



## About Medications for Combat PTSD

By Jonathan Shay, M.D., Ph.D. Staff Psychiatrist, Boston VA Outpatient Clinic

A note to the reader: This article is applicable to anyone who seeks to understand the role of medication within the treatment framework of PTSD. Although it specifically addresses the veteran community, we have found the information given to be extremely valuable and well suited for any reader seeking information on this topic.

Dr. Shay sincerely regrets that he is not available for consultation on psychopharmacology or questions you may have related to this article. If you would like further information in regard to medication and PTSD, please contact the Sidran Help Desk.

### **A. Point of View**

Everything I say here is my point of view, and carries no claim of special authority. Also, what I say here is no way complete. I have left out many important subjects, such as drug interactions, what medical conditions forbid the use of a given drug, overdoses and toxicity, and most specific side-effects. Also, many psychiatrists who also care about combat veterans will disagree with what I say here, particularly about the benzodiazepines like Ativan. Combat PTSD is moral, social, philosophical, and spiritual injury. The biological nature of human beings is to be moral, social, philosophical, and spiritual, so the injury also shows itself as medical disorders.

Healing is psychological, social, spiritual—no medicine can cure combat PTSD. However, healing can never mean a return to 17-year old innocence. Healing means building a good human life with others—a life that a veteran can embrace as his own.

Combat trauma brings about long-lasting changes in brain chemistry. We do not know whether these are permanent or can be reversed by psychological/social healing. A few existing medications can help some men with some symptoms of PTSD. We also do not know whether this changes the long-term outcome for the better, but the human payoff in reduced suffering is unmistakable.

## **B. A Brief Course in Pharmacology *Therapeutic effects (benefits) and side-effects***

Drugs are dumb chemicals—they don't know what they are. They aren't born in a laboratory with a word spelled out across their foreheads "Anti-depressant!" or something like that. Most have been discovered by accident. Almost every drug known has multiple effects on the body. Which effect is a therapeutic (beneficial or main) effect and which is an unwanted side-effect is a human decision, not a chemical decision.

Illustrations: Think of the well-known drug Elavil (generic name: amitriptylene). What is it? An anti-depressant you say? Why is it used in the Intensive Care Unit to stabilize the heart beat of certain patients? Not because depression causes their irregular heart beat. Why is it used by neurologists to treat migraine? Not because depression causes migraine—and the doses that work for migraine are usually too small to touch a depression. The point is, of course that a drug doesn't know what it is. Its successful human uses make it an anti-depressant, a migraine drug, an anti-arrhythmic.

What about side-effects? Again, this is a matter of the human purposes involved. Think of the anti-depressant trazodone (most common trade name: Desyrel). Its most prominent side-effect is drowsiness. I prescribe trazodone fairly often as a sleep medication to veterans who are on fluoxetine. It has the advantage that it doesn't lose its effect with repeated use (which also means there's little withdrawal syndrome when the veteran stops it), and it's almost useless as a pill to kill yourself with. So here the side-effect is the main effect and the anti-depressant effect is a side-effect—Is anybody confused yet?

Important to remember: When a drug has several different effects, each effect has its own way of unfolding in time. How long a drug takes to produce its different effects, is often different for each effect. The side-effects may hit immediately and the main effect only develop after several

weeks! With another drug it's the opposite, with the main effect coming on immediately and the side effects happening later. An analogy: Think of a plant on your window sill. You've been away for the weekend and it's gotten dry and droopy. You give it water and the leaves begin to respond almost as soon as the water goes on—the plant responds as soon as the water reaches the roots. If the roots dry out, again the plant wilts again. This is like a pharmacokinetic effect. If you put some fertilizer in the water, on the other hand, this reaches the roots as fast as the water reaches them, but you may not see any result for days or weeks. This is because the plant has to build new parts in its own cells. This is like a pharmaco-dynamic effect.

