

# IPAP Post-Traumatic Stress Disorder Algorithm Notes

## INTRODUCTION

**Posttraumatic stress disorder** (PTSD) is a condition characterized by the development of symptoms following a traumatic event, including symptoms of intrusive thoughts and recollections, avoidance of reminders of the trauma, emotional numbing, and hyper-arousal. PTSD occurs in approximately 8% of the population and follows a chronic course in up to 50% of subjects (Kessler et al, 1995; Breslau et al, 1991; Kessler et al, 2000). According to the most recent major US epidemiological survey, as much as 12% of the population has active PTSD lasting over 20 years' duration (Breslau et al, 1998; Kessler, 2000). Receipt of treatment is associated with an overall shorter course of PTSD (LOE 3) (Kessler et al, 1995).

Existing PTSD treatment guidelines are based on reviews of the extent to which levels of evidence support particular treatments, but they do not address the all-important matter of treatment sequencing, or “what to do next” when the first treatment has failed to bring about remission or good response. Neither do they address the management of PTSD with other comorbidity. Five major PTSD treatment guidelines are those published by the Expert Consensus Group (Foa, Davidson and Frances, 1999), the International Society of Traumatic Stress Studies (ISTSS) (Foa, Keane and Friedman, 2000), the American Psychiatric Association (2004), The US Department of Veterans Affairs and Defense Joint Clinical Practice Guidelines (2005), and the United Kingdom's National Center of Clinical Excellence (NICE) (2005). To address issues of treatment management, for which the levels of evidence typically diminish as one travels down the sequence and/or considers using drug combinations, there is need to develop treatment algorithms.. Accordingly, we present this algorithm for the pharmacological management of PTSD. At the outset, however, it is acknowledged that two distinct approaches are of proven benefit in PTSD: the pharmacological and the psychosocial. Thus, the first choice to be made is whether to offer medication, psychotherapy, or both. Psychosocial treatments, if not used initially, can be added to, or replace pharmacotherapy. However, with one exception, we are unaware of any empirical data to support the augmentation of medication with a psychosocial treatment (Rothbaum et al, 2003). .

In this algorithm, we provide a sequenced approach to the pharmacotherapy of PTSD, taking into account salient symptomatology and diagnostic comorbidity, levels of evidence (LOE; see appropriate node), and extent of response. We also address special issues, including the following topics: acute aftermath of trauma, ongoing trauma and violence; pregnancy; other behavioral and health risks; treatment adherence; dosing guidelines; atypical antipsychotics; cross cultural issues; assessment tools for PTSD and acute stress disorder; the course of PTSD; legal system involvement; and use of medication in children and adolescents.

## NOTES TO THE NODES

**Node 1: Diagnosis of PTSD**

Posttraumatic stress disorder (PTSD) is a condition characterized by the development of a constellation of characteristic symptoms following a traumatic event, including symptoms of intrusive thoughts and recollections, avoidance of reminders of the trauma, emotional numbing, and hyper-arousal. The diagnostic criteria for PTSD, as put forth by the Diagnostic and Statistical Manual for Mental Disorders, 4<sup>th</sup> edition (DSM IV) and by the International Classification for Disease, 10<sup>th</sup> edition (ICD 10), are presented in Tables 1a and 1b.

**Table 1a. DSM-IV Diagnostic Criteria for PTSD<sup>a</sup>**


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A. Traumatic stressor
<ul style="list-style-type: none"> <li>• An event, or events, in which an individual experiences, witnesses, or is confronted with life endangerment, death, or serious injury or threat to self or others; and</li> <li>• The individual responds to the experience with feelings of intense fear, horror, or helplessness</li> </ul>
B. Re-experiencing symptoms (one or more)
<ul style="list-style-type: none"> <li>• Intrusive recollections; distressing dreams; flashbacks; dissociative phenomenon; psychological and physical distress with reminders of the event</li> </ul>
C. Avoidance and numbing symptoms (three or more)
<ul style="list-style-type: none"> <li>• Avoidance of thoughts, feelings, or conversations associated with the event; avoidance of places, situations, or people that are reminiscent of the event; inability to recall important aspects of the event; diminished interest; estrangement from others; restricted range of affect; sense of a fore-shortened future</li> </ul>
D. Hyperarousal symptoms (two or more)
<ul style="list-style-type: none"> <li>• Sleep disruption; impaired concentration; irritability or anger outbursts; hypervigilance; exaggerated startle reaction</li> </ul>
E. Minimum symptom duration of 1 month
F. Symptoms cause distress or functional impairment
Specifiers:
<i>Acute</i> : Symptom duration from 1 to 3 months
<i>Chronic</i> : Symptom duration greater than 3 months
<i>Delayed onset</i> : Symptom onset at least 6 months after the stressor

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1 American Psychiatric Association. Diagnostic and Statistical Manual for Mental Disorders, 4th edition. Washington, DC: American Psychiatric Press. 1994.

**Table 1b. ICD-10 Classification of Mental and Behavioral Disorders (ICD-10:DCR-10)<sup>1</sup> for Posttraumatic Stress Disorder**

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A.	The patient must have been exposed to a stressful event or situation (either short- or long-lasting) of exceptionally threatening or catastrophic nature, which would be likely to cause pervasive distress in almost anyone.
B.	There must be persistent remembering of ‘reliving’ of the stressor in intrusive ‘flashbacks’, vivid memories or recurring dreams, or in experiencing distress when exposed to circumstances resembling or associated with the stressor.
C.	The patient must exhibit an actual or preferred avoidance of circumstances resembling or associated with the stressor which was not present before exposure to the stressor.
D.	Either of the following must be present: <ul style="list-style-type: none"> <li>(1) inability to recall, either partially or completely, some important aspects of the period of exposure to the stressor;</li> <li>(2) persistent symptoms of increased psychological sensitivity and arousal (not present before exposure to the stressor), shown by any two of the following:                 <ul style="list-style-type: none"> <li>(a) difficulty in falling or staying asleep</li> <li>(b) irritability or outbursts of anger</li> <li>(c) difficulty in concentrating</li> <li>(d) hypervigilance</li> <li>(e) exaggerated startle response.</li> </ul> </li> </ul>
E.	Criteria B, C and D must all be met within 6 months of the stressful event or of the end of a period of stress. (For some purposes, onset delayed more than 6 months may be included, but this should be clearly specified).

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<sup>1</sup> Pocket Guide to the ICD-10 Classification of Mental and Behavioral Disorders. World Health Organization. American Psychiatric Press, Washington, DC. 1994;168-169.

**FURTHER READING:**

PTSD occurs in approximately 8% of the population and follows a chronic course in up to 50% of subjects (Kessler et al, 1995; Breslau et al, 1991; Kessler et al, 2000). A range of traumas may precede PTSD (e.g. interpersonal violence, motor vehicle accidents, natural disasters) and are highly prevalent throughout the world. According to the most recent major US epidemiological survey, as much as 12% of the population has active PTSD lasting over 20 years’ duration (Breslau et al, 1998; Kessler, 2000), and rates appear to be equally high in other parts of the globe. Given data that a significant number of cases of PTSD are under-diagnosed and under-treated, it is important to inquire about exposure to trauma, and to maintain a high level of awareness of the disorder. Receipt of treatment is associated with an overall shorter course of PTSD (LOE 3) (Kessler et al, 1995).

