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Allostatic versus Empirical Perspectives on Pharmacotherapy for PTSD

MATTHEW J. FRIEDMAN

The concept of allostatic load, as originally proposed (McEwen & Steller, 1993; McEwen, 1998) is a biological model of stability through change. In this book we have expanded that context to include intrapsychic, interpersonal, and social as well as biological domains, because allostasis is such a rich heuristic model through which to seek to understand the many complex biopsychosocial manifestations of posttraumatic stress disorder (PTSD). It is also a useful context in which to consider the specific treatments that have been tested and proposed for ameliorating the symptoms and general distress associated with this disorder. In this chapter, the focus is specifically on the many psychobiological mechanisms that are disrupted in PTSD and on the various medications that have been tested and proposed for reversing such abnormalities.

When considering allostatic load models, it is important to keep in mind that there are a number of ways in which a system can overshoot, undershoot, fail to recover, or become otherwise dysregulated because it is incapable of accurately titrating its adaptive repertoire to environmental demands (McEwen, 1998). Furthermore, even if the organism's overall response capability has remained intact, it may become encumbered by allostatic load because its antennae are not well calibrated to accurately assess the challenge at hand. Here the problem lies with signal detection rather than response potential so that the organism either fails to recognize all the

stressors to which it must respond (e.g., false negatives) or it tends to misperceive harmless stimuli as threats to survival (e.g., false positives). In PTSD, it is well recognized that the appraisal process is biased toward perceiving danger rather than safety (e.g., false positives) and hence the response bias is toward over rather than underreaction. Such a hypervigilant, hyperreactive posture for engaging the environment is a prescription for shifting from a homeostatic to an allostatic steady state.

From an allostatic perspective, PTSD is extremely complex. As has been stated elsewhere (Friedman, Charney, & Deutch, 1995, pp. xix–xx), this is because humans who fail to meet the demands of traumatic stressors utilize and perturb the many psychobiological mechanisms that have evolved through evolution for coping, adaptation, and preservation of the species. This is why it should come as no surprise that people with PTSD exhibit abnormalities in almost every psychobiological system that has been investigated. Indeed, in the same way that many different pathological circumstances may produce the same clinical abnormality (e.g., fever or edema), many different psychobiological abnormalities may lead to PTSD. Furthermore, it is not too far fetched to anticipate that a spectrum of posttraumatic syndromes may be elucidated by future research and that each syndrome will be associated with a unique allostatic configuration. Furthermore, each syndrome may respond optimally to a different medication. But we are getting ahead of ourselves. First, we must consider current evidence that allostatic load is present in PTSD by reviewing the many different psychobiological abnormalities associated with this disorder. Next we consider a rational pharmacotherapeutic strategy based on this analysis. Then we consider how such an allostatic perspective compares with the current empirical approach to pharmacotherapy. And finally we review the decision process in pharmacotherapy and the many factors by which it is influenced.

WHAT IS THE CURRENT EVIDENCE FOR ALLOSTATIC LOAD IN PTSD?

The best evidence for allostatic load in PTSD comes from research with the two systems that have been most associated with the human stress response: the adrenergic and hypothalamic–pituitary–adrenocortical (HPA) systems. There is also evidence for allostasis in the serotonergic, opioid, and other systems.

Allostasis and the Adrenergic System

It is well recognized that adrenergic reactivity is enhanced in PTSD patients. This conclusion is based on psychophysiological research on the sympathetic nervous system (SNS), which consistently shows heightened cardiovascular

and acoustic startle responsivity (see the review by Pitman, Orr, Shalev, Metzger, & Mellman, 1999). Likewise, research on the adrenergic nervous system consistently indicates elevated catecholamine levels and heightened sensitivity to the adrenergic alpha-2 receptor antagonist yohimbine (see the review by Southwick et al., 1999)

Despite the heightened adrenergic reactivity observed in PSD, resting SNS and adrenergic activity is not elevated. For example, PTSD patients do not show elevated blood pressures or heart rates at rest; it is only when they are challenged by some psychological probe (e.g., trauma-related stimuli) or pharmacological probe (e.g., yohimbine) that such adrenergic abnormalities can be unmasked. In short, at rest the PTSD patient exhibits adrenergic and SNS stability. But such stability comes at a price. This price is what McEwen (1998) has termed allostatic load. With respect to PTSD, the adrenergic price of stability appears to be a reduction (or downregulation) of alpha-2 adrenergic receptors (Perry, 1994). The potential impact to the person with PTSD of excessive adrenergic stimulation is blunted by an adaptive reduction in the number of receptor sites available to react to such increased neurotransmitter levels. During the relative "quiet" of baseline function, a physiological stability is apparent that is indistinguishable from the homeostatic steady state seen in individuals without PTSD. During a stressful episode or some other provocation, however, the downregulation of adrenergic receptors is unequal to the task and therefore unable to maintain stability. Hence, under such circumstances, PTSD patients exhibit the heightened reactivity mentioned above. This is another aspect of allostatic load, another price that must be paid because the adrenergic systems of PTSD patients are inadequately equipped to cope with the demands of stress, in contrast to the systems of people without this disorder.

Allostasis and the Hypothalamic–Pituitary–Adrenocortical Systems

The case for allostasis in PTSD is easier to make with resect to the HPA system because of elegant research that has investigated the different components of HPA function more thoroughly than has been the case with the adrenergic system (see the review by Yehuda, 1999). Here the allostatic balance appears to be the reverse of that seen with adrenergic mechanisms. Whereas excessive adrenergic reactivity is partially offset by downregulation of alpha-2 receptors, in the HPA system reduced serum cortisol levels are offset by upregulation and increased sensitivity of glucocorticoid receptors. The principle is the same—only the direction of change is different. The price of stability is an adaptive change at the receptor level that can be unmasked by psychological or pharmacological probes. I have suggested elsewhere (Friedman, 1998) that, behaviorally speaking, the price of such stability is stress intolerance because people with PTSD appear less able to cope with the nor-

mal hassles and vicissitudes of life. Pharmacologically, allostatic load is evident because people with PTSD (in comparison to those without PTSD) exhibit supersensitivity or supersuppression of HPA function in response to the glucocorticoid dexamethasone (Yehuda et al., 1993).

Allostasis and the Serotonergic System

The third example of psychobiological allostasis in PTSD is admittedly much more speculative. It is worth discussing, however, because of the importance of serotonin (5-hydroxytryptamine, or 5-HT) in the human stress response and because of the recently demonstrated efficacy of drugs that modify 5-HT function in PTSD. Southwick and associates (1997) have shown that some Vietnam veterans with PTSD are especially sensitive to the 5-HT agonist *m*-chlorophenylpiperazine (mCPP) which interacts primarily with 5-HT_2 and 5-HT_{1c} receptors.

One interpretation of these results is that those veterans who exhibited a panic/flashback response to MCPP did so because of upregulation or supersensitivity of 5-HT receptors. If that were the case, one would predict that administering a drug that could downregulate 5-HT receptors might be an effective treatment for PTSD. Indeed, sertraline, a selective serotonic reuptake inhibitor (SSRI), does downregulate postsynaptic 5-HT receptors. Sertraline is also an effective treatment for PTSD (see below). Is this a coincidence? Or is this circumstantial evidence in support of the allostatic load hypothesis?

