GUIDELINE 6

Psychopharmacotherapy for Adults

Description

There is a strong rationale for pharmacotherapy as an important treatment in posttraumatic stress disorder (PTSD). Alterations in a number of key neurobiological mechanisms appear to be associated with this disorder. These include dysregulation of adrenergic, hypothalamic–pituitary–adrenocortical (HPA), serotonergic, glutamatergic, gamma-aminobutyric acid (GABA)-ergic, and dopaminergic systems. Furthermore, there is considerable overlap between symptoms of PTSD, depression, and other anxiety disorders. Finally, PTSD is frequently comorbid with psychiatric disorders that are responsive to pharmacological treatment (e.g., major depression and panic disorder). Medication treatment is one of the most feasible treatments for PTSD. It is generally accepted by most patients, although the occurrence of side effects, lack of patient compliance with prescribed medication regimens, patient and family concerns about pharmacotherapy, and the high commercial cost of new therapeutic agents lessen their full impact.

Despite these scientific findings, pharmacotherapy for PTSD has primarily been guided by empirical evidence that a specific drug has efficacy against a specific symptom. Indeed, at present there are very few data in all psychiatric disorders, including PTSD, linking psychobiological abnormalities to specific medication effects. In research (and in clinical practice) almost every class of psychotropic agent has been prescribed for patients with PTSD. Most studies involve antidepressants: selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), and other serotoner-

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gic agents (trazodone and nefazodone). Antiadrenergic drugs tested include the alpha-1 receptor (prazosin), the alpha-2 receptor agonists (clonidine and guanfacine) and the beta receptor antagonist (propranolol). Recent developments include tests of mood-stabilizing anticonvulsants and augmentation strategies with atypical antipsychotics for SSRI partial responders.

General Strength of the Evidence

The strength of the evidence is best for the different classes of antidepressant agents tested in most of the randomized clinical trials (RCTs) on pharmacotherapy. There is also good evidence from augmentation trials with atypical antipsychotic agents. Finally, there are encouraging results with the antiadrenergic agent, prazosin, the antidepressant, mirtazapine, and older antidepressants, such as MAOIs and TCAs.

SSRIs (Sertraline/Paroxetine/Fluoxetine—Level A)

SSRIs can be recommended as a first-line treatment for PTSD. They not only reduce PTSD symptoms and produce global improvement but are also effective against comorbid disorders and associated symptoms. They have fewer side effects and greater safety than other antidepressants, but they may produce insomnia, agitation, gastrointestinal symptoms, and sexual dysfunction. Results with veterans are difficult to interpret because of the severity and chronicity of PTSD in veteran cohorts tested thus far.

SNRI (Venlafaxine—Level A)

Large, multisite trials indicate that venlafaxine can be recommended as a first-line treatment for PTSD. It is as effective as SSRIs and useful for comorbid depression. Its most significant contraindication is that it may exacerbate hypertension.

Other Second-Generation Antidepressants

- *Mirtazapine—Level A*. Mirtazapine has been shown to be effective in small, randomized trials. It may produce somnolence, increased appetite, and weight gain.
- *Bupropion—Level C*. Bupropion has been effective in small, open-label trials.
- *Nefazodone—Level A*. In the United States, Serzone, but not generic nefazodone, has been withdrawn from the market because of liver toxicity, although it appears to be as effective as SSRIs. Different regulatory decisions may apply in other countries.

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- *Trazodone—Level C.* Trazodone has only modest efficacy, although it is a useful adjunct to SSRIs to promote sleep. It may be too sedating during the day and may also produce priapism.

MAOIs (Phenelzine—Level A)

MAOIs have been shown to be effective for DSM-IV Criterion B symptoms and global improvement, with some efficacy against Criterion D symptoms; however, they have not been tested extensively. They are also effective antidepressants and antipanic agents. Compliance with MAOI dietary restrictions is an important limitation of MAOI treatment. Furthermore, they are contraindicated in patients likely to use alcohol, illicit drugs, or certain drugs prescribed for other clinical conditions. Cardiovascular, hepatotoxic, and other side effects also must be monitored with MAOIs.

TCAs (Imipramine/Amitriptyline/Desipramine—Level A)

Imipramine and amitriptyline have been shown to be moderately effective treatments, whereas desipramine has been without effect in RCTs. Taken as a whole, TCAs generally are moderately effective in reducing DSM-IV Criterion B symptoms and promoting global improvement. They appear to be less effective than MAOIs in this regard, but they have fewer serious side effects. Side effects from TCAs include hypotension, cardiac arrhythmias, anticholinergic side effects, sedation, and behavioral activation.