PTSD is associated with significant morbidity and comorbidity. Recent studies show greater levels of disability, use of welfare, use of prescription medication and healthcare visits, as well as work impairment, to as much as four days per month (Amaya-Jackson et al, 1999; Greenberg et al, 1999; Kessler, 2000). Individuals with PTSD also demonstrate impaired resilience with greater difficulty coping with stress and adversity when compared to the general population, primary care outpatients and those with depression or

other anxiety disorders.(Connor and Davidson, 2003). Increased rates of attempted suicide have been noted in PTSD, and the adverse physical health consequences related to PTSD are enormous (Davidson et al, 1991; Boscarino, 1997). There is mounting evidence that PTSD is a risk factor for medical illness (Schnurr & Green, 2004).. Among all anxiety disorders, PTSD was found to be the most costly with, among other things, substantial work loss and/or cutback (Greenberg et al, 1999). PTSD is poised to become a major public health problem world-wide (Davidson, 2001). Projections from the World Health Organization suggest that in the next 20 years the global burden associated with PTSD will increase dramatically, with road traffic accidents, war-related injuries, and other violence – traumas widely associated with PTSD - are among the top 12 causes of disability worldwide (Murray and Lopez, 1997).

The particular response to any traumatic event reflects multiple factors including the subjective reaction of the individual and symptom severity in a particular patient, therefore it requires individual assessment, for assessing trauma and response to the event.

## **Node 2: Consider at Diagnosis and at Each Evaluation**

Particular symptoms associated with PTSD and comorbid psychiatric or medical diagnoses (particularly depression and other anxiety disorders) in patients being evaluated for PTSD may complicate proper diagnosis and alter treatment. Initially, the patient should have a full psychiatric and medical history with appropriate consideration of referral for lab and physical exam if indicated. As part of the initial diagnostic evaluation, and after each subsequent treatment trial if the response is unsatisfactory, the clinician should evaluate symptoms associated with PTSD (e.g. suicidality, insomnia or nightmares, psychosis), comorbid diagnoses (including depression, bi-polar disorder, other anxiety disorders, substance abuse), as well as other issues such as medical illness, pregnancy, ongoing trauma, and litigation issues, confounding undiagnosed medical illness (e.g., thyroid disease), ongoing use of anxiety producing substances such as caffeine, and problematic adherence to treatment. Those with PTSD, with and without depression, are at increased risk for suicidality, and it is important to assess suicide risk both at the initial evaluation and subsequent follow up visits. In general, a thorough review of the differential diagnosis of the anxiety symptoms should be done, ruling out or treating co-present psychiatric diagnoses and medical causes.

### **FURTHER READING:**

Numerous studies have reported increased rates of a wide range of medical disorders in trauma survivors and PTSD, including hypertension, respiratory distress, peptic ulcer, musculoskeletal disorders (Davidson et al, 1991; Boscarino, 1997) and greater health care utilization (Amaya-Jackson et al, 1999). Schnurr and Greene (1994) consider PTSD to be a mediator of poor health. It is important to recognize and treat other comorbid disorders early in the course of the assessment. Patient safety is a crucial concern and clinicians should evaluate the threat of harm by others to the patient and family members, such as in the setting of incest or domestic violence. Dangerousness to self or others is particularly important to assess, given the risk of aggression, impulsivity, and suicidal behavior in PTSD. Psychosocial factors and high risk health behaviors can also have a tremendous impact on immediate and long-term functioning. In particular, certain traumas can place individuals at increased risk for additional health problems, as demonstrated by the increased risk of hepatitis B and C and HIV transmission following sexual trauma. Thorough assessment of social support is also important, as the presence of social supports predicts improved outcome (Brewin et al, 2000).

## **A. SUICIDALITY**

Increased rates of attempted suicide have been reported in PTSD patients even among those without depression. (Davidson, et al. 1991.) (LOE 3) This elevated rate of attempted suicide has been reported (Horowitz, 1986) in traumatized patients. Cluster B personality features or disorder, total number of PTSD

symptoms, depression, substance use problems, attention deficit hyperactivity disorder and lack of social support are additional risk factors for suicidality that need to be considered. Patients who are suicidal need to be treated in an environment where they will be safe from immediate self-harm and where adequate pharmacotherapeutic and psychosocial treatment as well as attempts to build and engage social support can be initiated. Although suicidal patients are typically excluded from controlled trials, it would be rational to begin standard first-line antidepressants for PTSD in these patients. While rare, there is the possibility of early activation or agitation in the first few days when an antidepressant is given, with the result that it may provoke suicidal or aggressive behavior.

## **B. CO-MORBID DIAGNOSIS**

Other symptoms and comorbid psychiatric or medical diagnoses can often present in patients being evaluated for PTSD and may complicate proper diagnosis and alter treatment. Initially, the patient should have a full psychiatric and medical history with appropriate consideration of referral for lab and physical exam if indicated. As part of the initial diagnostic evaluation, and after each subsequent treatment trial if the response is unsatisfactory, the clinician should look for commonly co-present psychiatric conditions such as depression and other anxiety disorders and for confounding insomnia, psychosis or substance abuse, as well as undiagnosed medical illnesses (e.g., thyroid disease), and ongoing use of anxiety producing substances such as caffeine.

Although PTSD begins after trauma by definition, that trauma may play a causal role in a range of other disorders (Kendler et al, 1999), and PTSD is often accompanied by other comorbid disorders. In the National Comorbidity Survey (NCS), major depression was the most common comorbid disorder in PTSD (Kessler et al, 1995), and similarly high rates of depression are found in clinical samples of PTSD (Shalev et al, 2000). Patients with PTSD and depression are more distressed, have more role impairment, and are more likely to report suicidal ideation (Brady et al, 2000). Other common comorbid disorders in PTSD include substance use disorders, and anxiety disorders (Kessler et al, 1995; Brady et al, 2000).

From the perspective of an algorithmic approach to the management of PTSD, the first line pharmacotherapy for PTSD, SSRI's, are thought to be useful whether or not comorbidity with depression and anxiety disorders are present. Certainly, several of the positive SSRI trials in PTSD have included large numbers of subjects with comorbid depression. Similarly, cognitive-behavioral therapy can be used for PTSD with comorbid depression and anxiety disorders, although there is less data in this area (LOE 4), and the form of the therapy may need to be altered to address the range of symptoms found.

On the other hand, comorbidity of certain other disorders requires an adjustment in therapeutic approach. In patients with comorbid substance use, it may be important to initially target the substance use disorder. In patients with comorbid bipolar disorder it is important to ensure that a mood stabilizing agent is used before an antidepressant is begun. Thus a careful evaluation for comorbidity is needed prior to initiation of treatment, and the choice of treatment in patients with comorbidity needs to be formulated with appropriate clinical judgment.