This speculative example is also a good place to illustrate how a rational approach to pharmacotherapy could be based on an understanding of allostasis. The pharmacological agent of choice would be a medication that reduces allostatic load by pushing the system back toward a homeostatic steady state. Thus SSRI-mediated downregulation of allostatically upregulated 5-HT receptors is definitely a therapeutic step in the correct homeostatic direction.

The presumption that selective reduction of allostatic load will produce clinical improvement is the guiding principle for the subsequent discussion of rational pharmacotherapy for PTSD.

Before leaving the 5-HT system, it is instructive to consider an additional finding in the MCPP study (Southwick et al., 1997). Whereas some veterans with PTSD exhibited panic and flashback reactions following administration of MCPP, others did not. Among those who did not were many who displayed panic and flashback reactions to the adrenergic agent yohimbine. Thus some veterans were MCPP (but not yohimbine) responders, indicating excessive serotonergic sensitivity, whereas others were yohimbine (but not MCPP) responders, indicating excessive adrenergic reactivity. Veterans without PTSD did not react to either drug. Therefore, this provocative study suggests that different people may implement different psychobiological adaptive strategies for coping with chronic stress. For some veterans allostatic load

was best understood as an adrenergic abnormality, whereas for others allostatic load was best understood as a serotonergic adaptation.

Allostasis and the Opioid System

Although there is little clinical research on the opioid system in PTSD, there is abundant evidence that endogenous opioids (endorphins, dynorphins, and enkephalins) play an important role in the stress response of animals. A well-established laboratory phenomenon, stress-induced analgesia (SIA), occurs when experimental animals are exposed to stressful stimuli such as electric shock, forced swimming, or restraint. Under such circumstances, laboratory animals exhibit a reduced responsiveness to pain (e.g., SIA) that can be reversed by narcotic antagonists, thus indicating that SIA is an opioid response to stress (Stout, Kilts, & Nemeroff, 1995). There is one experiment suggesting that SIA can also be produced in humans with PTSD (Pitman, van der Kolk, Orr, & Greenberg, 1990), although these findings have never been replicated. Other studies have shown additional abnormalities in opioid function among PTSD patients (reviewed in Friedman & Southwick, 1995).

With respect to allostasis, there is one very interesting report concerning an open-label trial with a narcotic antagonist that was administered to Vietnam veterans with PTSD (Glover, 1993). The guiding hypothesis was that emotional numbing in PTSD is mediated by opioids. It was expected that by reversing opioid activity the narcotic antagonist would reduce numbing symptoms and thereby diminish PTSD severity. Indeed, several veterans responded as predicted and reported that they felt more alive, less numb, and less constricted emotionally. Unfortunately, other veterans reported that their PTSD became dramatically worse because of intolerable anxiety, panic, arousal, and even flashbacks, in some cases.

How can we understand such diametrically opposite effects among a cohort of apparently similar people (male Vietnam veterans) who all received the same medication? One explanation is that opioid-related allostatic load was balanced differently in different veterans. If we accept the hypothesis that opioid activity is an adaptive (allostatic) response to blunt/numb the excessive (adrenergic) arousal associated with this disorder, we can propose that individuals may differ in their capacity to mobilize opioid mechanisms to achieve allostatic stability. Thus, we might expect that those veterans who exhibited excessive emotional numbing (hypothetically because of excessive opioid activity) experienced relief from the narcotic antagonist because their elevated opioid function was reduced toward homeostatic levels. We might suggest that, in contrast to their "numbed out" colleagues, those veterans who had a severe anxiety reaction were those whose allostatic steady state consisted of a much smaller opioid component. They were at high risk to experience a severe anxiety reaction because the narcotic antagonist blocked what little opioid activity they had been able to mobilize to antagonize adrenergic hyperarousal.

There are several points to underscore here regarding how adaptive psychobiological strategies may differ from one individual to the next. In some cases, the difference may be (quantitatively) related to the capacity to mobilize one particular (e.g., opioid) mechanism to achieve stability. On the other hand, the yohimbine versus MCPP example suggests that different people with PTSD may utilize (qualitatively) different psychobiological allostatic strategies (e.g., adrenergic vs. serotonergic) to achieve stability. Finally, if different quantitative and/or qualitative adaptations can underlie PTSD, then different medications may be indicated for different people even though they appear to have the same DSM-IV disorder.

Allostasis and Corticotropin-Releasing Factor

Corticotropin-releasing factor (CRF) is a neuropeptide that ignites the complex cascade of adrenergic, HPA, immunological, and other psychobiological systems that participate in the human stress response. As a neurotransmitter, CRF activates adrenergic neurons in the locus coeruleus (Aston-Jones, Valentino, Van Bockstaele, & Meyerson, 1994) while as a neurohormone, CRF promotes the HPA response by releasing adrenocorticotropic hormone (ACTH) from the pituitary gland. Two studies indicate that CRF activity is increased in PTSD. CRF levels are elevated in the cerebrospinal fluid (CSF) (Bremner et al., 1997), and hypothalamic release of CRF is apparently enhanced (Yehuda et al., 1996) in people with PTSD. It would be impossible at this time to calculate the total allostatic load produced by excessive CRF activity because it has such far-reaching direct and indirect effects on so many psychobiological systems. Certainly adrenergic, HPA, 5-HT, and opioid abnormalities (described above) are important parts of this picture but there are many other elements as well.

Allostasis and Neuropeptide Y

Neuropeptide Y (NPY) is heavily concentrated in brain structures that mediate the human stress response. Clinical trials suggest that it is an anxiolytic, and laboratory research suggests that it antagonizes the actions of CRF and other stress-released neuropeptides. Recent evidence with military personnel exposed to the intense rigors of extremely stressful training exercises indicate that those individuals with the highest NPY levels tolerated this experience better than those with lower levels (Morgan, Wang, Southwick, Rasmusson, Hazlett, Hauger, & Charney, 2000).

Such findings suggest that allostasis does not always promote vulnerability. Indeed, achieving an allostatic stability characterized by higher NPY levels might be a psychobiological signature for resilience rather than vulnerability. Hence, rather than allostatic load, we may need to think in terms of allostatic support. From this perspective, homeostatic stability may not always

be optimal. Improved coping with stress may be achieved through psychobiological strategies that promote resilience. Enhancing NPY function to achieve allostatic support may turn out to be such a strategy.

Another implication of these findings is that NPY activity might be reduced in people with PTSD. A deficiency in NPY function would mean the loss of a major system that can buffer the intense impact of the human stress response. Since NPY can attenuate the actions of CRF (Stout et al., 1995), it might be expected to lighten the allostatic load in PTSD through allostatic support. Given that CRF plays such a decisive role in the human stress response, the potential salutary actions of NPY may be of enormous significance.

Allostasis and Thyroid Function

Thyroid function is enhanced in PTSD, as indicated by elevated levels of both active thyroid hormones triiodothyronine (T3) and thyroxine (T4). In fact, PTSD symptom severity was positively associated with such increases in thyroid function (Mason et al., 1995; Wang & Mason, 1999).

