugees rarely exhibited alcohol problems. In summary, it can be difficult to make a diagnosis of PTSD with refugee patients and when PTSD is present, it is usually associated with depression and often with psychosis or schizophrenia.

THE COURSE OF TRAUMATIC SYMPTOMS

Our clinical experience and a long-term study of Cambodians in the community indicate that, as with other chronic disorders, PTSD has a long course with exacerbations and remissions. In an earlier report on Cambodian refugees (Kinzie, Frederickson, & Ben, 1984), PTSD was first described. A follow-up study indicated that the symptoms were greatly reduced at 1 year (Boehnlein, Kinzie, Ben, & Fleck, 1985). All these patients, however, had a clinically significant exacerbation of their symptoms over the next several years. Sack, Clarke, Him, Dickason, Goff, Lanham, et al. (1993) followed Cambodians in the community and initially found a 50% rate of depression and PTSD. After 12 years, the rate of PTSD dropped to about 30%, while depression almost completely disappeared. Several subjects who did not meet PTSD diagnostic criteria at one time did so at another time, indicating a fluctuating clinical course. In a reactivation study, Cambodians exhibited a marked

TABLE 21.2 Diagnosis in 2002

	Cambodians	Bosnians	Somalians
<i>N</i> =	110	58	31
% PTSD + depression	79	57	58
% Depression	6	19	3
PTSD	0	0	3
PTSD + psychosis	0	5	13
Schizophrenia	7	12	7
Schizophrenia + PTSD	4	5	16
Alcohol dependence	2	0	0
Total with PTSD + another diagnosis	82 (91/110)	67 (39/58)	90 (28/31)

increase in pulse rate when exposed to traumatic stimuli (that were not limited to war or Cambodian scenes) in comparison to control and Vietnam veteran subjects (Kinzie, Denney, Riley, Boehnlein, McFarland, & Leung, 1998). In all refugee patient groups, stressful personal experiences such as assaults, surgeries, and accidents exacerbated the original symptoms. Community stress, such as televised scenes about the Gulf War and World Trade Center attacks, greatly increased PTSD symptoms among all of our refugee groups.

In a recent study on the effects of viewing the 9/11 events on television, it was found that Somalis and Bosnians reported the greatest increase in subjective distress and symptoms (Kinzie, Boehnlein, Riley, & Sparr, 2002), whereas Cambodians and Vietnamese refugees exhibited surprisingly little intensification of symptoms. This probably was related to the warfare in Bosnia and Somalia being more recent than in other groups. Their Muslim religion also might have given them a sense of vulnerability in America. A chart review of 25 Cambodian patients treated for at least 10 years indicated that half (13) still had abnormal elevations in PTSD symptom severity, whereas only 4 had elevated depressive symptomatology. In summary, it is clear that for many if not most refugees, PTSD is a chronic disorder subject to stress-induced exacerbations when there is perceived risk of threats or danger. Clearly, all therapy must be aimed at chronic treatment with the expectation of periodic exacerbations in symptom severity. Follow-up studies limited to a 6-week, 12-week, or even 1-year follow-up are not adequate for evaluating longitudinal outcome.

PATIENT DEMOGRAPHICS AND EXPECTATION

The vast majority (70%) of the 1,000 refugees who participate in the Intercultural Psychiatric Program are female, varying 84% among Somalis to 69% of Bosnians. Many refugee women have not been educated so there is a high level of functional illiteracy even in their own language. Less than 4 years of education, but usually none, was present in 66% of Cambodians, and 58% of Somalis, but in only 20% of Bosnians. Many Cambodians and Somalis could not read medical instructions even in their own language, and therefore were even more confused by instructions written in English. In addition to patient education, the cultural beliefs about mental illness and expectations about medical treatment have a major influence on acceptance of medicine, tolerance of side effects, and compliance.