## **C. INSOMNIA OR NIGHTMARES**

Insomnia is a symptom of an underlying disorder or condition that may have medical, psychiatric or behavioral origins.

Sleep disruption characterized by insomnia and nightmares are core symptoms of PTSD, and may therefore respond to standard first-line interventions. However, the sleep disturbance or nightmares often persist despite treatment with some SSRI agents and may even be exacerbated by these medications

(Meltzer-Brody, et al 2000; Davidson et al, 2002). Under such circumstances, we recommend first assessing lifestyle factors, such as over the counter medications or heavy caffeine use, which may be contributing to the sleep disturbance. The addition of the alpha<sub>1</sub> adrenergic antagonist prazosin can be quite effective in ameliorating nightmares and insomnia in PTSD (LOE 2, 3) (Raskind et al, 2002; Raskind et al, 2003). Hypotension, syncope and tachycardia are potential side-effects with prazosin, to wit, the patient's pre-disposition to and risk from hypotension should be considered and blood pressure monitoring utilized if prazosin is prescribed. Other pharmacologic options include nefazodone (LOE 2), low dose sedating tricyclic antidepressants (LOE 4), mirtazapine (LOE 4), trazodone (LOE 4), olanzapine (LOE 4), quetiapine (LOE 4) or zolpidem (LOE 4) at night (Davidson, 1990; Hertzberg et al, 1996; Taylor, 2003; Stein et al, 2002; Hamner et al, 2003; Dieperink and Drogemuller, 1999). The role of the benzodiazepines here is less clear and while they may be helpful in reducing hyperarousal symptoms during treatment, they do not appear to confer any additional benefit with respect to the course of PTSD (LOE 2, 3)(Mellman et al, 2002; Gelpin et al, 1999; Braun et al., 1990). Despite evidence for tiagabine's effectiveness in improving sleep (LOE3), risk of seizures has led us to exclude it from the first line recommendations for treating insomnia in patients with PTSD.

One nonpharmacologic approach which has shown promise in decreasing nightmares and in improving overall PTSD symptom severity is imagery rehearsal therapy (LOE 1) (Krakow et al, 2001).

In the event of continued poor response, sleep-related breathing disorders such as obstructive sleep apnea (OSA), periodic limb movement disorder or other sleep disorders should be considered and, if appropriate (Krakow et al, 2001) based on clinical features, a polysomnogram obtained. If OSA is confirmed, then treatment with continuous positive airway pressure (CPAP) is indicated (LOE 4). If the test does not reveal an obvious cause, an alternative medication may be selected from the above list.

## **D. PSYCHOSIS**

Psychotic features may be found in as many as 40% of PTSD patients (Hamner et al, 1999), with commonly reported symptoms including hallucinations, delusions, and paranoid ideation. It is essential, at the outset to determine whether such psychotic features are best explained as part of the overall PTSD syndrome or whether they are most consistent with a comorbid psychotic disorder. If the former, treatment for PTSD should be initiated with SSRIs with the recognition that in many cases, these individuals may not adequately respond to those medications. Flashbacks, hyper-vigilance/paranoia, and dissociation can all manifest with psychotic features. For these, antiadrenergics and anticonvulsants are believed to be beneficial (LOE 4). Failure to respond to such agents would suggest using augmentation with atypical antipsychotics. Indeed, fearful, paranoid, hyper-vigilant and psychotic patients might benefit from atypical antipsychotics.

If, on the other hand, PTSD is comorbid with a psychotic disorder, augmentation with atypical antipsychotics should be considered from the beginning.

Much work in this area has focused on augmentation of SSRI's with atypical antipsychotics. The presence of psychotic symptoms may call for addition of an atypical neuroleptic, with evidence being limited so far to risperidone (LOE 2), olanzapine (LOE 3) and quetiapine (LOE 3), studies of which appear largely limited to combat veterans (Monnelly et al, 2003; Hamner et al, 2003; Stein et al, 2003; Hamner et al, 2003; Bartzokis et al, 2005), and to one study in civilians (Reich et al, 2004) at the present time. Further, the evidence is mixed, in that some drugs may have not always separated from placebo (e.g. Butterfield et al, 2001) or have done so only on limited dimensions (e.g. psychotic symptoms (Hamner et al, 2003) or on sleep and mood (e.g. Stein et al, 2003). Inadequate response to the first antipsychotic could be followed by switching to a different medication. If that fails, then diagnostic re-evaluation is suggested. The spe-

cific atypical neuroleptic medication should be chosen after considering the risk of side effects such as weight gain, aggravation of diabetes, metabolic syndrome, hyperlipidemia, or hyperprolactinemia. The atypical antipsychotics, aripiprazole and ziprasidone, may possibly have a more favorable side-effect profile and could, theoretically, be used in the treatment of PTSD, but no data exist (LOE 4).

## **E. SUBSTANCE ABUSE**

### **(i) Patients with Current or Recent Substance Dependence or Abuse**

The patient is first required to undergo withdrawal from his or her substance(s) of abuse/dependence. The patient must make a commitment to abstain from future use of these substances. Of course, he or she may not succeed in meeting this commitment, and compliance with this commitment must be monitored closely. Algorithm recommendations (and their associated evidence base) will not be relevant to patients returning to active drug dependency or abuse. As a general principle with such patients, use conservative and less complicated regimens when possible. Early use of SSRI's may benefit these patients, although the largest (LOE 2) trial showed no greater benefit from sertraline than placebo (Brady et al, 2005). Comorbidity of substance abuse and PTSD is a relative contraindication for the use of benzodiazepines except as part of a withdrawal/detoxification program from alcohol or sedatives.

For the algorithm's recommendations to apply, the patient should have completed withdrawal from his or her drug of dependence and from any pharmacotherapy used for withdrawal, and be abstinent for at least one additional week. This appears to be the minimum time after which drug-placebo differences have been demonstrated in the treatment of anxiety and depressive disorders that persist following, for example, alcohol withdrawal (Kranzler et al., 1994; Mason et al., 1996). Symptoms present after abstinence of less than a week may be due in part to the residual effects of the substance. If symptoms appear to be diminishing over the first week of sobriety, and there is no history of these symptoms prior to onset of the substance abuse/dependency or during previous periods of extended sobriety, it is reasonable to wait at least another week before initiating pharmacotherapy.

Withdrawal from some substances can be prolonged, and the residual effects of their presence can affect subsequent medications that may be given. For example, methadone has a half-life of about two days and its effects as an inhibitor of cytochrome P450 2D6 could therefore persist for more than a week.

A group not specifically addressed in this algorithm is individuals who use drugs of abuse but who do not meet DSM-IV criteria for abuse or dependence. Should the sequence of treatments for these "recreational" users be any different from the standard approach? These frequently encountered patients have received little research attention.