Example: Most anti-depressants reach the brain quickly, but take several weeks to have an anti-depressant effect. This is probably because the changes that have to take place in the cells take that long to happen. However, some side-effects like a dry mouth or drowsiness happen quickly because they do not require cells to make anything new, but only to do what they're already doing faster or slower.

### ***Tolerance and withdrawal***

I will use alcohol as the example, because most people have considerable knowledge about it. They just haven't realized that they can transfer this knowledge to other drugs. Pharmacologic tolerance is a critically important subject.

Consider a very heavy drinker, who drinks every day and more or less all day. Most of the time he is not drunk, in the sense of staggering or slurring or not thinking clearly. He may function quite well at his job with a blood alcohol level that would put a non-drinker almost in a coma. This is because the drinker has developed a tolerance to alcohol. His brain has adjusted to alcohol's presence and slowly adapted its machinery to get everything back to normal. This adjustment is called pharmacologic tolerance, and it takes a while to happen. The brain has developed a steady, compensating excitation to balance the steady sedating effect of chronic alcohol. When the two are exactly in balance, the drinker thinks and behaves more-or-less normally. If the alcohol is suddenly removed, the brain becomes dangerously over-excited, resulting in delirium tremens, DTs. The compensating excitation corrects itself much more slowly than the alcohol leaves the body. This whole set of events is called a withdrawal syndrome.

The same kind of DT-like withdrawal syndrome of dangerous over-excitement (seizures, hallucinations, etc.) happens after sudden withdrawal from high doses of other sedating drugs that people get tolerant to, such as barbiturates, benzodiazepines (such as Valium), etc. A good rule of thumb is that a patient who has become tolerant to a given drug effect will get a withdrawal syndrome if he or she stops it suddenly. Often, the withdrawal syndrome is the “mirror image” of the original effects of the drug.

Not all of the effects of a drug are detectable by the person taking it, so tolerance to these changes may not be subjectively felt, either. However, during cold-turkey withdrawal from the drug, a withdrawal syndrome may develop that is the mirror image of effects that the person was never aware of. An example of this is caffeine withdrawal headaches. Most people are unaware of the blood-vessel-narrowing effect of caffeine, but once tolerant to this effect, abrupt discontinuation of caffeine can cause headaches due to blood-vessel dilation.

The greatest tolerance and the most severe withdrawal reactions happen with long-term use. However, with some drugs, there can be a miniature version of the whole picture with a single dose. Again, alcohol gives a good example: A man who knocks many drinks back one after another and then stops is much more drunk when his blood alcohol level passes a given point on the way up than later when his blood alcohol level passes the same point on the way down. This is called acute tolerance, because his body has already adjusted to the presence of the alcohol in the few hours since he started drinking. The next morning, during the hangover, he has a mini-withdrawal syndrome making his nervous system overly sensitive—how loud every sound seems!—the mirror image of how much alcohol deadened sound when he was drunk.

An analogy: You are running a motor boat on a certain compass heading, say due north, on a windless day (no alcohol). Now a cross-wind begins to pick up (gradually increasing steady drinking) and you gradually adjust the rudder to keep on the same heading. Now you are still heading due north, despite the heavy cross-wind. Suppose the wind suddenly dies (suddenly stopping drinking, cold-turkey) and you keep the rudder where it was—you start going in circles (withdrawal syndrome).

How much tolerance develops to each drug effect varies a lot from effect to effect and from person to person. A person may develop rapid tolerance to a nasty side-effect, such as dizziness. This means the dizziness actually goes away, not that the patient just gets used to it. So this person can bear with the drug and wait around for the therapeutic effect to kick in. Another person may never get tolerant to the dizziness side-effect and cannot make use of that

particular drug. There's no iron-clad way to predict a given person's sensitivity to each of the effects of a given drug or how fast, if at all, he will become tolerant to each effect.

