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A GUIDE TO THE LITERATURE ON PHARMACOTHERAPY FOR PTSD

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We are beginning to reap the benefits of the upsurge in multi- and single-site clinical trials with newer pharmacological agents that began in the mid-1990s. Although we eagerly await publications on large industry-sponsored trials currently in progress, this is a good time to take stock of the current and older literature on pharmacotherapy for PTSD. The two major developments are publication of guidelines on best pharmacotherapeutic practices in PTSD and recent approval by the Food and Drug Administration (FDA) of sertraline as a treatment for PTSD.

Best practices. Two recent publications address the question of best practices in pharmacotherapy from somewhat different perspectives. The empirical evidence on drug efficacy is thoroughly evaluated in a chapter by Friedman et al. (in press) that will appear in the forthcoming treatment guideline commissioned by the International Society for Traumatic Stress Studies (ISTSS). This comprehensive overview evaluates results from both randomized and open label trials and determines the level of evidence for the efficacy of each medication that has been the focus of an article in the PTSD treatment literature. A very different kind of overview is represented in a recent monograph summarizing the responses of an expert consensus panel of 57 international experts to a questionnaire on prescribing preferences for PTSD (Foa et al., 1999). There are some very interesting differences between these two practice guidelines. Conclusions in the ISTSS chapter (Friedman et al., in press) are based on empirical data derived from monotherapy efficacy studies. In contrast, the panel of experts (Foa et al., 1999) offer opinions based on clinical experience on complex treatment questions about treatment strategies for partial and non-responders to medication treatment as well as on questions about what to prescribe for patients with co-morbid psychiatric, medical, and chemical abuse/dependency disorders.

Selective serotonin reuptake inhibitors (SSRIs). FDA approval of sertraline as the first medication indicated for treating PTSD patients is an important milestone in our field. The data that convinced the FDA to take this action came from two large multisite trials in which approximately 200 subjects (in each trial) were randomly assigned to either sertraline or placebo, respectively. A description of the first of these studies is currently in press (Brady et al., in press). Since results of the second trial are still being prepared for publication, I have included an abstract of the data that were presented at a scientific meeting (Davidson, Londborg, et al., 1997). Both studies demonstrate what others have previously reported from single-site trials with sertraline, paroxetine, fluvoxamine, and fluoxetine: that selective serotonin reuptake inhibitors have a broad spectrum of action on all three (re-experiencing, avoidant/numbing, and hyperarousal) clusters of PTSD symptoms (Davidson, Malik, et al., 1997; Marmar et al., 1996; Marshall et al., 1998; Rothbaum et al., 1996). Van der Kolk and associates (1994), who conducted the first randomized clinical trial with the SSRI fluoxetine, also found clear evidence for the efficacy of this agent, although their results suggest a more constricted spectrum of action since it reduced numbing and hyperarousal, but not re-experiencing or avoidant PTSD symptoms.

Randomized clinical trials (RCTs). I have presented abstracts of all the randomized clinical trials conducted with PTSD patients since I believe that that is the best and most valuable data in this field. Citations on SSRI trials have already been discussed. Chronologically speaking, the first trials were with older antidepressants, tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs). Three studies with TCAs, all with Vietnam veteran subjects, report positive results with imipramine (Kosten et al., 1991), mild-to-moderate effects with amitriptyline (Davidson et al., 1990), and negative results with desipramine (Reist et al., 1989). Two trials with the MAOI phenelzine report very positive results in one study (Kosten et al., 1991) and negative results in a methodologically flawed investigation (Shestatzky et al., 1988). Although interest in these older agents has waned because of the more recent interest generated by SSRIs and other new agents, it is important to consider the fact that neither TCAs nor MAOIs have been systematically evaluated and that there may be good reasons to include them in future drug trials.

Other RCTs worth noting are a negative trial with the benzodiazepine, alprazolam (Braun et al., 1990), a negative trial with the second messenger, inositol, which had previously shown promise in treatment of depression and panic disorder (Kaplan et al., 1996), and a negative trial with the serotonin antagonist cyproheptadine, which had previously appeared

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to reduce PTSD flashbacks and traumatic nightmares (Jacobs-Rebhun et al., in press). The published results from two large multi-site trials with brofaromine must be mentioned. This interesting medication combines an SSRI action with reversible MAO-A inhibition. Findings with brofaromine were modestly promising in one study (Katz et al., 1994/1995) and negative in another (Baker et al., 1995). This is only of academic interest, however, since its manufacturer has withdrawn brofaromine from the market and it is not available to clinicians.

Results from open trials. The remainder of the literature consists of open trial and case reports on a number of medications that are often utilized by practitioners despite the fact that there is little published evidence to support such prescribing practices. The best study of this sort is with the adrenergic beta receptor antagonist, propranolol, which was administered to 11 sexually and physically abused children with good results. Propranolol was administered according to an A-B-A design: six week baseline-six week active treatment-six week post-treatment after discontinuation of treatment (Famularo et al., 1988). Other open trials worth noting are a successful open trial of the SSRI sertraline for patients with co-morbid PTSD and alcohol dependence (Brady et al., 1995); this study stands out as a model for clinical trials designed to treat PTSD and a comorbid psychiatric disorder simultaneously. Given the high prevalence of comorbid disorders in PTSD patients, this strategy needs to be emulated in future research. Positive results with the reversible MAO-A inhibitor moclobemide (Neal et al., 1997) are of great interest, since this agent is much easier to prescribe than traditional MAOIs such as phenelzine. Only one small open trial with nefazadone has been published (Hertzberg et al., 1998), despite the fact that this antidepressant is widely prescribed by clinicians and greatly favored by the expert consensus panel mentioned earlier (Foa et al., 1999). Representative open trials with a variety of medications are also cited for the sake of completeness, although in every case much more research is needed. These include reports concerning the anticonvulsant carbamazepine (Lipper, 1990); the antidepressant trazadone (Hertzberg et al., 1996); the adrenergic alpha-2 agonist, clonidine (Harmon & Riggs, 1996); and an interesting report on dramatically mixed results with the experimental narcotic antagonist, nalmafene (Glover, 1993).