### **(ii) Patients with History of, But No Current, Substance Dependence or Abuse**

If the patient is not actively dependent upon or abusing substances presently but has a history of such dependence or abuse, this problem may require relapse prevention treatment. The patient may have recently been detoxified, be under unusual stress, or may be experiencing strong cravings for his or her substance and are therefore at high risk of relapse. This would suggest that management of this problem would be at least as high, if not a higher, priority for treatment compared with treating the PTSD.

If the patient's problem is with alcohol, evidence-supported pharmacotherapy options could include (Sri-surapanont and Jarusuraisin, 2005) naltrexone (O'Malley, 1995), acamprosate (Verheul et al, 2005), or topiramate (Johnson et al, 2004), (All LOE 1 for the index disorder) Topiramate has also been reported helpful for PTSD (Berlant et al, 2002) (LOE 4) and with more research may emerge as a particularly good choice for the patient with comorbid alcohol craving and PTSD. (LOE 4)

Disulfiram may be of value for prevention of relapse in cocaine dependent patients (Carroll et al, 2004). [PTSD (LOE 4); cocaine (LOE 2)].

All pharmacotherapy options for substance abuse/dependence seem to work best in the context of ongoing intensive, structured psychotherapeutic treatment focused on abstinence, compliance and relapse prevention (O'Malley, 1995). Indeed, without such treatment, pharmacotherapy may not be better than placebo.

If the patient with the history of substance abuse has been assessed (and treated if appropriate), the clinician may then follow the PTSD algorithm starting with the recommendations at nodes 1-3. The clinician's vigilance towards detecting comorbid substance abuse needs to be continued through-out treatment.

## **F. TREATMENT NON-ADHERENCE**

Clear explanation about the expected effects of medication and how to deal with problems which arise is essential at the initiation of any new medication. Non-adherence rates to antidepressants in depression can be as high as 50% at 3 months (Lin et al, 1995; Lin et al, 2003). Shemesh et al (2000; 2001; 2004) have demonstrated that patients (adults, secondary to myocardial infarction and children, secondary to liver transplantation) with PTSD have high rates of medication non-adherence. In the presence of non-response, the physician should consider whether non-adherence is at the root. Lin et al have suggested a number of strategies to help improve adherence in depression. The following educational messages to patients may also prove helpful in adherence in PTSD : 1) take the medication daily; 2) antidepressants must be taken for 4-6 weeks for a noticeable effect; 3) continue to take medicine even if you are feeling better; 4) do not stop taking an antidepressant without checking with your physician; 5) specific instructions regarding what to do to resolve questions concerning medication; and (6) scheduling of pleasant activities. However, issues unique to PTSD should also be considered, such as the fact that a patient is often reluctant to be in treatment, blaming his or her plight on the unwelcome trauma.

## **G. ONGOING TRAUMA**

It is generally believed that recovery is unlikely as long as the patient continues to experience the trauma, such as with continued exposure to abusive violence in a relationship (LOE 4). This opinion is an extrapolation from the Cognitive behavioral therapy (CBT) literature. Intervention to provide an environment safe from ongoing trauma is essential. It is not known, however, whether medication can even ameliorate PTSD symptoms of patients who remain in an abusive or dangerous environment.

## **H. ISSUES RELEVANT TO WOMEN OF CHILDBEARING POTENTIAL**

### **Post Traumatic Stress Disorder in Pregnancy and the Postpartum Period**

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The prevalence and course of Post Traumatic Stress Disorder (PTSD) during pregnancy and the postpartum period has received sparse attention. The majority of reports have documented traumatic obstetrical experiences, e.g., labor, delivery, miscarriage, fetal demise, stillbirth, etc., as precipitants of trauma-related symptomatology. An initial study assessing the incidence of PTSD following 'normal' childbirth found that 3% (Czarnocka and Slade 2000) had clinically significant symptoms in all dimensions of PTSD. Similarly, a second study excluding women with pre-existing symptoms found that 2.8% fulfilled diagnostic criteria for PTSD at 6 weeks postpartum, decreasing to 1.5% by 6 months postpartum (Ayers

and Pickering 2001). Whether these percentages represent an increase in PTSD or simply the incidence of new onset PTSD in a cohort of women of childbearing age is obscure. Notably, one group found that stress-related symptoms in the postpartum period were associated with the occurrence of two or more pregnancy complications and depression during pregnancy (Cohen MM et al 2004). More recent investigations have sought to determine the impact of severe stressful life events on pregnant women, e.g., those living in metropolitan New York during the 9/11 attack. A recent prospective study (Loveland-Cook CA et al 2004), found that 7.7% of pregnant women met diagnostic criteria for PTSD. The majority of these subjects had comorbid mood and/or other anxiety disorders. It is remarkable that only 12.3% of the pregnant women with PTSD had sought treatment in the preceding 12 months.

The course of pre-existing PTSD during pregnancy remains an enigma. However, given the high rate of comorbidity, prenatal alterations in sleep architecture, and the neuroendocrine/psychosocial stress of pregnancy and childbirth, there is no reason to anticipate improvement of PTSD symptoms over the course of pregnancy and the postpartum period. Furthermore, depending on the obstetrical course and occurrence of complications, there appears to be an increase in new cases of PTSD in postpartum women.

The interface of these limited data with the available reproductive safety data on psychotropic medications and the proposed PTSD treatment algorithm, while empirical, provides a conservative modification for peri-natal PTSD management that reduces fetal/neonatal risk. These recommendations and their justification are summarized below:

1. In women of reproductive years, document method of birth control before initiating treatment.
2. During pregnancy and lactation, consider psychosocial treatments as first intervention.
3. When pharmacotherapy is indicated for pregnant or breast feeding women, use medications with published reproductive safety data, i.e., fluoxetine, sertraline, paroxetine, citalopram.
4. Maximize dose of monotherapy prior to any medication switch and/or adjunctive pharmacotherapy.
5. If the treatment response inadequate and adjunctive pharmacotherapy is indicated, some general rules should govern use in pregnant and/or breast feeding women: a) avoid valproate, MAOI's; b) avoid adrenergic agents; c) typical antipsychotic agents have more reproductive safety data than atypical agents – though the use of anticholinergic agents to manage extrapyramidal symptoms should be avoided; d) if benzodiazepines are indicated – clonazepam has considerable reproductive safety data, and alprazolam does not require hepatic metabolism.
6. If pharmacotherapy has already been used during pregnancy, do not decrease or switch medications for breast feeding.
7. All women who experience obstetrical complications, traumatic delivery, or fetal/neonatal loss should be evaluated for symptoms of PTSD.
8. Document method of birth control in breast feeding women.

## **I. CULTURAL ISSUES**

It has been suggested that PTSD is characterized not by a normal stress response, but rather by pathological sensitization of particular psychobiological systems (Yehuda and McFarlane, 1995). It is not surprising therefore that there is a good deal of evidence demonstrating that PTSD symptoms are similar in different historical eras and in different cultures (Marsella et al, 1996). At the same time, it is important to

acknowledge that types of trauma differ across cultures, and that PTSD may be experienced and expressed differently in different societies (Njenga et al, 2004).