Since glucocorticoids (e.g., cortisol) normally suppress thyroid activity (Michelson, Licinio, & Gold, 1995) and since cortisol levels are reduced in PTSD, it appears that elevated thyroid function in PTSD may be a secondary effect caused by the lower cortisol levels due to the disturbance in HPA function described earlier. Thus the allostatic load due to altered thyroid activity appears to be a downstream component of HPA-related allostasis. This is a good example of how disturbed function in one system can produce additional abnormalities in other systems.

Allostasis and Sensitization

Sensitization is a well-established laboratory phenomenon concerning progressive alterations in neuronal reactivity, especially in the limbic system and cerebral cortex. In a typical sensitization experiment, neurons are repeatedly (e.g., once a day) exposed to a subthreshold dose of a stimulant drug such as cocaine (or electrical stimulation). Initially the subthreshold dose of cocaine produces no effects. With the passage of time, the single daily dose of cocaine begins to produce prominent behavior or neurophysiological effects. This is called "sensitization." If there is continued daily administration beyond the sensitization phase, the same dose of cocaine can produce seizures. This is called "kindling" (as if a neuronal fire has slowly been building up until it erupts into the flames of a seizure). Sensitization/kindling models have been proposed for a variety of neurological and psychiatric disorders including epilepsy, recurrent psychosis, and PTSD (Post, Weiss, & Smith, 1995; Post, Weiss, Li, Leverich, & Pert, 1999).

In certain respects, sensitization is a highly dramatic example of allosta-

tic load. A potentially explosive steady state is produced that may be very difficult to reverse. It is also an extremely complicated process that is mediated through profound alterations in a wide spectrum of synaptic (first, second, third, etc.) messenger systems and in regulator genes that control neuronal reactivity (Post et al., 1995, 1999).

To summarize, we have described eight psychobiological examples of allostatic load in PTSD. They illustrate that allostatic load may be expressed in a number of interrelated manifestations:

1. Allostatic stability may not be apparent in the baseline state (e.g., normal blood pressure). During stressful stimulation, however, the adaptation may be unable to preserve normal function, as in the adrenergic system, which is hyperreactive in PTSD.
2. Allostasis may be unmasked by psychological probes (e.g., stress, trauma-related stimuli) or pharmacological probes (e.g., yohimbine, MCPP, dexamethasone).
3. Qualitatively different allostatic adaptations may be detected in different people with PTSD as shown in excessive serotonergic (e.g., MCPP but not yohimbine responders) versus excessive adrenergic (e.g., yohimbine but not MCPP responders) sensitivity.
4. Quantitative differences may be detected in allostatic adaptation, as in PTSD patients who found a narcotic antagonist therapeutic in comparison to those who found that the same drug produced severe anxiety and distress.
5. Allostatic load detectable in one system may have far reaching consequences affecting other systems, as shown by downstream effects produced by CRF-induced allostatic load which clearly affects adrenergic, HPA, serotonergic, opioid, and thyroid hormone (T3 and T4) systems.
6. Allostatic alterations are not always deleterious; hence excessive NPY may actually provide allostatic support (e.g., resilience) rather than allostatic load (e.g., vulnerability).
7. Some allostatic changes may be easier to ameliorate than others. Altered neuronal excitability as in sensitization/kindling may be much more resistant to reversal than allostatic load in neurotransmitter, neuropeptide, and neurohormonal systems.

RATIONAL PHARMACOTHERAPY BASED ON ALLOSTATIC LOAD

Table 4.1 summarizes the previous discussion and shows the kinds of allostatic load proposed to occur in people with PTSD. The findings on adrenergic

TABLE 4.1. Rational Pharmacotherapy Based on Allostatic Load

Psychobiological system	Allostatic load	Clinical manifestations	Proposed treatment
Adrenergic	Hyperreactivity, downregulation of alpha-2 receptors	Hyperarousal, hypervigilance, hyperreactivity, panic/anxiety, intrusion/dissociation	Adrenergic antagonists (clonidine, propranolol)
HPA	Enhanced negative feedback, upregulation of glucocorticoid receptors, reduced cortisol levels	Stress intolerance	Glucocorticoids? SSRIs?
5-HT	Systemic dysregulation, upregulation of 5-HT_2 receptors?	Intrusion/avoidant/ numbing/arousal, impulsivity, rage, aggression, depression, panic, obsessional thoughts alcoholism/chemical dependency	SSRIs, nefazodone
Opioid	Sytemic dysregulation	Numbing, chemical dependency	Opioid agonists/ antagonists?
CRF	Elevated activity, enhancement of stress response	Hyperarousal, hypervigilance, hyperreactivity, intrusion/dissociation, stress intolerance, numbing	CRF antagonists
NPY	Reduced activity, enhancement of stress response	Same as CRF	NPY agonists
Thyroid	Elevated activity, secondary to reduced cortisol	Hyperarousal, anxiety	Normalization of HPA function
Sensitization/ kindling	Neuronal excitability (limbic/cortical)	Hyperarousal, intrusion	Anticonvulsants

and HPA function have reasonably secure empirical support. The rest of this table is highly speculative, based on my own interpretations of a relatively sparse literature—although these speculations are consistent with most of the published research in this field.

The third column presents my suggestions as to the clinical implications of allostatic load in each system and is modified from earlier speculations of this sort (Friedman, 1998).

The fourth column is most relevant to the present discussion. It illustrates the kind of pharmacological agent that might be selected to normalize each specific allostatic abnormality. As will be shown later, very few of these agents have been systematically tested in empirical medication trials. Indeed, the lion's share of attention has been devoted to drugs affecting 5-HT mechanisms such as SSRIs. There have only been a few (nonrandomized trials) with antiadrenergic agents and anticonvulsants. We can expect that CRF antagonists will be tested once the pharmaceutical companies have developed safe and effective medications in that category.

Had the knowledge about allostatic load influenced research on the clinical pharmacology for PTSD, there would have been many more trials of antiadrenergic (and possibly anticonvulsant) medications. We shall consider why this has not been the case below as we consider the empirical approach to pharmacotherapy that has been the dominant research strategy up to this time.

EMPIRICAL FINDINGS ON PHARMACOTHERAPY IN PTSD

Selective Serotonin Reuptake Inhibitors

Without doubt, the most important new development in the clinical pharmacology of PTSD is the recent decision by the U.S. Food and Drug Administration (FDA) to designate the SSRI sertraline as a drug indicated for treatment of PTSD. This decision was based on findings from two large clinical trials in which approximately 400 men and women (approximately 200 in each trial) were randomly assigned to receive either sertraline or a placebo (Brady et al., 2000; Davidson, Malik, & Sutherland, 1996). There are a number of notable findings to report from these studies. First, sertraline effectively reduced symptoms in all three PTSD diagnostic clusters (e.g., intrusion, avoidant/numbing and hyperarousal). This was a surprising and welcome result, since previous studies had suggested that there was not a broad spectrum drug (e.g., a "magic bullet") for PTSD. Indeed, a few years ago Friedman and Southwick (1995) seriously questioned whether there was a single drug that could ameliorate all three clusters of PTSD symptoms, and suggested that optimal pharmacotherapy might consist of one class of drug for intrusion symptoms, another class for avoidant/numbing symptoms, and a third class for arousal symptoms.