## C. Things That Help

### *Characteristics of good drugs for combat PTSD*

- Makes something better for the veteran
- Does not lead to tolerance
- Does not lead to abuse
- Cannot be used to commit suicide
- Does not require blood tests
- Does not cut a person off from the world or from himself
- Causes few, bearable side-effects

### *Some good drugs for combat PTSD*

–Serotonin reuptake inhibitors: fluoxetine (Prozac), sertraline (Zoloft), paroxetine (Paxil), etc.

The main effect of fluoxetine on combat vets with PTSD whom I've worked with is to allow them more time to think before they act, particularly in anger. It does this without sedation or cutting a man off from himself or the world. The duration of anger, once aroused, is also shorter. Greater self-mastery of anger leads to an increase in self-respect and relief from a sense of humiliation. Most men feel humiliated after they go off on people in situations they really would not have, if they had had the freedom to choose. In addition to this, fluoxetine may have a direct anti-depressant effect in combat PTSD. Fluoxetine effects on self-control and rage may take many weeks to kick in, although I've seen it as soon as a week.

Fluoxetine is practically useless as a drug to overdose on, if the goal is suicide. All anti-depressants have been known to give long-time depressed people the energy to kill themselves, and fluoxetine is no different. Many combat veterans go through brief periods of intense despair during the first few months that they are feeling generally better, more alive, and are coming out of their bunkers. Support from other veterans, family, therapists is especially important during those times—nobody should try to go through it alone, or have to.

Someone trying to go through it alone might try to kill himself during one of these times of despair. Remember that this is no special risk with fluoxetine, but is a risk when anyone recovers from severe depression. Several vets I've treated have had bouts of despair like this, but none has ever tried to kill himself during one, because support and therapy are built into the program I'm a part of. The much-publicized claim that Prozac has special powers make a previously non-suicidal person violently suicidal is without good foundation. Fluoxetine does have side effects, which not everyone can stand, and it doesn't work for everyone. A full discussion of side-effects, some of which depend on the dose and others not, would be too long for this summary.

Fluoxetine is the first drug of its type to be released for use. Other drugs in the same family have now come along, sertraline (Zoloft) and paroxetine (Paxil). They have been tried by many combat vets around the country, and from what I hear they are not a lot different than fluoxetine as far as main and side-effects. In the relatively limited number of men I have treated with paroxetine and sertraline, this has been what I have heard from them. Paroxetine has a 24 hour half-life and no active metabolites [what the body turns the parent drug into], so if the actions of the drug are otherwise identical to fluoxetine, it will be a superior drug from a safety point of view, because it doesn't hang around in the body so long. But on the down side, paroxetine may be expected to (and is reported to) have a withdrawal syndrome because it leaves the body so fast.

#### -Buspirone (Buspar)

This anti-anxiety drug works differently from the benzodiazepines (like Valium). Like anti-depressants it takes a few weeks to kick in. It takes effect gradually, like the tide coming in. It usually has few side-effects and may help some people with intrusive thoughts and nightmares. Buspirone has no street value and is almost useless as a suicide pill. I am not aware of other drugs in this family coming along, but I hope there will be. I have recently read the report of a colleague who works with combat veterans that the best results with buspirone come at doses above 60mg/day. I do not yet have enough personal experience with patients who have tried this, to confirm or deny this report.

#### -Beta-blockers: propranolol (Inderal), nadolol (Corgard), atenolol (Tenormin), etc.

This family of drugs breaks the mind-body-mind vicious cycle in rage reactions, by blocking the body effects of adrenalin. For example, if someone at work says something offensive about Vietnam vets, the words start the mind working into rage. The rage starts in the mind—but within a second the body responds with adrenalin, which makes the gut burn, the heart pound, the muscles tense. These body changes send loud messages back up to the mind. For some veterans, the roar of the body drowns out all thought and shuts out everything else coming in. When adrenalin is roaring, it's impossible for most people to think clearly and to take in non-combat possibilities in the situation. This is the mind-body-mind vicious cycle that beta-blockers break up. By blocking the adrenalin effect on the body they prevent the roar of the body from drowning out all thought and choice about what you really want. "Is it really in my interests to rip this guy's lungs out? Is it really what I want to do?" When adrenalin is roaring these questions sometimes cannot be heard.