Friedman and Marsella (1996), for example, suggest that while the re-experiencing and hyperarousal symptoms of PTSD are universal, the avoidant and numbing symptoms are more likely experienced in those ethno-cultural settings where avoiding and numbing behaviors are common expressions of distress. There may also be cross-cultural variation in extent of dissociation and somatization after trauma (Stamm and Friedman, 1999). Cultural and social factors may be important determinants of vulnerability to PTSD by shaping concepts of what constitutes a trauma, and by affecting known vulnerability factors such as early childhood experiences, comorbidity (e.g. alcohol abuse), and social resources for responding to trauma. Once again, however, many of these questions remain open for future rigorous empirical research (Marsella et al, 1996).

Nevertheless, a strong theoretical argument can be provided to the effect that particular cultural rituals, performed after exposure to trauma, do play a role in preventing PTSD (Shay, 1994). Conversely, it is possible to speculate that repression of trauma narratives in certain cultures exacerbates posttraumatic suffering. An interesting experiment at a national level recently took place in South Africa, where a Truth and Reconciliation Commission encouraged the public acknowledgment of past gross human rights violations (Stein, 1998). Although rates of PTSD were no lower in those who gave testimony, there was a relationship between increased psychopathology and decreased forgiveness. Other work has indicated that there may be a therapeutic effect of bearing witness to past human rights violations (Weine et al, 1998).

Given that the psychopathology of PTSD frequently involves not only discrete symptoms, but also a broader questioning of the self and of identity, understanding the patient's socio-cultural background is particularly important. Several authors have emphasized that inadequate appreciation of the socio-cultural context of trauma and of responses to trauma may impede the therapeutic process. On the other hand, a comprehensive and sensitive assessment of this context may allow appropriate individual and community interventions which promote symptomatic improvement as well as broader healing.

Several symptom rating scales have been used in multiple social and cultural contexts. These include the clinician-rated Clinician Administered PTSD Scale (CAPS) (Weathers et al, 2001), the Composite International Diagnostic Interview (CIDI, Kessler et al, 1995) and the patient-rated Harvard Trauma Questionnaire (HTQ) (Klein et al, 2001).

There is increasing understanding of the inter-individual differences that affect maximum tolerated dose. For example, variants of the cytochrome P450 may affect metabolism of the SSRI's. Particular variants may be more common in certain ethnic groups (Nasrallah, 2005).

Experienced clinicians in Africa suggest that Africans respond to much lower doses of tricyclics in the treatment of depression (50-150 mg) and that are also very sensitive to the side effects-(LOE 4). Generalizing from pharmacokinetic research, Lin et al (1996) suggest that Asians may also respond to lower doses of psychotropic medication than Caucasians.

Financial and formulary constraints often limit the use of a number of the medications suggested, but in ways which vary from one country to another.

## J. LITIGATION ISSUES

If a patient is involved in legal action related to a traumatic event, it is quite likely that symptoms will be exacerbated on occasions when the traumatic event has to be recalled, especially when circumstances are adversarial. Moreover, if the survivor believes that compensation is essential to recovery, this may influence the extent of response to pharmacotherapy. (LOE 4). However, no empirical data exist on this matter.

## K. PSYCHOSOCIAL TREATMENT

The first choice to be made is whether to offer medication, psychosocial treatment or both. Each type of treatment alone has been shown to be efficacious. (LOE 1) Psychosocial treatment if not used initially can be added to or can replace pharmacotherapy. However, with one exception (Rothbaum et al., 2003), we are unaware of any empirical data to support the augmentation of medication with a psychosocial treatment.

Cognitive behavioral therapy (CBT), prolonged exposure (PE) and other psychosocial treatments, such as eye movement desensitization and reprocessing (EMDR), are of proven efficacy (LOE 1) in PTSD (Foa, Keane and Friedman, 2000), and are credible first (or subsequent) choices, provided that a qualified therapist is available and that the patient is willing to make the necessary efforts (willing to do homework and potentially experience more distress).

Similarly, the patient given medications must be willing to work through potential side-effects with the clinician and wait for several weeks for major benefits and have no medical contra-indications to the use of the medication.

Patient preference and the availability of qualified therapists will influence the modality of treatment.

One nonpharmacologic approach which has shown promise in decreasing nightmares and in improving overall PTSD symptom severity is imagery rehearsal therapy (LOE 1) (Krakow et al, 2001).

### **Node 3: SSRI or SNRI (or TCA if unavailable): Four-to-six-week evaluation with adequate dosage and duration and no intolerance**

Following a diagnosis of PTSD, the recommended first line pharmacological intervention is an SSRI (sertraline, paroxetine, fluoxetine), based on strong Level 1 evidence (Brady et al, 2000; Davidson et al, 2001; Marshall et al, 2001; Tucker et al, 2001; Connor et al, 1999; Martenyi et al, 2002; van der Kolk et al 1994). The starting dose can be low (fluoxetine 10mg.; sertraline, 25mg; paroxetine, 10mg.) reflecting a subset of patients with exaggerated sensitivity to somatic anxiety cues or the doses used in the trials (fluoxetine 20mg.; sertraline, 25-50 mg; paroxetine, 20mg). While other drugs in these categories may be beneficial, such as citalopram (LOE 3) (Seedat et al, 2001), fluvoxamine (Davidson et al, 1993; Escalona et al, 2002), there is no evidence at all in the case of escitalopram (LOE 4).

Based on published data, statistically and clinically significant improvement is often seen with the SSRI's by weeks 2 to 4 in the major studies. One study by Davidson et al (2002) noted a marked improvement in anger/irritability after one week on sertraline, which may be a useful prognosticator of eventual response (LOE 1) (Davidson et al, 2004). An adequate trial requires 6-12 weeks, but the clinician should expect some response after 4-6 weeks with adequate dosage. A study of bupropion (LOE 2) showed no difference between the drug and placebo (Davis et al, 2005).

Two recent large trials suggest promise for the SNRI venlafaxine. The results are published as of this date only as abstracts (Davidson et al., 2004a; 2004b). Hypertensive and other cardiovascular side-effects, particularly at high doses may be a limitation.

Small trials of the NaSSA agent mirtazapine (LOE 2, 3) (Connor et al, 1999; Davidson et al, 2003) also show efficacy in PTSD.

The older antidepressants, such as tricyclic antidepressants (TCA's) and MAO inhibitor (MAOI) drugs, are of demonstrated efficacy in combat veterans with PTSD (LOE 2)(Davidson et al, 1990; Kosten et al, 1991). In locations where formulary or cost considerations preclude the use of SSRI's or SNRI's, the tricyclics imipramine or amitriptyline may be considered first line treatments. Aside from two trials of reversible MAOI's with mixed results in civilians and combat veterans (LOE 1) (Baker et al, 2000; Katz et al, 1995), the TCA and MAOI drugs have not been studied in controlled trials in civilian samples, in part because of the advent of the SSRI's in recent years. Issues of toxicity have also been a concern with these drugs, in terms of cardiotoxicity, seizure risk, and anticholinergic effects with the TCA's and dietary restrictions and risk of hypertensive crisis with the MAOI's. Considering the levels of evidence in the face of their safety profiles, we do not recommend MAOI'S as first line treatments.