Treatment of recently traumatized individuals. As the PTSD field begins to emphasize early intervention for populations at risk, three studies are worth noting concerning pharmacotherapy. The most exciting of these is a successful prospective trial of the TCA imipramine for pediatric burn patients with Acute Stress Disorder (Robert et al., 1999). Second, a prospective trial of Israeli emergency room patients with benzodiazepines was not successful (Gelpin et al., 1996)—further evidence that there is little evidence supporting the use of this class of medications to prevent or ameliorate core PTSD symptoms. Third, a pilot study in which the hypnotic temazepam was administered specifically to promote better sleep among patients with Acute Stress Disorder suggested that such an approach might reduce the development of PTSD after exposure to traumatic stress (Mellman et al., 1998). Friedman and colleagues (1993) present guidelines for pharmacotherapy for recently evacuated medical and psychiatric casualties during war.

Review articles. There are also a number of review articles that should be useful for anyone who wishes to understand this literature. Davidson et al. (1997) consider response characteristics of patient cohorts treated with antidepressants in randomized clinical trials; important questions such as predicting responsivity, latency of detectable therapeutic effect, and other matters are thoughtfully addressed. Donnelly et al. (1999) review the disappointingly small literature on medication treatment for children and adolescents. Friedman (in press) reviews the psychobiology of PTSD and predicts new classes of pharmacological agents that need to be developed and tested in the future.

There are also a number of older reviews that should not be forgotten because they discuss clinical trials that tend to be overlooked in more recent reviews. The most comprehensive review on TCAs is by ver Ellen and van Kammen (1990); on MAOIs by DeMartino et al. (1995); and on ethnopharmacology and the treatment of PTSD by Lin et al. (1996). Southwick et al. (1994) provide a quantitative review of older (randomized and open) trials with TCAs and MAOIs showing the effectiveness of both classes of drugs on global improvement and PTSD reexperiencing symptoms. Friedman and Southwick (1995) remains the most detailed and comprehensive review of the literature up to 1995, but does not contain more recent studies with SSRIs and newer agents.

Interpreting the data. There are many questions about the published data regarding gender, type of trauma, comorbidity, and chronicity. Most clinical trials with women include women exposed to sexual trauma. Most clinical trials with men involve Vietnam veterans exposed to war-zone trauma. Furthermore, the male cohorts have tended to have more comorbid disorders and greater chronicity and severity of their PTSD. Therefore, it would be a serious mistake to interpret the findings of van der Kolk et al. (1994) as demonstrating greater responsivity of women than men, or greater responsivity of sexual trauma than of war-zone trauma survivors to Drug X or Drug Y. Future research must systematically evaluate the importance of gender, type of trauma, comorbidity, chronicity, and other factors as predictors of response to medication.

Conclusion. After a five-year hiatus, research on pharmacotherapy for PTSD began to increase in the mid-1990s. Much of this activity was spurred by the interest of pharmaceutical companies in testing the efficacy of SSRIs and related agents on patients with PTSD. Such activity has not only resulted in FDA approval of sertraline and multisite trials with other agents such as nefazadone but has also stimulated the development of new classes of drugs, such as corticotropin releasing factor antagonists, substance P

antagonists, and new anticonvulsants such as lamotrigine and gabapentin (see Friedman, in press) that may eventually prove efficacious in PTSD. As we are swept along by this exciting momentum, however, we should not neglect to consider that older agents such as antiadrenergic agents, MAOIs, anticonvulsants, and possibly TCAs may yet find their niche in PTSD pharmacotherapy after they have been evaluated systematically.

SELECTED ABSTRACTS

BAKER, D.G., DIAMOND, B.I., GILLETTE, G.M., HAMNER, M.B., KATZELNICK, D., KELLER, T.W., MELLMAN, T.A., PONTIUS, E.B., ROSENTHAL, M., TUCKER, P., VAN DER KOLK, B.A., & KATZ, R.J. (1995). **A double-blind, randomized, placebo-controlled, multi-center study of brofaromine in the treatment of post-traumatic stress disorder.** *Psychopharmacology, 122,* 386-389. A large multi-center, double-blind, parallel trial to assess the efficacy of brofaromine in the treatment of PTSD failed to show a significant difference between the brofaromine and placebo treatment groups. The placebo response rate in this study was higher than that in previously published double-blind, placebo-controlled studies of PTSD.