Another important finding from the sertraline trials is that the SSRI's efficacy is not due to its potency as an antidepressant. When subjects who had PTSD plus a history of major depressive disorder (MDD) were compared to PTSD subjects without MDD, there was no difference. Both groups exhibited an equal reduction in PTSD symptoms, suggesting that sertraline is an effective and specific treatment for PTSD.

A final set of results from these important studies raise provocative questions about gender and type of trauma. First, women appeared to be much more responsive to medication than men. Second, people with sexual trauma appeared to be more responsive than those with other types of trauma. Indeed, men with a history of sexual trauma appeared to respond well to sertraline, suggesting that it is not simply a matter of gender but something much more complicated that determines responsivity to sertraline that needs to be clarified in future research. After considering this evidence very carefully, the FDA concluded that sertraline is definitely effective for women with PTSD and that its efficacy for men has not been demonstrated conclusively. It is important to recognize that the FDA *did not* conclude that sertraline is ineffective in men.

There are other studies with SSRIs that must be mentioned. Two randomized clinical trials with fluoxetine of van der Kolk et al. (1994) and Davidson et al. (1997) showed marked improvement in PTSD symptoms and the Clinical Global Improvement (CGI) Scale, respectively, in mostly female cohorts with a history of sexual trauma. On the other hand, Vietnam veterans with PTSD were largely unresponsive to fluoxetine (van der Kolk et al., 1994). I have argued elsewhere (Friedman, 1997) that poor results with Vietnam veterans may have less to do with either male gender or combat trauma and much more to do with the fact that these veterans have much more severe, chronic, and treatment-refractory PTSD than do nonveteran subjects enrolled in similar treatment protocols.

Recent open-label trials with sertraline in rape trauma survivors (Rothbaum, Ninan, & Thomas, 1996), fluvoxamine in Vietnam combat veterans (Marmar et al., 1996), and paroxetine in subjects previously traumatized by rape, criminal assault, or accidents (Marshall et al., 1998) have all had positive results. In fact, the data from randomized and open trials all show effectiveness of SSRIs in reducing all three PTSD symptom clusters. Data from trials with fluoxetine, fluvoxamine, and paroxetine are consistent with the sertraline data detailed previously, although they have all been small single-site studies as compared to the large multisite sertraline trials.

At the present time, SSRIs are the treatment of choice as first-line drugs in PTSD. Two recent large-scale initiatives to assess the effectiveness and efficacy of current PTSD treatments have confirmed this conclusion. In the first, an extensive survey by mail in which 57 international experts in PTSD pharmacotherapy were asked a variety of questions about treatment, SSRIs were clearly selected as the top choice by this expert consensus panel (Foa, Davidson, & Frances, 1999). In the second, a treatment guideline developed by the International Society for Traumatic Stress Studies (ISTSS), it was concluded that the empirical literature strongly supports that SSRIs are the most effective medication for PTSD at the present time (Friedman, Davidson, Mellman, & Southwick, 2000).

There are several other reasons why SSRIs have emerged as first-line

treatments for PTSD. First, they have proven efficacy against disorders that are frequently comorbid with PTSD. These include depression, panic disorder, social phobia, and obsessive–compulsive disorder. SSRIs also effectively reduce a number of clinically significant symptoms that are frequently associated with PTSD such as rage, impulsivity, suicidal intent, and misuse of alcohol or drugs (Friedman, 1990). Brady, Sonne, and Roberts (1995) reported that sertraline effectively reduced both PTSD and alcohol-related symptoms in patients with comorbid PTSD and alcohol dependence. Finally, SSRIs generally produce fewer disturbing side effects than other medications that have been prescribed for this disorder.

Other Serotonergic Agents

Nefazodone

Nefazodone is an effective antidepressant that combines SSRI activity with postsynaptic 5-HT_2 blockade. Although there is a little evidence from one open trial (Hertzberg, Feldman, Beckham, Moore, & Davidson, 1998) and no published randomized clinical trial, nefazodone was strongly endorsed as a second choice (after SSRIs) by the aforementioned expert consensus panel (Foa et al., 1999). It is curious that nefazadone should be so strongly favored by experts in the absence of a convincing proof of efficacy. I can only understand this as the result of the following: clinician awareness of nefazodone's effectiveness against MDD, with which PTSD is frequently comorbid; its lack of side effects; its conspicuousness to practitioners because of aggressive marketing strategies by pharmaceutical companies; and the expectation among clinicians that it will prove to have the same spectrum of action as SSRIs. There are multisite trials with nefazodone currently in progress, and we await their results with interest.

Trazodone

Trazodone, like nefazodone, is an SSRI plus 5-HT_2 antagonist. It has shown only modest effectiveness in one small open trial with PTSD patients (Hertzberg, Feldman, Beckham, & Davidson, 1996). It differs from nefazodone in that it is less potent as an antidepressant but much more sedating as a hypnotic. Trazodone has been rediscovered by clinicians in recent years because its serotonergic action is synergistic with SSRIs and its sedative action often overcomes the insomnia produced by SSRIs (Cook & Conner, 1995).

Venlafaxine

Venlafaxine is a potent antidepressant that, in addition to possessing an SSRI action, is a strong reuptake inhibitor of norepinephrine and a weak reuptake

inhibitor of dopamine. There are no published randomized or open trials with venlafaxine in PTSD. Despite the lack of evidence for efficacy, it was selected as the third-most-favored drug by the expert consensus panel, after SSRIs and nefazodone (Foa et al., 1999). One can only guess that the reasons for its popularity with experts are similar to those cited above concerning nefazodone. It is important to keep this in mind, and to recognize that evidence supporting the use of venlafaxine in PTSD has yet to make an appearance.

Cyproheptadine

Cyproheptadine is a 5-HT antagonist that has been suggested as an effective treatment for traumatic nightmares. Evidence for this claim was based on two brief reports on a total of six patients, although there are unpublished reports supporting these results (reviewed in Friedman & Southwick, 1995). A recent two-site randomized clinical trial with veterans has not confirmed these findings. It was found that cyproheptadine was no better than placebo in reducing PTSD symptoms, preventing traumatic nightmares, or improving sleep (Jacobs-Rebhun, Schnurr, Friedman, Peck, Brophy, & Fuller, 2000). Based on these latter findings, cyproheptadine cannot be recommended for PTSD treatment.

Buspirone

Buspirone is an anxiolytic that acts as a 5-HT_{1A} partial agonist. One published case report on three veterans indicated that buspirone ameliorated anxiety, insomnia, flashbacks, and depression (see Friedman & Southwick, 1995). As yet, no further data are available on the usefulness of this drug.

Antiadrenergic Agents

Perhaps the best evidence that clinical pharmacological research in PTSD has been driven by the empirical rather than the allostatic perspective can be found by perusing the published findings regarding antiadrenergic agents. Since we have known about elevated urinary catecholamines, downregulation of alpha-2 receptors, yohimbine sensitivity, and SNS hyperreactivity for many years (see Southwick et al., 1999), one would have expected the literature to be full of reports on the effectiveness of antiadrenergic agents such as postsynaptic antagonists (e.g., propranolol) or presynaptic alpha-2 agonists (e.g., clonidine and guanfacine). Surprisingly, this is not the case.