Antiadrenergic Agents

Antiadrenergic agents appear to reduce arousal, reexperiencing, and possibly dissociative symptoms. They have been tested inconsistently in clinical trials. They are generally safe, although blood pressure and pulse rate must be monitored routinely. Special caution must be observed when prescribing these agents for patients with low blood pressure or those who are receiving antihypertensive medications.

- *Prazosin—Level A* effectively reduces traumatic nightmares. In one study, it also reduced overall PTSD symptom severity.
- *Propranolol—Level B* has shown promise as both a treatment for children and as a prophylactic agent to prevent the later development of PTSD. It may exacerbate asthmatic and depressive symptoms.
- *Clonidine—Level C* has shown promise in open trials for PTSD and dissociative symptoms.
- *Guanfacine—Levels A and C* was ineffective in a randomized trial despite promising open-label results.

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Anticonvulsants (Lamotrigine—Levels A and B; Tiagabine—Level A; Carbamazepine/Valproate/Topiramate—Level B; Gabapentin/Vigabatrin—Level F)

Many open-label trials with anticonvulsants have had promising but inconclusive results; these medications have many side effects (see Table 9.3). A large, randomized trial with tiagabine had negative results, whereas a small trial with lamotrigine was modestly favorable. Anticonvulsants cannot be recommended for PTSD treatment at this time.

Benzodiazepines (Alprazolam—Level A; Clonazepam—Level B)

Although these drugs are both effective anxiolytics and antipanic agents, they are contraindicated for PTSD treatment. They produce their typical antiarousal effects without reducing either reexperiencing or avoidant/numbing symptoms. In addition, they should not be prescribed for patients with past or present alcohol/drug abuse dependency. Finally, they also may produce psychomotor slowing and exacerbate depressive symptoms. Benzodiazepines do not have any advantage over other classes of medications; therefore, they cannot be recommended for use as monotherapy in PTSD at this time.

Other Serotonergic Agents (Cyproheptadine—Level A; Buspirone—Level F)

A randomized trial with cyproheptadine was negative, and reports on the beneficial effects of buspirone have been anecdotal. There is no basis for recommending either drug at this time.

Atypical Antipsychotics (Risperidone/Olanzapine—Level A; Quetiapine—Level B)

Several small, randomized trials have shown the effectiveness of augmentation with atypical antipsychotics for partial responders to SSRIs or other treatment-refractory patients. These agents may also be useful for patients with PTSD who exhibit extreme hypervigilance/paranoia, physical aggression, social isolation, or trauma-related psychotic symptoms. They may produce weight gain, and olanzapine treatment has been associated with type 2 diabetes. Conventional antipsychotic agents are contraindicated in PTSD.

Course of Treatment

Current research findings suggest that controlled drug trials in PTSD should last at least 8–12 weeks because shorter trials have generally been ineffective.

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More recent and much larger-scale studies (with SSRIs) suggest that maximum benefit, for some, may not be achieved until the 36th week of treatment.

Recommendations

Although some medications qualify as Level A treatments, their overall efficacy is not as great as that achieved with some cognitive-behavioral treatments. Furthermore, discontinuation of medication following a successful response is often followed by relapse. Finally, most medications have side effects that, if significant, may make it impossible for certain patients to remain in treatment despite reduction of symptoms. Regardless of these considerations, many patients prefer medication to psychotherapy; medication may be the only available option, if there are no qualified CBT therapists in the area; many patients tolerate side effects without problems; and many achieve complete remission and are willing to remain on medication as long as necessary.

Summary

The best evidence supports the use of SSRIs and SNRIs as first-line drugs for PTSD. There is also good evidence that augmentation with atypical antipsychotic agents is effective. Recent results with prazosin and mirtazapine are also promising. MAOIs are moderately effective and TCAs are mildly effective agents, although both may produce adverse side effects. Evidence supporting the use of anticonvulsants is weak, not because of negative findings, but because there have been so few randomized trials with either class of drugs. There is good evidence to suggest that benzodiazepines are not useful in treating PTSD. Finally, there is reason to believe that new, as yet untested, pharmacological agents that work through different mechanisms of action may prove to be more effective than medications that are currently available.

Suggested Readings

Davidson, J., Bernik, M., Connor, K. M., Friedman, M. J., Jobson, K. O., Kim, Y., et al. (2005). A new treatment algorithm for posttraumatic stress disorder. *Psychiatric Annals, 35*, 887–900.

Friedman, M. J., & Davidson, J. R. T. (2007). Pharmacotherapy for PTSD. In M. J. Friedman, T. M. Keane, & P. A. Resick (Eds.), *Handbook of PTSD: Science and practice* (pp. 376–405). New York: Guilford Press.

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