One clear advantage of the antidepressants is their well-established efficacy in treating major depression and other anxiety disorders which are frequently comorbid with PTSD. However, as noted above, these drugs can be associated with troublesome side effects. For example, common side effects with the SSRI's include nausea, loose stools, headache, insomnia and agitation with initial treatment and, over the long term, weight gain and sexual dysfunction.

#### **Node 4: Response**

Response to treatment after a trial period is described as **adequate-**, **partial-** or **non-response**. After 12 weeks of treatment :

**Non-response:** minimal (less than 25%) or no improvement. Very little reduction in symptoms.

**Partial response:** 25-50% or more reduction in symptoms.

**Adequate response:** at least a 50% improvement—at a 50% reduction in symptoms or a rating of 1 or 2 (very much or much improvement) on the Clinical Global Impressions of Improvement scale (CGI-I. see Assessment Tools for PTSD).

After 3-6 months of treatment, or longer, many patients will attain a state of remission, which is indicated by at least a 70% reduction in symptom severity relative to pre-treatment (i.e. “70% better”) and is considered to be the treatment goal for PTSD. Clinical remission would correspond to a CGI-I score of 1.

#### **Node 5: Continue at least one year**

After 12 weeks of treatment, many patients will experience improvement, with at least a 50% reduction in symptoms. However, further improvement is often noted with continued treatment, with additional improvement in the core PTSD symptoms, disability, and overall functioning. Three studies have demonstrated robust relapse-prevention effects for sertraline (Davidson et al 2000) and fluoxetine (Marrtenyi et al, 2002; Davidson et al, 2005) when these treatments are continued for one year. (LOE 1) After 6 months, we would be looking to see a 70% reduction in symptoms, representing a state of remission. If symptoms persist and this goal is not attained, refer to the algorithms above according to the symptoms present. Because chronic PTSD has a tendency to relapse or deteriorate in as many as 50% of patients if treatment is stopped, we recommend continuation of medication for at least a year. (LOE 1)

## **Node 6: Some symptoms remain unresponsive?**

If there is a partial response to treatment by 4-6 weeks, the second step would be to assess for the presence of persistent, non-responsive symptoms, determined by patient's symptom profile and comorbidity. Common symptoms and comorbidities include persistence of core PTSD symptoms (intrusion; avoidance, numbing, and hyperarousal), sleep disturbances, other PTSD symptoms e.g. irritability, hostility, aggression, panic, psychotic symptoms, bipolar spectrum disorder, and substance abuse. In addition, in some individuals, the SSRI's may be somewhat anxiogenic. Patients with anxiety disorders are often more sensitive to these effects and in some cases a lower starting dose or slower titration may be indicated.

At this stage the clinician will need to consider whether to make a change in pharmacotherapy or to persist at the same (therapeutic) dose, since there is evidence (Londborg et al, 2001) that non-responders to sertraline at 12 weeks may convert to responders after 4-6 months of treatment.

## **Node 7: Augment according to salient symptoms**

After 4-6 weeks of treatment with an appropriate dose of an SSRI (sertraline, 150 mg, fluoxetine 40 mg), if there is a partial response, the clinician should assess on-going symptoms and treat accordingly with augmentation by a second agent—e.g., prazosin (LOE 2); trazodone (LOE 3), nefazodone (LOE 2) (Davis et al, 2004), imipramine (LOE 2), or amitriptyline (LOE 2) in low doses. Any of these treatments can benefit not only sleep disturbance, but also other aspects of PTSD (LOE 2). In some instances, while there are no published guidelines, the clinician may choose to increase the dose and augment simultaneously. It is important to establish that symptoms are not due to anxiogenic effects of treatment.

Most clinical trials with medication for PTSD have tested the efficacy of monotherapy with one pharmacological agent or another. Indeed, with the exception of trials with atypical antipsychotics, there are no clinical trials that have systematically evaluated the relative effectiveness of different augmentation strategies. Therefore, our recommendations for augmentation strategies for partial responders are extrapolations from monotherapy trials.

## **Node 8: Adjust to maximum tolerated dose (Table 3)**

If there is a partial response to an adequate dose of an SSRI (sertraline, 150 mg, fluoxetine 40 mg), suggesting that the initial treatment was somewhat helpful but the clinical response was less than adequate, the dose should be titrated to the maximum suggested dose (sertraline 200mg; paroxetine, 50 mg. fluoxetine, 60 mg.) (see Table 3).

## **Node 9: Switch within SSRI class or between classes (SNRI, TCA, or $\alpha$ 1AA)**

After failure of response (i.e. less than 25% improvement) to an SSRI with core PTSD symptoms persistent after 4-6 weeks with an adequate dose (e.g., fluoxetine 40 mg/day, sertraline 150 mg/day), the clinician should switch to another SSRI, SNRI, NaSSA, tricyclic or prazosin, or alternatively augment the same medication with another pharmacotherapeutic agent, even though there are very limited data on augmentation and none on switching to SNRI/NaSSA, or SNRI to NaSSA (all LOE 4). Further, data are not available as to whether a sequential trial of a second SSRI is as effective as switching to an SNRI or NaSSA after the first unsuccessful SSRI trial.

**Node 10: Response after six to twelve weeks?**

If the dosage is already at the maximum and symptoms persist, it is time to introduce a second treatment, while maintaining the initial medication as prescribed. The next course of action will be determined by the presence or absence of specific symptoms and comorbidities, including the persistence of core PTSD symptoms (intrusion; avoidance, numbing, and hyperarousal), sleep disturbances, other core PTSD symptoms, psychotic symptoms, bipolar spectrum disorder, and substance abuse. Sometimes the choice of an augmentation agent may be driven more by clinically significant symptoms, as illustrated by the recommendations for insomnia, psychosis, and substance abuse (see nodes 15, 20, and 24). Here, the empirical basis for choosing one agent over another is not very solid, therefore the following suggestions are based more on clinical lore and known pharmacological actions. For example, patients exhibiting excessive arousal, hyper-reactivity, and, possibly, dissociation, might benefit from the addition of an antiadrenergic agent. Patients exhibiting aggressive, impulsive, or labile behavior might benefit from an anticonvulsant/mood stabilizer. Fearful, paranoid, hypervigilant, and psychotic patients might benefit from an atypical antipsychotic. Treatment success (or failure) will be determined by the adequacy of the clinical response and side-effects.