An open trial with both propranolol and clonidine in Vietnam veterans with PTSD, conducted by Kolb, Burris, and Griffiths (1984), reported marked symptom reduction with both medications. Patients reported diminution of intrusive recollections, traumatic nightmares, hypervigilance, startle reactions, insomnia, and angry outbursts. An A-B-A designed study (6

weeks off—6 weeks on—6 weeks off) of propranolol in 11 children with PTSD due to sexual and/or physical abuse was likewise successful, with significant reductions observed in reexperiencing and arousal (but not avoidant/numbing) symptoms during the active treatment phase which rebounded to predrug severity after propranolol was discontinued (Famularo, Kinscherff, & Fenton, 1988).

Despite such promising data, there have been no randomized clinical trials with any antiadrenergic agent and very few open trials (see Friedman, 1998). In general, clonidine has been more successful than propranolol (in trials with abused children, Cambodian refugees, and Vietnam veterans), but the data are much too sparse to enable us to draw any conclusions with confidence.

I use antiadrenergic agents, especially alpha-2 agonists, extensively in my practice. This enthusiasm is clearly based on my allostatic perspective, since there is very little empirical support for prescribing such drugs. In addition to selecting antiadrenergic agents to reduce allostatic load from hyperarousal and hyperreactive symptoms, I use such agents to treat dissociation and flashbacks. I formulated such a strategy by extrapolation from the previously mentioned studies in which yohimbine produced dissociation/PTSD flashbacks in Vietnam veterans. It seemed to me that if an alpha-2 antagonist such as yohimbine could produce such symptoms, a drug with the opposite action, an alpha-2 agonist such as clonidine, should be an effective antidote.

Case 1: KM

KM was a 42-year-old divorced mother of two school-aged children who had become unable to maintain employment at the large banking firm where she had previously been functioning very well at an executive level. She was totally incapacitated by a resurgence of traumatic memories (of childhood sexual abuse) and other PTSD avoidant/numbing and hyperarousal symptoms. Most distressing, by far, were the dissociative episodes that could disrupt any activity at any time and which consisted of complex behavioral sequences over which she had no control and about which she had no recollection. An incisive and thorough historian regarding information that was accessible to her memory, KM recalled that amnestic episodes were usually preceded by escalating levels of arousal and anxiety.

When prescribed clonidine 0.2 mg twice daily, KM reported marked reduction in dissociative episodes within the first week of treatment. She also reported reduced anxiety, improved concentration, and better sleep. Three weeks later the dose had to be increased to 0.2 mg thrice daily because her dissociative symptoms started to return. This dosage adjustment was also effective for several weeks until she again began to become tolerant to the medication as evidenced by a return of dissociative symptoms.

At this point, I was hesitant to increase the clonidine any further for fear that it might provoke a reduction in blood pressure (since clonidine is used clinically in

the treatment of hypertension). Therefore, I switched KM to guanfacine 1 mg twice daily because that drug has the same pharmacological actions as clonidine but is less likely to produce tolerance because of its longer half-life (Horrigan, 1996). This was quite successful, and KM remained on the same dose of guanfacine for 4 years. Not only were her dissociative and other PTSD symptoms well controlled, but she was able to resume her previous duties at the bank.

Recently, KM had to undergo treatment for cancer. Her oncologist discontinued the guanfacine because of concerns about drug interactions with some of the powerful antineoplastic drugs that needed to be prescribed. Within a week's time, dissociative symptoms that had been well controlled for years returned with alarming intensity. Resumption of guanfacine once again negated the dissociative symptoms and restored her psychiatric remission.

This vignette illustrates the successful treatment of dissociative symptoms that had failed to respond to SSRIs, nefazodone, or other medications. It shows how a treatment strategy based on allostatic concerns may produce clinical success. I should note that I have had many patients like KM who have had good responses to antiadrenergic agents. I make this statement with full knowledge that proof of efficacy must await a conclusive randomized clinical trial. KM's case also illustrates the not uncommon occurrence that clonidine responders may become tolerant to this agent. It shows that clonidine-tolerant patients may subsequently be stabilized indefinitely on guanfacine. Finally, beta blockers such as propranolol are often as effective as alpha-2 agonists such as clonidine or guanfacine, although I hesitate to prescribe them for patients who have MDD in addition to PTSD.

Tricyclic Antidepressants

The first reports on effective pharmacotherapy for PTSD concerned tricyclic antidepressants (TCAs) (see the extensive review of this literature by ver Ellen & van Kammen, 1990). Clinicians found TCAs to be useful agents for reducing reexperiencing and hyperarousal (but not avoidant/numbing) symptoms. Three randomized clinical trials, all with Vietnam veterans, had mixed results. Imipramine produced moderate reduction in reexperiencing symptoms and clinically significant global improvement (Kosten et al., 1991). Amitriptyline produced global improvement and modest reduction in avoidant/numbing symptoms (Davidson et al., 1990). In the third randomized clinical trial, which lasted only 4 weeks in contrast to the 8-week duration of the other studies, desipramine was no better than placebo (Reist et al., 1989). Finally, in a quantitative review of all randomized and open trials with tricyclics, Southwick and associates (1994) concluded that 45% of patients (mostly Vietnam veterans with PTSD) showed global improvement in PTSD that was mostly due to amelioration of intrusion symptoms.

Based on the above reports, TCAs have largely fallen out of favor as

first-line treatment for PTSD. Reasons for this are as follows: (1) they have a more complicated spectrum of side effects than newer agents such as SSRIs, nefazodone, and venlafaxine; (2) the newer agents are equipotent to TCAs as antidepressants, so TCAs are prescribed much less frequently, in general, by practicing psychiatrists; (3) no new clinical trials with TCAs have been published in almost 10 years; and (4) aggressive strategies have been engaged in by pharmaceutical companies to promote SSRIs and other new antidepressants, both through the launching of multisite clinical trials and through promotion of their use for comorbid disorders (e.g., depression, panic disorder, social phobia, and obsessive–compulsive disorder). For all these reasons, TCAs have faded from the short list of medications most favored by prescribing clinicians in the treatment of PTSD (and other psychiatric disorders).

It is useful to ask ourselves whether the verdict against the usefulness of TCAs was declared prematurely. Certainly their array of side effects would place them behind SSRIs, but is there evidence that they might actually exhibit greater efficacy against PTSD symptoms under certain circumstances? First, their pharmacological action—to block reuptake of both 5-HT and norepinephrine—suggests, from an allostatic load perspective, that they may still have a place in PTSD treatment. Second, the randomized trials that produced mixed results were all conducted on Vietnam veterans seeking treatment in VA (Veterans Administration) hospital-based PTSD programs. As I have argued elsewhere (Friedman, 1997), these patients appear to be a severe, chronic, and treatment-refractory cohort who have also failed to respond to SSRIs (van der Kolk et al., 1994). Perhaps TCAs have more to offer than both the empirical literature and PTSD experts (Foa et al., 1999) would suggest. They may well deserve reconsideration either with less chronic cohorts or with SSRI-refractory patients.