BRADY, K., PEARLSTEIN, T., ASNIS, G.M., BAKER, D., ROTHBAUM, B., SIKES, C.R., & FARFEL, G.M. (in press). **Double-blind, placebo-controlled study of the efficacy and safety of sertraline treatment of posttraumatic stress disorder.** *Journal of the American Medical Association.* CONTEXT: Despite the high relevance, chronicity, and associated comorbidity of PTSD in the community, few placebo-controlled studies have evaluated the efficacy of pharmacotherapy for this disorder. OBJECTIVE: To determine if acute treatment with sertraline hydrochloride can effectively treat symptoms of PTSD of moderate-to-marked severity. DESIGN: Patients completed a 2-week single-blind, placebo lead-in prior to being randomized to 12 weeks of double-blind treatment with either sertraline or placebo. SETTING: Outpatient psychiatric clinics in 8 academic medical centers and 6 clinical research centers. INTERVENTION: Acute treatment with sertraline hydrochloride in flexible daily doses in the range of 50-200 mg, following one week at 25 mg, or placebo. PATIENTS: A total of 187 outpatients with a DSM-III-R diagnosis of PTSD and a Clinician Administered PTSD Scale part 2 (CAPS-2) minimal total score > 50 at baseline (73% were female, mean age 40 years, mean duration of illness 12 years, 61% were the victims of physical or sexual assault). MAIN OUTCOME MEASURES: Baseline-to-endpoint change in CAPS-2 total severity score, the Impact of Event Scale total score (IES), and Clinical Global Impression Severity (CGI-S), and CGI-Improvement (CGI-I) ratings at endpoint. RESULTS: Sertraline treatment yielded significantly ($p < 0.02$) greater improvement on 3 out of the 4 primary outcome measures, with the fourth measure, the IES, showing a trend toward significance ($p = 0.071$). Using a conservative LOCF analysis, treatment with sertraline resulted in a responder rate of 53% at study endpoint compared to 32% for placebo ($p = 0.008$; with responder defined as > 30% reduction from baseline in CAPS-2 total severity score and a CGI score of 1 (very much improved), or 2 (much improved). Significant ($p < 0.05$) efficacy was evident for sertraline from week 2 on the CAPS-2 total severity score. Sertraline had significant efficacy vs. placebo on the PTSD symptom clusters of avoidance / numbing ($p = 0.015$) and increased arousal ($p = 0.027$) but not on the reexperiencing / intrusion ($p = 0.143$). The beneficial effect of sertraline was confirmed by a highly significant improvement both on the patient-rated Davidson Trauma Scale (DTS; $p = 0.003$), as well as on functional and quality of life measures. Sertraline was well-tolerated, with insomnia being the only side effect significantly different from placebo (16% vs. 4%). CONCLUSIONS: The results of this study suggest that sertraline is a safe, well-tolerated, and effective treatment for PTSD.

BRADY, K.T., SONNE, S.C., & ROBERTS, J.M. (1995). **Sertraline treatment of comorbid posttraumatic stress disorder and alcohol dependence.** *Journal of Clinical Psychiatry, 56,* 502-505. BACKGROUND: PTSD often co-occurs with alcohol dependence, yet little is known about treatment of this comorbidity. The serotonin selective reuptake inhibitors have been shown preliminarily to be effective in decreasing symptoms of PTSD but have not been studied in individuals with comorbid alcohol dependence. This is of particular interest as the SSRIs also have a modest effect in decreasing alcohol consumption. METHOD: In this preliminary trial, 9 subjects with comorbid PTSD and alcohol dependence were treated in an open-label trial with sertraline for a 12-week period. Symptoms of PTSD and depression were monitored monthly with the Impact of Event Scale and the Hamilton Rating Scale for Depression (HAM-D). Alcohol consumption was monitored by a self-report instrument (Time-Line Follow-Back). RESULTS: There were significant decreases in all 3 symptom clusters of PTSD measured by overall PTSD symptom scores ($p < .001$) and in HAM-D scores ($p < .001$) during the follow-up period. Days of abstinence increased and average number of drinks decreased during the follow-up period. 4 subjects claimed total abstinence during the follow-up period. CONCLUSION: While limited by small sample size and the open-label, nonblinded study design, this study suggests that sertraline may be useful in the treatment of PTSD complicated by alcoholism. The medication was well tolerated and subjects showed improvement in PTSD symptoms as well as decreased alcohol consumption. A controlled trial of sertraline in this population would be of interest.

BRAUN, P., GREENBERG, D., DASBERG, H., & LERER, B. (1990). **Core symptoms of posttraumatic stress disorder unimproved by alprazolam treatment.** *Journal of Clinical Psychiatry, 51,* 236-238. The authors report a random-assignment, double-blind crossover trial comparing alprazolam and placebo in PTSD. 10 patients fulfilling DSM-III criteria for PTSD completed 5 weeks of treatment on each agent. Improvement in anxiety symptoms was significantly greater during alprazolam treatment but modest in extent. Symptoms specific to PTSD were not significantly altered. The impact of nonspecific symptomatic effects on the outcome of drug trials in PTSD is considered.

DAVIDSON, J.R.T., KUDLER, H.S., SMITH, R.D., MAHORNEY, S.L., LIPPER, S., HAMMETT, E.B., SAUNDERS, W.B., & CAVENAR, J.O. (1990). **Treatment of posttraumatic stress disorder with amitriptyline and placebo.** *Archives of General Psychiatry, 47,* 259-266. Amitriptyline hydrochloride was compared with placebo in 46 veterans with chronic PTSD. Treat-

ment continued up to 8 weeks, and efficacy was measured by five observer and two self-rated scales. Percent recovery rates were higher for amitriptyline than placebo on two measures. In patients who completed 4 weeks (n = 40), better outcome with amitriptyline was noted on the Hamilton depression scale only. In the group completing 8 weeks of treatment (n = 33), the drug was superior to placebo on Hamilton depression, Hamilton anxiety, Clinical Global Impression severity, and Impact of Event scales. There was no evidence for drug effects on the structured interview for PTSD. Drug-placebo differences were greater in the presence of comorbidity in general, although recovery rates were uniformly low in the presence of major depression, panic disorder, and alcoholism. At the end of treatment, 64% of the amitriptyline and 72% of the placebo samples still met diagnostic criteria for PTSD.