Many patients originally complain of multiple somatic symptoms (headache, backache, weakness, poor sleep), and even after sensitive interviewing have difficulty focusing on psychological symptoms such as depressed mood, anxiety, irritability, nightmares, poor concentration, or anger outbursts. If the patient's symptomatic concerns are not acknowledged and alleviated there is little chance for continued engagement in

therapy. The implication is that many patients for whom it is difficult to understand current medical diagnosis will also have difficulty following written instructions (or even remembering oral ones) and will have very different concepts about the goals of treatment.

GUIDELINES

The above information, summarized from a large, growing database about several different refugee groups, underscores the biopsychosocial complications associated with pharmacotherapy for traumatized refugees. The guidelines presented here should serve as a preliminary list for the treating psychiatrist. Two points must be emphasized. First, treatment with medicine can only succeed if it is part of a total program, which includes supportive psychotherapy, medical evaluation, guidance regarding financial security, attention to housing needs, and opportunities for vocational rehabilitation. Second, the treatment team must include a trusted, competent, and ethical mental health counselor (or at least an interpreter) who provides both linguistic and cultural continuity for the patient and doctor.

- Take a full history of the patient including his or her life before and after the trauma, the trauma itself, the symptoms of PTSD, depression and psychosis, and the presence of other medical conditions and medicines taken.
- Determine from the patient and family (when available) what are the most disturbing symptoms or behaviors. Develop a mutual agreement on the target symptoms, such as insomnia, nightmares, irritability, depression, and pain, which are often common concerns.
- Use medicines that directly or indirectly alleviate the target symptoms of the patient complaints.
- Keep medicines very simple. Remember patients often cannot read and easily get confused. It is good to show patients the pills so they can recognize the color and shape.
- Carefully explain the benefits and some possible side effects and the need to continue medicine.
- Prepare the patient for long-term treatment. The ideal therapeutic stance is to both expect improvement and that treatment will continue.
- Do frequent evaluations, weekly at first, since there is almost universal confusion and misunderstanding with starting medicine. Always ask about compliance and get blood levels if they are available.
- Expect exacerbations, making adjustment to give symptomatic relief as needed, but don't fine-tune the medicine too often. Provide an accepting and predictable presence to the patient.
- Consider cost if there is no health insurance or third-party payer, as is true with many refugees and with all asylum seekers.

SPECIFIC MEDICINES BASED ON CLINICAL EXPERIENCE WITH THE ABOVE GUIDELINES

The use of psychotropic medicines among refugees has rarely been addressed in the published literature, but there is a large experimental clinical base on which to base these guidelines. The Intercultural Psychiatric Program has treated over 4,000 refugee patients in 25 years and currently has 1,000 adults in treatment. In a review conducted a few years ago concerning the actual clinic practice patterns of five faculty psychiatrists who had collectively treated 240 refugee patients, it was found that 41% received tricyclic antidepressants; 42% received an SSRI; and 17% received trazodone. This represented the personal preference of the physicians rather than any special clinical or economic considerations. Indeed, the use of SSRIs varied from 17% to 79% by specific physicians. Of the 77% of refugees taking SSRIs, 74% were taking another psychotropic medicine for insomnia; the secondary medicines included a low dose of trazodone, a sedative tricyclic, or benzodiazepine. A major concern for patients has been poor sleep, for which SSRIs are often ineffective. Almost no patients on TCAs were on a secondary medicine for insomnia.

Antidepressants

SSRIs

Since depression often occurs conjointly with PTSD in traumatized refugees, and since SSRIs are effective for both depression and PTSD, they are a good choice for initial treatment. As stated earlier, two SSRIs (sertraline and paroxetine) have received FDA approval as indicated treatments for PTSD. They have been considered the first drug of choice in both practice guidelines reviews (Friedman, Davidson, Mellman, & Southwick, 2000) and by international consensus groups on treatment of PTSD (Ballenger, Davidson, & Lecrubier, 2000). SSRIs have a broad spectrum of action on all three PTSD symptom clusters, have a high safety profile, are effective against most comorbid conditions (e.g., affective and anxiety disorders), relieve clinically significant symptoms associated with PTSD (e.g., impulsive, aggressive, irritable, and suicidal behavior), and only need to be taken once a day. Fluoxetine (now sold as a generic compound) has a long half-life so that missing a day or two of dosage is not as crucial as with other medicines. In our experience, SSRIs usually have modest effects on refugees' nightmares and insomnia. Approximately 75% of patients on SSRIs also receive clonidine, primarily for control of nightmares. The sexual dysfunction side effects of SSRIs are frequently mentioned by Latin American and African patients, but are rarely considered a problem by Asian patients, even when such information is directly asked about.