In this regard, the first publication in several years on TCA treatment for traumatized patients recently appeared concerning the prospective use of imipramine for pediatric burn patients (aged 2–19 years) who suffered from acute stress disorder (ASD) in addition to their burn injuries (Robert, Blakeney, Villarreal, Rosenberg, & Mayer, 1999). Twenty-five children with a mean total-burn surface of 45% were randomly assigned to 7 days of treatment with either imipramine or chloral hydrate (a sleeping medication currently used extensively in burn units to ameliorate insomnia and traumatic nightmares). Imipramine produced marked symptom relief to complete symptom relief in 83% of the children in contrast to chloral hydrate, which was only effective for 38% of the children. Furthermore, after completion of the 7-day trial, 20% of the 25 children and their parents elected to continue imipramine treatment for approximately the next 6 months. Intrusion, avoidant/numbing, arousal, and dissociative symptoms were well controlled during that period, and there was no rebound of PTSD symptoms when imipramine was discontinued.

Obviously larger and additional studies are needed to confirm these results, but there are two important points raised by this study: first, TCAs may have an important role in treatment of ASD and prevention of PTSD; second, TCAs may be worth reconsidering for treatment of PTSD.

Monoamine Oxidase Inhibitors

The story with monoamine oxidase inhibitors (MAOIs) is similar to that with TCAs except that MAOIs have been used much less extensively than TCAs and their performance against PTSD symptoms has generally been better. As with TCAs, however, they have been largely replaced by SSRIs and other new antidepressants in PTSD treatment.

From an allostatic perspective, MAOIs also foster downregulation of 5-HT and adrenergic receptors through a metabolic action that blocks destruction of these neurotransmitters by the intracellular enzyme, MAO. Psychiatrists have generally not been predisposed to prescribe MAOIs as first-line treatments (despite their powerful efficacy as antidepressants and antipanic agents) because patients must be extremely compliant and reliable; they must adhere to strict dietary restrictions, avoid a number of medications (including illicit drugs), and abstain from alcohol. Failure to adhere to such dietary, drug, and alcohol restrictions can result in a sudden large-scale elevation in blood pressure that precipitates a hypertensive crisis that is a medical emergency.

In two published randomized trials with the MAOI phenelzine, excellent global improvement and reduction of intrusion symptoms was found in one study (Kosten et al., 1991) whereas the second, a methodologically flawed investigation, demonstrated no efficacy of the MAOI in reducing PTSD severity (Shestatzky, Greenberg, & Lerer, 1988). In addition, a number of successful open trials and positive case reports concerning MAOI (usually phenelzine) treatment for PTSD have been reported (see the review by De Martino, Mollica, & Wilk, 1995).

In recent years, there have been trials with RIMAs, reversible inhibitors of monoamine oxidase A (MAO-A) that appear to share the pharmacological action of traditional MAOIs without the serious side effects. Results with RIMAs have not been as impressive as with traditional MAOIs but have not been without promise. An open trial with 20 patients who received moclobemide (a RIMA not available in the United States) produced clinically significant improvement in reexperiencing and avoidant symptoms (Neal, Shapland, & Fox, 1997). Two randomized multisite clinical trials with the experimental RIMA/SSRI agent brofaramine had mixed results. Patients in both studies exhibited 52–60% reduction in PTSD severity, but high response rates in the placebo group (Baker et al., 1995) nullified any treatment effect whereas a lower placebo response in the second study suggested moderate efficacy in PTSD (Katz et al., 1994/95). Unfortunately, the manufac-

turers have discontinued testing of brofaramine, so there is presently no possibility that it will be used in PTSD or any other treatment.

Finally, in the same quantitative review of TCAs mentioned earlier (Southwick et al., 1994), MAOIs appeared to be more effective than TCAs, having produced moderate-to-good global improvement in 82% of all patients, primarily due to amelioration of reexperiencing symptoms, in contrast to only 45% improvement with TCAs.

Benzodiazepines

Benzodiazepines are proven anxiolytic agents for which there is no proof of efficacy in PTSD. In the only published randomized clinical trial, alprazolam reduced insomnia, general anxiety, and irritability but was without effect on PTSD intrusion, avoidant/numbing, startle response, or hypervigilance symptoms (Braun et al., 1990). A prospective study in which clonazepam was given to recently traumatized emergency room patients did not demonstrate that such a prophylactic approach prevented the later development of PTSD (Gelpin, Bonne, Peri, Brandes, & Shalev, 1996). Other open trials have yielded similarly negative results (see Friedman & Southwick, 1995). The only positive finding was a pilot study in which temazepam (a hypnotic benzodiazepine) prescribed at bedtime specifically to improve insomnia among trauma survivors with ASD, was associated with a marked reduction in PTSD symptoms subsequently (Mellman, Byers, & Augenstein, 1998).

Current evidence suggests that benzodiazepines exhibit no efficacy against PTSD intrusion, avoidant numbing, hypervigilant, or startle symptoms. Furthermore, there is a report of exacerbation of such symptoms marked by intense arousal and flashbacks among PTSD patients undergoing abrupt discontinuation of alprazolam (Risse et al., 1990). In short, there is no empirical justification for prescribing benzodiazepines to PTSD patients.

Anticonvulsants

The anticonvulsants carbamazepine and valproate have been prescribed in open trials with PTSD patients because such drugs have exhibited antikindling actions in research protocols with laboratory animals. Results have been mixed but generally favorable in small open trials. Carbamazepine appears effective in reducing intrusion and arousal symptoms, while valproate has reduced avoidant/numbing and arousal (but not intrusion) symptoms (see Friedman & Southwick, 1995, for references). Based on the theoretical importance of sensitization/kindling models in PTSD, discussed earlier, it is hoped that there will be more extensive and rigorous research with anticonvulsants in the future. Both carbamazepine and valproate have an extensive side effect profile, although the latter medication is used widely in current pharmacotherapy for bipolar affective disorder. Given current interest in the

usefulness of newer anticonvulsants such as lamotrigine and gabapentine in affective disorders, there will most likely be research in the future on the effectiveness of old and new anticonvulsants for PTSD.

Antipsychotics

The final class of medications to be considered here are antipsychotics. Both conventional and newer atypical antipsychotic agents are potent dopamine antagonists. There are a few studies suggesting allostatic load in the dopaminergic system of PTSD patients, although this has received little attention (see Friedman & Southwick, 1995, for references). Indeed, one might propose that dopaminergic abnormalities contribute to the hypervigilance/paranoia, social withdrawal, and trauma-related hallucinations seen in the most severely affected PTSD patients. Indeed, PTSD syndromes associated with auditory hallucinations (Mueser & Butler, 1987) and comorbid with psychotic disorders (Mueser et al., 1998) have been described. Finally, given favorable properties of newer, atypical antipsychotics including 5-HT_2 antagonism, safety, and lack of toxicity (with respect to tardive dyskinesia and extrapyramidal symptoms), we can expect that such agents will be investigated as PTSD treatments in the near future. Clinicians have already begun to use them with severely affected, treatment-refractory patients, and anecdotal reports have begun to appear in the literature regarding their successful use (Hamner, 1996).