DAVIDSON, J.R.T., LONDBORG, P.D., PEARLSTEIN, T., WEISLER, R., SIKES, C., & FARFEL, G.M. (1997). **Double-blind comparison of sertraline and placebo in patients with posttraumatic stress disorder (PTSD).** *American College of Neuropsychopharmacology Abstracts, 36th Annual Meeting,* 147. The lifetime prevalence of PTSD has been reported to be 7.8% in the general population and twice as common in females as in males. Symptoms can persist for years after the traumatic event. A multicenter, 12-week, double-blind, flexible dose study of adult outpatients (n = 208) with a DSM-III-R diagnosis of PTSD was conducted at 12 U.S. centers to evaluate the safety and efficacy of sertraline (50-200 mg / day) compared to placebo in the treatment of PTSD. The primary efficacy ratings were the Impact of Event Scale (IES), the Clinician Administered PTSD Scale (CAPS) and the Clinician Global Impression ratings of severity and improvement. At endpoint, sertraline patients exhibited significantly (p < .05) greater improvement than placebo patients on all primary efficacy measures. Sertraline-treated patients experienced mean decreases of approximately 49% and 44% in IES and CAPS scores respectively, compared to approximately 35% mean reductions on both the IES and CAPS scores in placebo-treated patients. The Davidson Self-Rating Trauma scale (DTS) was administered as a secondary efficacy measure, and at endpoint sertraline-treated patients exhibited a mean decrease of approximately 43% compared to 27% in the placebo group (p < .01). Sertraline was generally well tolerated. The most frequently reported adverse events (>10%) that occurred significantly more in sertraline-treated patients than placebo-treated patients were insomnia, diarrhea, nausea, fatigue, and anorexia. Treatment discontinuations due to adverse events occurred in approximately 10% of the sertraline-treated patients compared to 5% of the placebo-treated patients, and this difference was not statistically significant. There were no clinically meaningful changes in laboratory values nor any significant changes in vital signs or ECGs between treatment groups. In this study, sertraline in doses of 50-200 mg / day was shown to be a safe and effective treatment for patients with PTSD.

DAVIDSON, J.R.T., MALIK, M.L., & SUTHERLAND, S.N. (1997). **Response characteristics to antidepressants and placebo in post-traumatic stress disorder.** *International Clinical Psychopharmacology, 12,* 291-296. Characteristic response patterns are described for 2 antidepressant drugs and placebo in PTSD. Early onset and steady improvement occurred on a global rating scale for both drugs and placebo in those who ultimately met responder criteria at the end of treatment. In certain cases, the magnitude of global response was greater for drug than for placebo. At weeks 2 or 4, the Clinical Global Impressions score for fluoxetine, but not for amitriptyline, served as a good predictor of eventual response. In a review of numerous completed placebo-controlled trials, antidepressants were superior to placebo in 7 out of 8 comparisons using the Clinical Global Impressions, although specific effects on PTSD scales were more variable. Drug response rates are similar for combat and civilian trauma samples, but placebo response rates may be higher in the latter. Effect sizes suggested a moderate-to-good effect for drug therapy.

FAMULARO, R., KINSCHERFF, R., & FENTON, T. (1988). **Propranolol treatment for childhood posttraumatic stress disorder, acute type.** *American Journal of Diseases of Children, 142,* 1244-1247. We report 11 cases of PTSD. Each child had been physically abused or sexually abused or both and presented in an agitated, hyperaroused state. Using a B-A-B (off-on-off) medication design in a clinical setting, the children were treated with the beta-adrenergic antagonist propranolol. Scores on an inventory of symptoms of PTSD indicated that patients exhibited significantly fewer symptoms while receiving medication than either before or after they received medication.

FOA, E.B., DAVIDSON, J.R.T., & FRANCES, A.J. (1999). **Treatment of posttraumatic stress disorder** [Expert consensus guideline series]. *Journal of Clinical Psychiatry, 60* (Supplement 10). The Expert Consensus Guidelines for the treatment of PTSD are based on surveys of 52 experts on the psychotherapy treatment and 57 experts on the medication treatment of PTSD. We first created a skeleton algorithm based on the existing research literature and other guidelines to identify key decision points in the everyday treatment of patients with PTSD. We then developed two written questionnaires, one on medication treatments and one on psychotherapy treatments. The actual questions and results of the medication and psychotherapy treatment surveys are presented. These guidelines can be viewed as an expert consultation, to be weighed in conjunction with other information and in the context of each individual patient-physician relationship. [Adapted from Text]

FRIEDMAN, M.J., DAVIDSON, J.R.T., MELLMAN, T.A., & SOUTHWICK, S.M. (in press). **Guidelines for pharmacotherapy and position paper on practice guidelines.** In E.B. Foa, T.M. Keane, & M.J. Friedman (Eds.), *Effective treatments for post-traumatic stress disorder: Practice guidelines from the International Society for Traumatic Stress Studies.* New York: Guilford. PTSD appears to be a very complex disorder that is associated with stable and profound alternatives in many psychobiological systems that have evolved for coping, adaptation, and survival of the human species. The most substantial available evidence supports the use of the broad category of antidepressant medications, especially SSRIs, which appear to promote global improvement in most, but not all, randomized clinical trials. Antiadrenergic agents such as clonidine, guanfacine, and propanolol may prove to ameliorate arousal and reexperiencing symptoms by reducing the excessive adrenergic activity associated with PTSD. Unfortunately there is very little clinical data to substantiate this speculation at this time. There is a great deal of evidence suggesting that pharmacotherapy will successfully reduce most disorders comorbid with PTSD. There is good reason to anticipate exciting breakthroughs in the foreseeable future that should equip clinicians with a greater variety of effective drugs that will benefit patients with PTSD. [Adapted from Text]

FRIEDMAN, M.J., & SOUTHWICK, S.M. (1995). **Towards pharmacotherapy for post-traumatic stress disorder.** In M.J.