TCA's

The tricyclic antidepressants have probably been overlooked as an effective first-line treatment (Diamond, Holden, Rotonda, & Tobey, 2002). The tertiary amines, imipramine, amitriptyline, and doxepin, have sedative/hypnotic actions that effectively induce sleep, especially at the usual therapeutic doses of 100–150 mg at night. They also can be given once a day at bedtime, have analgesic properties, and the anticholinergic properties can help with some gastrointestinal symptoms. Doxepin has an antihistaminic (H₂) blocking capacity equal to that of cimetidine. The side effects of dry mouth, constipation, and postural hypertension are sometimes disturbing to some. Concerns about fatal overdose with tricyclics has been exaggerated among refugees. Patients with Buddhist and Islamic traditions where suicide is strongly prohibited have a very low rate of suicide. In 25 years of treating several thousand refugees we have had no depressed PTSD patients commit suicide. The five suicides that have occurred, occurred among our schizophrenic, not PTSD, patients and were not due to an overdose. A final consideration is the ease of blood level monitoring to determine compliance. This has been an extremely valuable clinical strategy when noncompliance is found, which generally facilitates a productive discussion of the patient's problem with the medicines.

Antiadrenergic Agents

Clonidine and the related compound guanfacine and probably prazosin should be considered a mainstay of treatment along with an antidepressant. Clonidine is a medicine with a long and successful record as an effective treatment for hypertension; it is safe and cheap. Given once at night it can help promote sleep because of its sedative properties. It can greatly reduce nightmares. We have increased the nightly dose until nightmares have been reduced in frequency to once every one or two weeks. Clonidine also helps ameliorate symptoms of intrusive thoughts and hyperarousal. A common starting dose is .2 h.s., and many patients have needed a maintenance dose of .2 in the morning and .4 h.s. at bedtime. Since many patients have hypertension (40% in our clinic), it is also an effective medicine for the comorbid PTSD and hypertensive combination. It can be combined well with an antidepressant (75% of our patients receiving an antidepressant are also on clonidine). It is important to emphasize that, since TCAs interact with clonidine to block its antihypertensive effects, a non-TCA antidepressant should be used in combination with clonidine for hypertensive patients. Clonidine comes in a transdermal patch, which can be applied once a week. This sometimes causes a local rash and is more expensive. There have been anecdotal reports that patients sometimes become tolerant to clonidine, so that the medication loses its effectiveness. In our experience, however, we found no loss of efficacy in patients who have received such treatment

for over 15 years. If and when tolerance to clonidine does occur, guanfacine, which has a similar pharmacological action, has proven an effective replacement (Friedman, Davidson, Mellman, & Southwick, 2000). In our experience, when patients choose to decrease the number of medicines they are taking, they will prefer to discontinue antidepressants rather than clonidine. Consequently, many of our refugee patients are now taking clonidine alone.

PTSD With Psychosis

PTSD with psychosis is a surprisingly common problem among refugees. It usually presents with auditory hallucinations or delusions of thought control in addition to PTSD symptoms and sometimes clinical depression. Often it is accompanied by agitation and aggressiveness. The first goal of treatment is to control the psychotic symptoms and agitation. Risperidone has been useful, usually in the 1 to 4 mg nightly dose range. Clonidine for PTSD symptoms, as above, is started at the same time although risperidone alone sometimes controls nightmares by its adrenergic blocking action. Adding an antidepressant is delayed to determine if it is needed. Starting out with three different medicines is often very difficult for both patient adherence and clinical management.