**Node 11: Inadequate response to core PTSD symptoms -- Switch to another SSRI or to SNRI or from SNRI to NaSSA**

If there is inadequate response of core PTSD symptoms to 6-12 weeks of treatment with a maximum recommended and tolerated dose of an SSRI (e.g., fluoxetine 60 mg; sertraline, 200 mg) (see Table 3), the clinician should switch, for example, to another SSRI or to an SNRI, or from an SNRI to a NaSSA, or to a tricyclic drug or prazosin. At present, there are no published data on any of these strategies (LOE 4). Further, data are not available as to whether a sequential trial of a second SSRI is as effective as switching to an SNRI or NaSSA after the first unsuccessful SSRI trial.

**Node 12: Response -- see Node 4 above.****Node 13: Add TCA, AAP, anticonvulsant,  $\alpha$ 1AA,  $\alpha$ 2A, BDZ,  $\beta$ -blocker, or azipirone; CBT**

Most clinical trials with medication for PTSD have tested the efficacy of monotherapy with one pharmacological agent or another. Indeed, with the exception of trials with atypical antipsychotics, there are no clinical trials that have systematically evaluated the relative effectiveness of different augmentation strategies. Therefore, our recommendations for augmentation strategies for partial responders are extrapolations from monotherapy trials. For example, if a patient fails to respond to an SSRI, we recommend augmentation with an agent that has proven itself as an effective monotherapy agent. As a result, our first recommended set of options for augmentation includes: TCA, prazosin, atypical antipsychotics, etc. Lack of responsiveness to such medications might suggest further augmentation with an agent for which the level of evidence is less strong: anticonvulsants, clonidine, guanfacine, propranolol.

Sometimes the choice of an augmentation agent will depend on the presence of comorbid disorders. The presence of comorbid affective or anxiety disorders would suggest utilization of a medication that is effective for both PTSD and for that disorder (e.g., an antidepressant for comorbid PTSD and depression).

Partial response may be managed by augmentation, particularly for aggression, with the following medications: prazosin (LOE 2), divalproex sodium (LOE 3) or risperidone (LOE 2), lamotrigine (LOE 2), trazodone (LOE 3) for insomnia/nightmares; or atypical antipsychotics [risperidone (LOE 2), olanzapine,

quetiapine, (LOE 3)], buspirone (LOE 3), tiagabine (LOE 4), beta-blockers (LOE 4), and  $\alpha_2$  adrenergic agonists (LOE 4) for anxiety/agitation. Benzodiazepines can be used cautiously for panic in patients without substance abuse (LOE 4). No data exist as to the effects of benzodiazepines in augmentation treatment, although some data exist suggesting lack of efficacy for monotherapy with alprazolam in chronic PTSD (LOE 2)(Braun et al, 1990). Nonetheless, on occasion, benzodiazepines may be used adjunctively with other pharmacotherapy (LOE 4). Bupropion appears to be ineffective (LOE 2) (Davis et al, 2003). Trazodone may be effective (LOE 3) (Hertzberg et al, 1996), if all else fails, phenelzine can be considered in certain cases (Kosten et al, 1991) (LOE 2). Addition of Cognitive Behavioral Therapy (CBT) and Prolonged Exposure (PE) was found to enhance response in patients who had shown only partial improvement on sertraline (LOE 2) (Rothbaum et al, 2003).

**Node 14: Response -- see Node 4 above.**

**Node 15: Switch to TCA or MAOI or add third medication from above (Node 13) or re-evaluate diagnosis; consider PST**

If the patient has failed to achieve an adequate response, other options to consider are as follows, though data to support these recommendations are unavailable (LOE 4). Consider switching to TCA or MAOI or adding a third medication from the list above (node 12).

Before initiating treatment with an MAOI, due attention should be paid to the need for the appropriate medication-free period, if the patient has been receiving another antidepressant.

Efficacy has been shown for repetitive transcranial magnetic stimulation (rTMS) to the right dorsolateral prefrontal cortex in PTSD (LOE 2) (Cohen et al, 2004).

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*For PST see "K: Psychosocial Therapy" above.*

**Node 16: Treatment for inadequate response with persistent insomnia, nightmares -- Add  $\alpha_1$ AA, low-dose TCA, other sedating antidepressants**

Sleep disruption characterized by insomnia and nightmares are core symptoms of PTSD. The sleep disturbance or nightmares often persist despite treatment with some SSRI agents and may even be exacerbated by these medications (Meltzer-Brody, et al 2000; Davidson et al, 2002). Under such circumstances, we recommend first assessing lifestyle factors, such as over the counter medications or heavy caffeine use, which may be contributing to the sleep disturbance. The addition of the  $\alpha_1$  adrenergic antagonist prazosin can be quite effective in ameliorating nightmares and insomnia in PTSD (LOE 2, 3) (Raskind et al, 2002; Raskind et al, 2003). Hypotension, syncope and tachycardia are potential side-effects with prazosin; therefore, the patient's pre-disposition to and risk from hypotension should be considered and blood pressure monitoring utilized. In addition, it may take some time to build up to a therapeutic dose (4-9 mg), and little is known about the metabolism of prazosin, or its effects upon the cytochrome P450 isoenzyme system. Other pharmacologic options for which there is considerably less evidence, but which may be of benefit include trazodone (LOE 4), low dose sedating tricyclics (LOE 4), mirtazapine (LOE 4),

tiagabine (LOE 4), olanzapine (LOE 4), quetiapine (LOE 4) or zolpidem (LOE 4) at night (Davidson, 1990; Hertzberg et al, 1996; Taylor, 2003; Stein et al, 2002; Hamner et al, 2003; Dieperink and Droge-muller, 1999). The role of the benzodiazepines here is less clear and while they may be helpful in reducing hyperarousal symptoms during treatment, they do not appear to confer any additional benefit with respect to the course of PTSD (LOE 2, 3) (Mellman et al, 2002; Gelpin et al, 1999). Despite evidence for tiagabine's effectiveness in improving sleep (LOE 3), the side-effect profile, including risk of seizures, has lead us to exclude it from the first line recommendations for treating insomnia in patients with PTSD.

One non-pharmacologic approach which has shown promise in decreasing nightmares and in improving overall PTSD symptom severity is imagery rehearsal therapy (LOE 1) (Krakow et al, 2001).

**Node 17: Response -- see Node 4 above.**

**Node 18: Switch within group or switch to atypical antipsychotic**

If the response remains inadequate, consider switching to another augmenting agent within the same class or to an atypical antipsychotic (LOE 4).

**Node 19: Response -- see Node 4 above.**

**Node 20: Consider obstructive sleep apnea, restless legs syndrome, or other sleep disorders and re-evaluate diagnosis; consider PST**

In the event of continued poor response, polysomnography may be indicated to evaluate for suspected sleep-related breathing disorders and periodic limb movement disorders (Krakow et al., 2001). If obstructive sleep apnea (OSA) is confirmed, then treatment with continuous positive airway pressure (CPAP) is indicated (LOE 4). If the test does not reveal an obvious cause, an alternative drug may be selected from the above list.