Friedman, D.S. Charney, & A.Y. Deutch (Eds.), *Neurobiological and clinical consequences of stress: From normal adaptation to post-traumatic stress disorder* (pp. 465-481). Philadelphia: Lippincott-Raven. We review the current literature on the clinical psychopharmacology of PTSD. With our growing appreciation of the complexity of PTSD, we are beginning to understand why we may have failed to discover a single drug that will significantly reduce PTSD symptoms. There have been too few published randomized clinical trials. Even among these few published RCT's, there are enough questions about methodology, instrumentation, and sample selection to suggest the need for expansion and extension of RCT programs to include testing and retesting of more drugs. Despite these concerns, it does appear that certain drugs may be helpful in alleviating specific PTSD symptom clusters. A rational approach to pharmacotherapy for PTSD may require a multisystem approach in which multiple drugs, each one with a unique and distinct action, are administered simultaneously. [Adapted from Text]

GELPIN, E., BONNE, O.B., PERI, T., BRANDES, D., & SHALEV, A.Y. (1996). **Treatment of recent trauma survivors with benzodiazepines: A prospective study.** *Journal of Clinical Psychiatry, 57,* 390-394. BACKGROUND: Most types of psychotropic drugs have been tried in the treatment of chronic PTSD, but have yielded limited results. Theory and retrospective research predict that early treatment may be more efficacious. Specifically, high-potency benzodiazepines have been recommended for the treatment of acute responses to trauma and for prevention of PTSD. This study prospectively evaluates the effect of early administration of benzodiazepines on the course of PTSD and PTSD symptoms. METHOD: 13 trauma survivors (the benzodiazepine group) were treated within 6.7 + 5.8 days after the trauma (range, 2-18) with either clonazepam (n= 10, 2.7 + 0.8 mg / day) or alprazolam (n = 3, 2.5 mg / day). 13 other trauma survivors, pair-matched with subjects in the active treatment group for gender and symptom severity in the first week after the trauma, constitute the control group. Both groups were reevaluated 1 and 6 months after the trauma for PTSD symptoms (Horowitz Impact of Event Scale; Mississippi Rating Scale for Combat-Related PTSD civilian trauma version), PTSD status (Clinician Administered PTSD Scale), state anxiety, depression, and resting heart rate. RESULTS: Subjects in the benzodiazepine group did not differ from controls in 1-month and 6-month PTSD and anxiety scores. Repeated measures ANOVA showed no group or group-by-time effect on psychometric measures. A trend toward group-by-time interaction in resting heart rate was noted (progressive decrease in the benzodiazepine group). 9 benzodiazepine subjects and 3 controls met PTSD diagnostic criteria 6 months after the trauma. CONCLUSION: Contrary to expectations, the early administration of benzodiazepines to trauma survivors with high levels of initial distress did not have a salient beneficial effect on the course of their illness, while reducing physiologic expression of arousal.

KATZ, R.J., LOTT, M.H., ARBUS, P., CROCQ, L., HERLOBSEN, P., LINGJAERDE, O., LOPEZ, G., LOUGHREY, G.C., MACFARLANE, D.J., MCIVOR, R., MEHLUM, L., NUGENT, D., TURNER, S.W., WEISAETH, L., & YULE, W. (1994 / 1995). **Pharmacotherapy of post-traumatic stress disorder with a novel psychotropic.** *Anxiety, 1,* 169-174. This was a multicenter, randomized, double-blind, parallel trial conducted in outpatients in three countries. Following screening and placebo washout, patients received brofaromine (a combined MAO-A inhibitor / 5-HT transport inhibitor) or placebo in a flexible dosing design. Based upon the CAPS, a standardized PTSD interview, findings from a cohort involving both subchronic and chronic traumatic stress marginally favored brofaromine over placebo; however, not to a statistically significant degree. With a more conservation [sic] definition of the syndrome, employing a primary cohort of patients with PTSD of one year or greater duration, brofaromine significantly reduced PTSD symptoms in comparison with placebo. In all analyses a substantial proportion of patients in both drug and placebo groups remained symptomatic throughout. Findings were supported by an analysis of secondary measures. Brofaromine may be of benefit in the therapy of PTSD.

KOSTEN, T.R., FRANK, J.B., DAN, E., MCDOUGLE, C.J., & GILLER, E.L. (1991). **Pharmacotherapy for posttraumatic stress disorder using phenelzine or imipramine.** *Journal of Nervous and Mental Disease, 179,* 366-370. 60 male veterans with PTSD participated in an 8-week, randomized trial comparing phenelzine (n = 19), imipramine (n = 23), and placebo (n = 18). Mean treatment retention was better on phenelzine (7.4 weeks) than on imipramine (5.6 weeks) or placebo (5.5 weeks). By week 5, both medications significantly reduced PTSD symptoms, as assessed by the Impact of Event Scale (IES), but the 44% improvement on phenelzine was greater than the 25% improvement on imipramine. The intrusion, but not the avoidance, subscale of the IES showed significant improvement, and the initial mild to moderate depressive symptoms did not significantly improve.