Schizophrenia With PTSD

Several patients have presented with the entire schizophrenic syndrome including delusions, hallucinations, bizarre behavior, and limited functioning. By history, some symptoms were present before the trauma, and some clearly resulted from the trauma. When combined with PTSD, the syndrome can be a challenge to treat. The goal is to first control the psychosis, which often requires a moderately high level of an atypical antipsychotic; 20 mg of olanzapine has been helpful but the weight gain and tendency toward diabetes is a disadvantage. Ziprasidone and risperidone have been useful alternatives. Several cases have also required the administration of a conventional antipsychotic agent, such as perphenazine, to help control the symptoms. Clonidine is usually added to the antipsychotic medication for PTSD control. Because compliance has been a problem for some, approximately half of the refugees with schizophrenia receive a monthly injection of Prolixin or Haldol decanoate rather than oral antipsychotic treatment.

Mood Stabilizers

Because bipolar disorder has been rarely diagnosed among refugees, there has been little experience with mood stabilizers. Lithium treatment for several patients has been complicated by their refusal to permit venipuncture required for monitoring serum lithium levels; as a

TABLE 21.3 Summary of Clinical Experience on Pharmacotherapy on Refugees With PTSD

Medicine Class	Specific Medication	Dose Range	Comments
SSRI	Fluoxetine	20–60 mg	Generally effective in a wide range of symptoms Fluoxetine has a longer half-life and missing a dose doesn't affect response Fluoxetine is generic and less expensive Many patients complain of sexual dysfunction, and modest effect on nightmares and sleep
	Sertraline	50–200 mg	
	Paroxetine	20–40 mg	
	Citalopram	10–20 mg	
Tricyclic antidepressant	Imipramine	50–200 mg	Tertiary TCA help sleep and hyperarousal- amitriptyline too sedative for most refugees Very sedative, initially useful for sleep disturbance; constipation, dry, mouth and hypotension are side effects; blood level easily obtained for checking compliance; analgesic properties help pain symptoms (efficacy for desipramine has not been shown)
	Doxepin	50–200 mg	
	Amitriptyline	50–200 mg	
	Desipramine	50–200 mg	
Antiadrenergic agent alpha-2-agonist alpha-1- antagonist B-Blocker	Clonidine	2–16 mg	Very effective for nightmares, reexperiencing, and agitation Useful with coexisting hypertension (not with a TCA, however) Prazosin useful in veterans; clearly clinical experience indicates effective in Cambodians
	Guanfacine	1–3 mg	
	Propranolol	40–160 mg	
	Prazosin		

TABLE 21.3 Continued

Medicine Class	Specific Medication	Dose Range	Comments
Atypical antipsychotic	Risperidone	1-4 mg	Effective for coexisting psychosis and agitation and may control nightmares; olanzapine; tendency for type II diabetes; a problem in refugees with high tendency to diabetes
	Olanzapine	2.5-20 mg	
Antidepressant	Carbamazepine	750-1750 mg	May be effective in some PTSD symptoms and hyperarousal Strict adherence to medicine and blood draws is a problem for many refugees
	Valproate	400-1600 mg	
Mood stabilizers	lithium, lamotrigine, gabapentin, topiramate		Not shown to be effective in PTSD at this point; no experience in refugee populations

Source: Modified from Friedman, Davidson, Mellman, & Southwick (2000).

consequence, such patients are on a low dose, 600 mg or less a day. Lithium does seem to help some patients with irritability. A trial with lamotrigine is currently under way in the general population; given its capacity to elevate depressed mood, it might prove to be a useful drug for refugees.

Benzodiazepines

Benzodiazepines generally are not helpful and can disinhibit patients who already fear a loss of control. Short-term use may be indicated, however, during extremely time-limited anxiety/stress provoking situations, such as deportation hearings.

Table 21.3 provides a summary of medicines useful for traumatized refugees. It represents clinical guidelines rather than findings in controlled studies since there is a paucity of such studies on multicultural refugees. This table is modified from Friedman, Davidson, Mellman, and Southwick (2000).

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