Summary of Empirical Findings

The results of clinical trials are summarized in Table 4.2.

1. In general, empirical research with PTSD has consisted of a small number of randomized clinical trials with medications that, for the most part, were initially designed as antidepressants and later shown to be effective in treating panic disorder, social phobia, and obsessive–compulsive disorder. No drugs specifically designed to target the allostatic load in PTSD have been tested.
2. Testing of older drugs (e.g., TCAs, MAOIs, older anticonvulsants) has largely been abandoned in favor of new antidepressants (e.g., SSRIs, nefazodone) and possibly new anticonvulsants (e.g., lamotrigine, gabapentine). This is especially unfortunate since older medications such as antiadrenergic (clonidine, guanfacine, and propranolol) and anticonvulsants (carbamazepine and valproate) may yet prove effective.
3. Many older trials were conducted on Vietnam veterans with severe, chronic, and treatment-refractory PTSD. Lack of demonstrable efficacy in such trials may be related to the specific responsivity of the

TABLE 4.2. Summary of Empirical Literature on Pharmacotherapy for PTSD

Medication class	Mechanism of action	Specific medication	Dose	No. RCTs	PTSD symptoms B	C	D	Remarks
SSRI	SSRI	Sertraline	50–200 mg	2	X	X	X	• Sertraline has FDA approval as an indicated treatment for PTSD
		Fluoxetine	20–80 mg	3	X	X	X	• SSRIs are effective for comoribid disorders such as depression, panic disorder, social phobia, and obsessive–compulsive disorder; They've also been used effectively for alcohol/drug abuse/dependence • They may also reduce symptoms associated with PTSD such as rage, impulsivity, suicidal thoughts, agression, panic/anxiety, obsessional thoughts, chemical abuse/dependency
		Paroxetine	20–50 mg	0	X	X	X	
		Fluvoxamine	100–300 mg	0	X	X	X	
Antidepressant	SSRI/5-HT_2 blockage	Nefazodone	300–00 mg	0	x/?	x/?	x/?	• Very few data: one small open trial; despite this, nefazodone is greatly favored by "expert consensus" as an excellent antidepressant
		Trazodone	25–500 mg	0	x/?	x/?	x/?	• Results from one small open trial: effective sleeping medication for patients with SSRI-induced insomnia; moderately effective as an antidepressant

(continued)

TABLE 4.2. ***cont.***

Medication class	Mechanism of action	Specific medication	Dose	No. RCTs	PTSD symptoms B	C	D	Remarks
	Strong reuptake inhibitor of 5-HT and NE Weak DA reuptake inhibitor	Venlafaxine	75–225 mg	0	?	?	?	• Never tested in PTSD; despite this, is third choice of expert consensus panel, after SSRIs and nefazodone
Serotonin antagonist	Postsynaptic 5-HT blockade	Cyproheptadine	4–28 mg	1	0	0	0	• Without effect on PTSD flashbacks and nightmares, despite early favorable anecdotal reports
Serotonin partial	$5HT_{1A}$ partial agonist	Buspirone	30–60 mg	0	x/?	0	x/?	• Few data—just a few case reports
Antiadrenergic	Alpha-2 agonist	Clonidine Guanfacine	0.2–0.6 mg 1–3 mg	0 0	X X	0 0	X X	• Few trials to date; patients tolerant to clonidine are often responsive to guanfacine
	Beta blocker	Propranolol	40–160 mg	A-B-A (see text)	X	0	X	• Few trials—mixed results in some; may exacerbate major depressive disorders
TCA	Inhibit reuptake of	Imipramine	150–300 mg	1	X	0	x/?	• Major effect on global improvement and B symptoms • Effective in prospective trial with pediatric burn patients with ASD
		Amitriptyline	150–300 mg	1	x/?	X	0	• Most effective on avoidant/numbing

			Desipramine	150–300 mg	1	0	0	0	• Ineffective in brief RCT • All TCAs have clinically significant cardiovascular, anticholinergic; and other side effects; they are good antidepressants and effective in panic disorder
	MAOI	Irreversible MAOI	Phenelzine	45–75 mg	2	X	0	X	• One very postive RCT, and one methodologically flawed RCT with negative results • Clinicians are reluctant to prescribe MAOIs because of dietary restrictions and serious side effects • Good antidepressants and antipanic agents
		Reversible MAO-A inhibitor (RIMA)	Moclobemide		0			0	• Promising medication but few data • Free of MAOI dietary restrictions and side effects.
	Benzodiazepines	BZD-GAA agonist	Alprazolam	0.5–6 mg	1	0	0	X	• Good general anxiolytic (reduce insomnia anxiety and irritability) but not effective against core PTSD symptoms • Serious withdrawal syndrome with exacerbation of PTSD symptoms
			Clonazepam	1–6 mg	0	0	0	X	• Ineffective in prospective trial of emergency room patients with ASD

(*continued*)

TABLE 4.2. ***cont.***

Medication class	Mechanism of action	Specific medication	Dose	No. RCTs	PTSD symptoms B	C	D	Remarks
Anticonvulsants	Antikindling action	Carbamazepine	600–1,000 mg	0	X	0	X	• Many side effects • Few studies • Good mood stabilizer
		Valproate	750–1,750 mg	0	0	X	X	• Few studies • Used widely as mood stabilizer
Antipsychotics	D-2 receptor antagonist	Thioridazine	200–800 mg	0	x/?	0	x/?	• Effective conventional antipsychotic • May produce tardive dyskinesia; also extrapyramidal and other side effects • Case reports only
	$5\text{-HT}_2/D_2$ receptor antagonist	Clozapine	300–900 mg	0	x/?	0	x/?	• Effective
		Risperidone	4–12 mg	0	x/?	0	x/?	• Atypical antipsychotics—fewer motor side effects but other potential toxicities • May have mood-stabilizing properties • Case reports only

Note. RCT, randomized clinical trial; PTSD B symptoms, intrusive recollections; PTSD C symptoms, avoidant/numbing; PTSD D symptoms, hyperarousal; 5-HT, serotonin; NE, norepinephrine; DA, dopamine; BZD, benzodiazepine; GABA, γ-aminobutric acid; D_2, dopamine-2 receptor; SSRI, selective serotonin reuptake inhibitor; TCA, Tricyclic antidepressant; MAOI, monoamine oxidase inhibitor; RIMA, reversible MAO-A inhibitor. Statistical significance in PTSD Symptoms column (column 6): X, definite positive effect; x, possible positive effect; 0, nonsignificant effect; ?, no data (never tested).

veteran cohort tested rather than the efficacy of the drugs themselves.
4. It is impossible to disentangle gender from trauma type in attempts to understand factors predicting a favorable response to medication, since most women tested have had sexual trauma while most men tested have been Vietnam veterans with chronic PTSD who are neither representative of males in general or of veterans in general.
5. Prospective studies are a very high priority. Two such trials have been reported: positive results in pediatric burn patients with ASD treated with imipramine, and negative findings with emergency room trauma survivors treated with clonazepam.
6. Recent FDA approval of sertraline as an indicated drug for treatment for PTSD is an important milestone in pharmacotherapy for this disorder that should affect current practice patterns and stimulate new research.