LIN, K., POLAND, R.E., ANDERSON, D., & LESSER, I.M. (1996). **Ethnopsychopharmacology and the treatment of PTSD.** In A.J. Marsella, M.J. Friedman, E.T. Gerrity, & R.M. Scurfield (Eds.), *Ethnocultural aspects of posttraumatic stress disorder: Issues, research, and clinical applications* (pp. 505-526). Washington: American Psychological Association. In this chapter, we first review the principles of how ethnicity may interact with drug metabolism and drug action. Next, the role that ethnicity plays in relation to the specific classes of medications that are commonly used to treat PTSD - antidepressants, neuroleptics, benzodiazepines, and lithium - is covered. Finally, we briefly discuss future research directions and the applicability of this research to clinical practice.

REIST, C., KAUFFMANN, C.D., HAIER, R.J., SANGDAHL, C., DEMET, E.M., CHICZ-DEMET, A., & NELSON, J.N. (1989). **A controlled trial of desipramine in 18 men with posttraumatic stress disorder.** *American Journal of Psychiatry, 146,* 513-516. 18 male U.S. veterans meeting DSM-III criteria for PTSD completed a 4-week double-blind, crossover study comparing administration of 200 mg / day of desipramine with placebo. Response was measured by using the Beck Depression Inventory, the Hamilton Rating Scale for Depression, the Hamilton Rating Scale for Anxiety, and the Impact of Event Scale. Overall, the only apparent response to desipramine was in some symptoms of depression; there were no changes in anxiety and other PTSD symptoms.

ROBERT, R., BLAKENEY, P.E., VILLARREAL, C., ROSENBERG, L., & MEYER, W.J. (1999). **Imipramine treatment in pediatric burn patients with symptoms of acute stress disorder: A pilot study.** *Journal of the American Academy of Child and Adolescent Psychiatry, 38,* 873-878. OBJECTIVE: Pediatric burn patients often exhibit acute stress disorder (ASD) symptoms. Information on psychopharmacological treatment of ASD symptoms in children is scarce. This pilot study used a prospective, randomized, double-blind design to test whether thermally injured children suffering ASD symptoms benefit from imipramine.

METHOD: 25 children, aged 2 to 19 years, received either imipramine or chloral hydrate for 7 days. A structured interview (clinically useful, but validity and reliability not yet established) was used to assess the presence and frequency of ASD symptoms both before treatment and 3 times during the treatment period. RESULTS: 11 females and 14 males participated, with a mean total burn surface of 45% (*SD* = 23%) and mean age of 8 years (SD = 6). Imipramine was more effective than choral hydrate in treating ASD symptoms ($\chi 2$ [1, n = 25] = 5.24, p < .02). Five of 13 were positive responders to chloral hydrate (38%). Ten of 12 were positive responders to low-dose imipramine (83%). CONCLUSIONS: This pilot study suggests a place for cautious initial use of imipramine to reduce ASD symptoms in burned children. Care must be taken to minimize cardiovascular risks in an off-label application of imipramine in children, especially those receiving additional medications.

SHESTATZKY, M., GREENBERG, D., & LERER, B. (1988). **A controlled trial of phenelzine in posttraumatic stress disorder.** *Psychiatry Research, 24,* 149-155. 13 patients meeting DSM-III criteria for PTSD participated in a random-assignment, double-blind crossover trial comparing phenelzine (45-75 mg / day) and placebo. 10 patients completed at least 4 weeks of each treatment phase. Clinical response to phenelzine did not differ from placebo, and overall improvement by the end of the study could not be attributed to the active drug. The findings are discussed in the light of preliminary reports suggesting that phenelzine may be an effective treatment for PTSD.

VAN DER KOLK, B.A., DREYFUSS, D., MICHAELS, M.J., SHERA, D., BERKOWITZ, R., FISLER, R.E., & SAXE, G.N. (1994). **Fluoxetine in posttraumatic stress disorder.** *Journal of Clinical Psychiatry, 55,* 517-522. Background: This study was designed to establish the efficacy of the serotonin reuptake blocker fluoxetine in the treatment of PTSD. Method: 64 subjects (22 women and 42 men; 31 veterans and 33 nonveterans) with PTSD entered a 5-week randomized double-blind trial comparing fluoxetine (n = 33) and placebo (n = 31). Results: By Week 5 fluoxetine, but not placebo, significantly reduced overall PTSD symptomatology, as assessed by the Clinician-Administered PTSD Scale (CAPS) score. Changes were most marked in the arousal and numbing symptom subcategories. Non-VA patients responded much better than VA patients. Fluoxetine was an effective antidepressant independent of its effects on PTSD. Conclusion: Fluoxetine is an effective pharmacotherapeutic agent for treating PTSD and its associated features, particularly in patients without chronic treatment histories.

ADDITIONAL PUBLICATIONS
Annotated by the Editor

DEMARTINO, R., MOLLICA, R.F., & WILK, V. (1995). **Monoamine oxidase inhibitors in posttraumatic stress disorder: Promise and problems in Indochinese survivors of trauma.** *Journal of Nervous and Mental Disease, 183,* 510-515.
Discusses the existing findings on the use of monoamine oxidase inhibitors for treating PTSD and presents 5 cases in which MAOIs were used to treat Indochinese refugees with PTSD. The authors suggest the use of a dose lower than that typically used for Caucasians.