*For PST see "K: Psychosocial Therapy" above.*

**Node 21: Inadequate response with comorbid psychosis -- Add AAP (or first generation AP if unavailable)**

It is important to distinguish between psychotic symptoms which are part of the PTSD complex vs those which signify a comorbid psychotic disorder. For the former, antiadrenergic, SSRI and anticonvulsant drugs are often beneficial (LOE 4). Failure to respond would then call for addition of an atypical antipsychotic. Indeed, fearful, paranoid, hypervigilant and psychotic patients might benefit from atypical antipsychotics. If, on the other hand, PTSD is comorbid with a psychotic disorder, then augmentation with atypical antipsychotics should be considered from the beginning.

Psychotic features may be found in as many as 40% of PTSD patients (Hamner et al, 1999), with commonly reported symptoms including hallucinations, delusions, and paranoid ideation. In many cases, these individuals may not adequately respond to SSRI's. As a result, much of the work done in the area has focused on augmentation of SSRI's with atypical antipsychotics.

The presence of psychotic symptoms which are part of PTSD would call for addition of an atypical neuroleptic, with evidence being limited so far to risperidone (LOE 2), olanzapine (LOE 3) and quetiapine (LOE 3), studies of which appear largely limited to combat veterans (Monnelly et al, 2003; Hamner et al,

2003; Stein et al, 2003; Hamner et al, 2003), and to one study in civilians (Reich et al, 2004) at the present time. Further, the evidence is mixed, in that some drugs may have not always separated from placebo (e.g. Butterfield et al, 2001) or have done so only on limited dimensions, e.g. psychotic symptoms (Hamner et al, 2003) or on sleep and mood (e.g. Stein et al, 2003). Inadequate response to the first atypical antipsychotic could be followed by switching to a different medication in the same class. If that fails, then diagnostic re-evaluation is suggested. The specific atypical neuroleptic should be chosen after considering the risk of side-effects such as weight gain, aggravation of diabetes, metabolic syndrome, hyperlipidemia, or hyperprolactinemia. Flashbacks, hypervigilance/paranoia, and dissociation can all manifest with psychotic features. For these, antiadrenergics and anticonvulsants are believed to be beneficial (LOE 4).

**FURTHER READING:**

PTSD remains a very challenging disorder to treat effectively. Often it requires the use of more than one psychotropic medication, with atypical antipsychotics being increasingly used. Mellman found that 17% of a statewide Medicaid PTSD population had received this form of treatment, a rate which was even higher when depression was also present. There is also growing evidence for efficacy of atypical antipsychotics as adjunctive treatments in PTSD (LOE 3). Thus, it is important to recognize their role in managing the disorder. While the new generation antipsychotics are less likely to produce extrapyramidal and acute cardiovascular side effects, as compared to the older generation drugs, there is concern about other problems, in particular weight gain, hyperglycemia, hyperlipidemia, diabetes, and long-term cardiac effects via the metabolic syndrome. Careful monitoring is therefore essential, and attention to recently published guidelines on the use of these drugs is recommended (e.g. Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes. *Journal of Clinical Psychiatry*, 2004;65:267-272).

Most clinical trials with medication for PTSD have tested the efficacy of monotherapy with one pharmacological agent or another. Indeed, with the exception of trials with atypical antipsychotics, there are no clinical trials that have systematically evaluated the relative effectiveness of different augmentation strategies. Therefore, our recommendations for augmentation strategies for partial responders are extrapolations from monotherapy trials.

**Node 22: Response -- see Node 4 above.**

**Node 23: Change antipsychotic or add mood stabilizer or anticonvulsant**

If the response remains inadequate, consider switching to another antipsychotic or adding a mood stabilizer or anticonvulsant (LOE 4).

Most clinical trials with medication for PTSD have tested the efficacy of monotherapy with one pharmacological agent or another. Indeed, with the exception of trials with atypical antipsychotics, there are no clinical trials that have systematically evaluated the relative effectiveness of different augmentation strategies. Therefore, our recommendations for augmentation strategies for partial responders are extrapolations from monotherapy trials.

**Node 24: Response -- see Node 4 above.**

**Node 25: Re-evaluate diagnosis; consider PST**

If response remains inadequate, consider diagnostic re-evaluation.

*For PST see “K: Psychosocial Therapy” above.*

## **Node 26: Inadequate response with comorbid depression, anxiety or stable bipolar disorder -- Add mood stabilizer, anti-convulsant, Lithium, or AAP**

Comorbid depression, anxiety and bipolar disorder are commonly found in association with PTSD. Common presentations in bipolar patients with PTSD may include mood lability, irritability, and aggression. In addition, in some instances, antidepressants used to treat PTSD may precipitate hypomania or mania in those predisposed to bipolar disorder. If the symptom picture suggests bipolar spectrum disorder, which can also be associated with PTSD, we recommend addition of either a mood stabilizer or anticonvulsant or an atypical neuroleptic. In terms of anticonvulsants and mood stabilizers, divalproex sodium/valproic acid, carbamazepine, topiramate or lamotrigine have been reported as efficacious in PTSD without comorbid bipolar features (Fesler, 1991; Petty et al, 2001; Lipper et al, 1986; Berlant and van Kammen, 2002; Hertzberg et al, 1996), again largely in combat veteran populations. There is no evidence (LOE 4) for their use in PTSD with comorbid bipolar disorder. Alternatively, we consider the use of atypical antipsychotics at this stage, even in the absence of supportive literature (LOE 4), given that the drugs separately are of benefit in bipolar disorder and in PTSD when associated with psychosis or mood disorder. Of note, some mood stabilizers and atypical neuroleptics may require periodic lab monitoring, e.g., blood levels of carbamazepine and valproic acid and for certain atypical neuroleptics, fasting lipid profile and fasting blood sugar.

The sequence of treatment will depend upon which syndrome is clinically the most salient. For stabilized bipolar disorder, the heretofore untreated PTSD will need addressing. For unstable bipolar disorder, this will need treating first.

For persistent PTSD with severe depression, it is possible that ECT may have value (LOE 4).

For persistent PTSD with other anxiety disorders, we recommend augmentation with treatments of proven or suggested efficacy in the specific disorder, e.g. hydroxyzine, buspirone, trazodone or benzodiazepines for Generalized Anxiety Disorder (GAD) (LOE 4); clonazepam, olanzapine or levetiracetam for Social Anxiety Disorder (LOE 4); and clomipramine or atypical antipsychotics for Obsessive Compulsive Disorder (OCD) (LOE 4).

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## **Node 27: Response -- see Node 4 above.**

## **Node 28: Switch or add from within group**

If the response remains inadequate, consider switching to another drug within this group or to adding another drug within this group (See Node 24 (LOE 4)).

Most clinical trials with medication for PTSD have tested the efficacy of monotherapy with one pharmacological agent or another. Indeed, with the exception of trials with atypical antipsychotics, there are no clinical trials that have systematically evaluated the relative effectiveness of different augmentation strategies. Therefore, our recommendations for augmentation strategies for partial responders are extrapolations from monotherapy trials.