PSYCHOBIOLOGICAL VERSUS PSYCHOLOGICAL ALLOSTASIS IN PTSD

The following case example is a sober reminder that PTSD is not only a complicated disorder to treat from a psychobiological perspective but that psychological factors may sometimes overwhelm the most thoughtful allostatically conceptualized pharmacological approach.

Case 2: DG

DG was a 55-year-old married man without children who had been horribly abused, both physically and sexually, by his father and mother from early childhood through adolescence, when he ran away from home. He got married in his early 20s and functioned reasonably well as a manual laborer despite recurrent traumatic nightmares, avoidant behaviors, problems with intimacy, and startle/hypervigilant symptoms. At age 25 he suffered a severe back injury while logging in the woods. In addition to pain and movement restrictions, this injury precipitated an overwhelming sense of vulnerability and helplessness that produced severe intensification of PTSD symptoms with which he had coped prior to the accident. In fact, although his back recovered during the next 6 months, his PTSD symptoms worsened to such an extent that he was unable to resume work because of his psychiatric disability. He remained incapacitated because of PTSD for the next 30 years.

He was referred by his primary care practitioner, who was currently prescribing an adrenergic beta receptor antagonist, metoprolol (similar to propranolol), for his elevated blood pressure, which was partially effective, and a sleeping medication for his insomnia, which was completely ineffective.

DG was an intense, agitated, unhappy man who was extremely jumpy, mistrustful, and hopeless. He thought constantly about his childhood trauma

and had distressing nightmares of such events on a daily basis that were so intense that he was afraid to go to sleep. In fact, his wife reported that he was so jumpy and apprehensive at night that she had reluctantly decided to sleep in another room since she felt that she needed her nocturnal rest to attend to his many emotional needs and physical complaints during the day. Other prominent PTSD symptoms were avoidance of thoughts, feelings, stimuli or situations that might evoke traumatic memories, social withdrawal, arousal symptoms, and psychic numbing that was easily and frequently overwhelmed by trauma-related feelings and memories.

Since he was already receiving a beta blocker, metoprolol, for hypertension, I increased the dose (rather than prescribe clonidine) with the expectation that it would take the edge off his arousal symptoms and might attenuate the re-experiencing symptoms as well. When DG reported some daytime benefit from metoprolol in the predicted direction, I suggested that he take it at bedtime with the hope that it might reduce his nocturnal anxiety sufficiently so that he might get some sleep. Two days later he phoned to announce that "that medication made me worse, Doc. It makes me so nervous that I won't take it anymore."

On careful questioning, he reported that the exact same dose of metoprolol that reduced anxiety and other symptoms during the day made him much worse at night. Given his refusal to try it at bedtime again, I suggested that he once again take the metoprolol twice a day, in the morning and at noon. He did so, with the same benefit as before, although he complained that he was so drowsy during the day that he sometimes couldn't get out of his chair.

Given his bitter distress about persistent insomnia, I then prescribed a small dose of trazodone at bedtime. Again he phoned within a few days with the same complaint—that trazodone made him unbearably anxious and wakeful at night. Again, when trazodone was rescheduled for daytime administration, it made him drowsy.

From a pharmacological perspective, it was impossible for me to explain how the same dose of the same drugs (both metoprolol and trazodone) had diametrically opposite effects depending on whether they were taken at bedtime or during daylight hours. I concluded that, since all of his sexual and physical abuse had occurred at night, it was too dangerous from a PTSD perspective for DG to make himself vulnerable at night, lest he be assaulted once again. In short, I concluded that DG could not respond to any medication that would blunt his hypervigilance or make him lose consciousness at night because of persistent trauma-related fears from childhood.

I believe that this vignette illustrates the difference between clinical pharmacology and therapeutics in PTSD treatment: DG's paradoxical response to two different medications cannot be understood pharmacologically. His response is not paradoxical, however, when the difference between his daytime and nighttime psychological states are taken into consideration. Medications that during the day successfully reduced his PTSD symptoms blunted his ability to protect himself at night. Even though the medications

were the same, DG was not the same person at these two different times of day. This may show that psychological allostasis (e.g., a steady state promoting hypervigilance and a defensive posture) was more salient than psychobiological allostasis with regard to alterations in key neurotransmitter/neurohormonal systems. On the other hand, it may also suggest that allostatic load may itself sometimes have a diurnal variation, so that psychobiological as well as psychological steady states may exhibit crucial differences at different times of day. Whatever the explanation, from a therapeutics perspective it made no sense to prescribe an antiadrenergic or sleeping medication at night. I told this to DG and gave him my reasons for this decision. He agreed that that made sense. Hence, my current attempts to help him are focused entirely on efforts to improve his PTSD symptoms during the day.

PHARMACOTHERAPY AS A PSYCHOTHERAPEUTIC INTERACTION

Pharmacotherapy is much more than clinical assessment and writing prescriptions. The patient and psychiatrist participate in a relationship which has therapeutic potential beyond the normalization of psychobiological abnormalities.

My own technique is a Rogerian approach (Rogers, 1951) in which the patient and I are in an active collaboration to reduce his or her distress. I am the expert on medications, while the patient is the expert on him- or herself. We both must share information and observations that each of us is uniquely positioned to provide. Although we speak about thoughts, feelings, behaviors, symptoms, interpersonal relationships, and side effects, the implicit communication is about acceptance and promotion of self-efficacy. In short, therapeutic momentum is always toward empowerment to help the patient acquire more control over his or her life.

Since an important aspect of PTSD is a pervasive sense of helplessness and personal incompetence, I believe that any treatment that promotes empowerment is an effective therapeutic approach. In other words, pharmacotherapy can also be an effective psychotherapeutic intervention.

Therefore, this approach not only provides a more efficient and accurate strategy for selecting the correct drug and finding the optimal dose, it also provides a context in which promotion of empowerment clearly enhances the benefits achieved with medication.

CONCLUSIONS

It is an exciting time. New discoveries about the psychobiology of the human stress response and about the pathophysiology of PTSD continue to expand

our understanding of this complex disorder. At the same time, renewed interest in testing recently developed medications holds great promise that more effective treatments will be discovered in the foreseeable future. My hope is that these two initiatives will not continue to proceed on parallel paths, as has been the case to date, but will soon intersect. As we begin the new century, it is heartening to realize that new classes of drugs currently under development may more effectively target stress-related mechanisms in general and PTSD allostasis in particular. I have suggested elsewhere some specific classes of new pharmacological agents that might address the unique pathophysiology of PTSD. Among such medications are the following: CRF antagonists; NPY agonists; substance P (a peptide neurotransmitter) antagonists; anticonvulsants with antikindling/antisensitization properties; agents that can downregulate glucocorticoid receptors; more specific serotonergic agents; medications to normalize opioid function; and agents affecting glutamatergic mechanisms that might ameliorate dissociation, memory, and information processing problems associated with PTSD (Friedman, 2000). We can certainly look to the future with anticipation and with the hope that we will not have to wait too much longer for the development of more effective medications for PTSD.

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