DONNELLY, C.L., AMAYA-JACKSON, L., & MARCH, J.S. (1999). **Psychopharmacology of pediatric posttraumatic stress disorder.** *Journal of Child and Adolescent Psychopharmacology, 9,* 203-220.
Provides the only comprehensive review of information about the pharmacological treatment of PTSD in children. The authors conclude that pharmacotherapy may be effective for children, but caution that there are few controlled trials.

FRIEDMAN, M.J. (in press). **What might the psychobiology of PTSD teach us about future approaches to pharmacotherapy?** *Journal of Clinical Psychiatry.*
Discusses the implications of the pathophysiology of PTSD for the development of pharmacological interventions, such as corticotrophin releasing factor antagonists, neuropeptide Y enhancers, anti-adrenergic compounds, more specific serotonergic agents, and anticonvulsants.

FRIEDMAN, M.J., SOUTHWICK, S.M., & CHARNEY, D.S. (1993). **Pharmacotherapy for recently evacuated military casualties.** *Military Medicine, 158,* 493-497.
Presents a rationally derived set of recommendations for using psychoactive medications to treat recent military psychiatric casualties. All medications should be withheld for at least 2 days prior to initiating new treatment, and then drugs such as clonidine, propanolol, lorazepam, and antidepressants should be used, depending on symptoms.

GLOVER, H. (1993). **A preliminary trial of nalmefene for the treatment of emotional numbing in combat veterans with post-traumatic stress disorder.** *Israel Journal of Psychiatry and Related Sciences, 30,* 255-263.
Administered nalmefene, an opiate antagonist, to 18 male veterans with combat-related PTSD. Eight of the participants showed notable improvements in numbing and other PTSD symptoms. Case descriptions are provided.

HARMON, R.J., & RIGGS, P.D. (1996). **Clonidine for posttraumatic stress disorder in preschool children.** *Journal of the American Academy of Child and Adolescent Psychiatry, 35,* 1247-1249.
Administered clonidine to 7 preschool children who had PTSD due to severe abuse or neglect and who had not responded to psychological or behavior therapy. The treatment, delivered in patch form, was well-tolerated. All children showed improvement in aggression and interpersonal function. Most children also showed improvements in other symptoms.

HERTZBERG, M.A., FELDMAN, M.E., BECKHAM, J.C., & DAVIDSON, J.R.T. (1996). **Trial of trazodone for posttraumatic stress disorder using a multiple baseline group design**. *Journal of Clinical Psychopharmacology, 16,* 294-298.
Administered trazodone to 6 male Vietnam veterans with combat-related PTSD. Four of the 6 were much improved following treatment. Statistical tests are not reported. The authors describe improvements in PTSD and sleep, but not in depression or social and occupational functioning.

HERTZBERG, M.A., FELDMAN, M.E., BECKHAM, J.C., MOORE, S.D., & DAVIDSON, J.R.T. (1998). **Open trial of nefazodone for combat-related posttraumatic stress disorder.** *Journal of Clinical Psychiatry, 59,* 460-464.

Administered nefazodone to 10 male veterans with combat-related PTSD. Most symptoms showed improvement after 12 weeks, and treatment gains generally were maintained at 16 weeks. Symptoms of hyperarousal showed the most improvement.

JACOBS-REBHUN, S., SCHNURR, P.P., FRIEDMAN, M.J., PECK, R., BROPHY, M., & FULLER, D. (in press). **Cyproheptadine for treating PTSD** [Letter to the Editor]. *American Journal of Psychiatry.*

Conducted a double-blind, randomized, placebo-controlled trial of cyproheptadine for treating sleep problems in 60 male Vietnam combat veterans with PTSD. Treatment did not improve sleep or PTSD outcomes, and poorer outcomes were associated with higher blood levels of cyproheptadine. The results reinforce the need for skepticism about open label or anecdotal findings and for careful scientific trials to replicate uncontrolled studies.

KAPLAN, Z., AMIR, M., SWARTZ, M., & LEVINE, J. (1996). **Inositol treatment of post-traumatic stress disorder.** *Anxiety, 2,* 51-52.

Administered inositol, a second messenger system precursor, to 13 patients with PTSD due to either combat or civilian trauma, drawn from two clinics. Using a double-blind placebo-controlled cross-over design, the authors found no effects of treatment on PTSD symptoms. Patients at one site showed some improvements in depression.

LIPPER, S. (1990). **Carbamazepine in the treatment of post-traumatic stress disorder: Implications for the kindling hypothesis.** In M.E. Wolf, & A.D. Mosnaim (Eds.), *Posttraumatic stress disorder: Etiology, phenomenology, and treatment* (pp. 184-203). Washington: American Psychiatric Press.

Administered carbamazepine to 10 male veterans with military-related PTSD. There were significant reductions in PTSD symptoms, depression, anxiety, and violence.

MARMAR, C.R., SCHOENFELD, F.B., WEISS, D.S., METZLER, T.J., ZATZICK, D.F., WU, R.M., SMIGA, S., TECOTT, L., & NEYLAN, T.C. (1996). **Open trial of fluvoxamine treatment for combat-related posttraumatic stress disorder.** *Journal of Clinical Psychiatry, 57* (Supplement 8), 66-72.

Administered fluvoxamine to 10 male Vietnam veterans with PTSD. There were large changes in PTSD symptoms from pre- to posttreatment. Depression, anxiety, and other symptoms also improved, although to a somewhat lesser extent.

MARSHALL, R.D., SCHNEIER, F.R., FALLON, B.A., KNIGHT, C.B.G., ABBATE, L.A., GOETZ, D., CAMPEAS, R., & LIEBOWITZ, M.R. (1998). **An open trial of paroxetine in patients with noncombat-related, chronic posttraumatic stress disorder.** *Journal of Clinical Psychopharmacology, 18,* 10-18.

Administered paroextine to 17 patients with PTSD due to civilian trauma. There were significant improvements in PTSD and other symptoms, and 65% of the patients were judged to be much or very much improved.

MELLMAN, T.A., BYERS, P.M., & AUGENSTEIN, J.S. (1998). **Pilot evaluation of hypnotic medication during acute traumatic stress response.** *Journal of Traumatic Stress, 11,* 563-569.

Administered temazepam to 4 trauma survivors with 1-3 weeks of traumatic exposure. Treatment was administered for 7 nights. There were significant improvements from baseline to 1 week after the medication was discontinued for total sleep time and PTSD symptoms.

NEAL, L.A., SHAPLAND, W., & FOX, C. (1997). **An open trial of moclobemide in the treatment of post-traumatic stress disorder.** *International Clinical Psychopharmacology, 12,* 231-237.

Administered moclobemide, a reversible inhibitor of monoamine oxidase-A, to 20 patients with PTSD due to military or civilian trauma. There were large improvements in PTSD and functioning, and 11 patients no longer met PTSD criteria when tested after 12 weeks of treatment.

ROTHBAUM, B.O., NINAN, P.T., & THOMAS, L. (1996). **Sertraline in the treatment of rape victims with posttraumatic stress disorder.** *Journal of Traumatic Stress, 9,* 865-871.

Administered sertraline to 5 female rape victims with PTSD. After 12 weeks, PTSD symptoms were reduced by 53% and 4 of the 5 were substantially improved. Initial severity was related to poorer treatment response.

SOUTHWICK, S.M., YEHUDA, R., GILLER, E.L., & CHARNEY, D.S. (1994). **Use of tricyclics and monoamine oxidase inhibitors in the treatment of PTSD: A quantitative review.** In M.M. Murburg (Ed.), *Catecholamine function in posttraumatic stress disorder: Emerging concepts* (pp. 293-305). Washington: American Psychiatric Press.

Combined data from studies that evaluated the efficacy of antidepressant treatment for PTSD in order to compare the relative efficacy of tricyclic antidepressants and monoamine oxidase inhibitors. Overall, MAOIs were found to be more effective than tricyclic antidepressants for PTSD symptoms. Efficacy of both treatments varied across types of symptoms.

VER ELLEN, P., & VAN KAMMEN, D.P. (1990). **The biological findings in post-traumatic stress disorder: A review.** *Journal of Applied Social Psychology, 20,* 1789-1821.

Presents one of the earliest reviews of the literature on the pharmacological treatment of PTSD. The authors also review psychophysiological and neurobiological studies on PTSD.

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PILOTS UPDATE

Last November, the Dutch organization ICODO hosted an "expert meeting" of traumatic stress bibliographers from eight countries. This meeting, titled "From Spider's Web to World Wide Web," brought eighteen of us to the lovely city of Utrecht, for three days of extensive consultation and planning. From this emerged the beginnings of a cooperative program to improve the indexing of traumatic stress literature and the provision of information services on PTSD and related disorders.

The meeting had three goals:

- to develop a social/personal network on psychotrauma
- to work toward a joint collection policy for information on psychotrauma
- to build a joint clearinghouse for information on psychotrauma.

These are ambitious goals to set, and it will be some time before we can assess our success in meeting them. Nevertheless, substantial progress is being made.

The first product of our meeting was the Psychotrauma Documentation Network, an organization of libraries and documentation working with the traumatic stress literature. Its initial membership is drawn from the institutions represented in Utrecht, and its purpose is to provide a mechanism for communication among these institutions and the people on their staff who work with the literature.

One of the first items to be communicated is a compilation of members' collection, access, and information policies. This will serve as the starting-point for discussions on ways to ensure comprehensive coverage of the worldwide psychotrauma literature while avoiding unnecessary duplication of effort. Among the ideas brought up at the Utrecht meeting were:

- a division of responsibility for identifying and collecting various portions of the literature
- a joint format for the recording of bibliographic information, to facilitate the use by PDN members of each other's work
- the development of a single thesaurus to standardize the indexing vocabulary used by traumatic stress bibliographers.

These are not issues that can be decided quickly. A joint format for bibliographical information cannot be established without careful consideration of the needs of each participating organization, and the users of its bibliographical records. A common thesaurus may not be practical when the participating organizations cover somewhat different subject matter. (Some PDN members focus on the problems of refugees, or war veterans, or torture survivors, and concern themselves with medical, legal, and educational issues of their constituencies. Others focus on PTSD and other aspects of mental health, their concern for the psychotrauma literature extending across the various groups affected by traumatic events.) But cooperation in these technical areas is not an all-or-nothing proposition. If a single thesaurus cannot meet the needs of everyone, we can agree upon a concerted effort to unify the terminology among psychotrauma thesauri wherever possible. If we cannot agree upon a standard format for recording the bibliographical facts of a publication, perhaps we can design our individual formats so as to minimize the difficulty of transferring information from one format to another.

These are technical issues, likely to interest nobody but librarians and bibliographers. But if they can be resolved, we shall be able to improve the service that we render to researchers and clinicians. If we can reach our goal of establishing a joint clearinghouse for psychotrauma information on the World Wide Web, it will be easier for information seekers to know exactly where to turn for the material that they need. Thanks to the initiative of ICODO, the eleven organizations of the Psychotrauma Documentation Network are taking the first steps toward achieving this goal.

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