Some vets feel that these medications weaken them, because they associate being pumped up with adrenalin with their personal strength. When someone is over-medicated on these drugs (which started life as blood pressure meds) he is weaker because his blood pressure is too unstable, but this is usually not a problem with a correct dose. Tolerance does not develop to the anti-adrenalin effects of these drugs. Massive overdoses of a beta-blocker can be fatal, by dropping the blood pressure and slowing the heart to the point that the brain is not getting enough blood flow.

#### -Low-dose lithium

Some respected practitioners of PTSD pharmacotherapy speak highly of lithium to help veterans maintain their self-control when they are angry. This means doses of about 600mg/day, far less than is usually needed to treat bipolar affective disorder (manic-depressive disorder), and does not imply that the doctor recommending this thinks that the veteran is manic-depressive.

I agree that this can help some veterans, but I have found fluoxetine to be more reliable. It is also safer, in that lithium is readily fatal in a large overdose. For a veteran who cannot tolerate fluoxetine and whose life has been blighted by explosive violence, low-dose lithium may be a good thing to try. [no blood tests because of low dose]

## ***Other drugs for special circumstances —***

### Trazodone (Desyrel) for sleep

Trazodone is a non-toxic anti-depressant that has a useful side-effect: It causes drowsiness, and people don't get tolerant to this effect. Because fluoxetine slows the rate that the liver breaks down trazodone, much lower doses are needed for sleep by patients on fluoxetine than people who are not on fluoxetine.

### –Quinine for nocturnal myoclonus

This is the “sleep jerks.” If quinine works, the veteran himself may not notice much but his wife has much better sleep.

### –Low-dose antipsychotics for violent urges: thioridazine (Mellaril), mesoridazine (Serentil), etc.

The key here is brief treatment on an as-needed basis, controlled by the veteran himself [for a limited time, when hospitalization is not possible]. The doses needed have been low, and I prefer the sedating anti-psychotics like thioridazine and mesoridazine, which appear to carry the least risk of dangerous (neuroleptic malignant syndrome) or possibly irreversible (tardive dyskinesia) complications. An unexpected additional use for these drugs also involves brief, low-dose treatment: to help someone who wants to get off marijuana get through the withdrawal syndrome.

## ***Future drugs***

Many combat veterans with PTSD feel dead inside. It is possible that this psychic numbing comes from the brain making its own opium-like substances, and that opiate blockers can give people back their feelings. It is not yet clear whether this works. I hope the future will bring a drug like clonidine (trade name: Catapres) that people do not develop a tolerance to. In my experience, about one out of five combat veterans with PTSD experience major improvement of almost all of their PTSD symptoms on clonidine—but the heartbreak has been that they grew tolerant to it in about a week. Any future drug in this family that does not induce tolerance to this effect will relieve much suffering. A new drug in this family, guanfacine (tradename, Tenex)

has recently appeared, but I have no experience with it and have not heard any reports of usefulness to combat veterans with PTSD.

The most helpful drugs are likely to be ones that don't yet exist.

## **D. Things to Avoid**

One of the useful things I do for veterans I see is help them identify and get off of drugs that they use (whether prescribed by doctors or not) that are harming them. Some of what I say here is likely to be controversial.

–Benzodiazepines: diazepam (Valium), alprazolam (Xanax), lorazepam (Ativan), etc.

Disinhibition: All the drugs in this class are similar to alcohol. Some people “lose all their inhibitions” on either alcohol or benzos or both. This “dis-inhibition” can affect practically anything that a person thinks he might like to do—but doesn't do—when sober. It has included suicide and murder, but most often involves saying things that cumulatively do great damage to a veteran's life. A lot of family stress among veterans comes from things said to wives and children the veteran wishes he hadn't said, the moment it was out of his mouth. One of the inhibitions that benzos weakens is the inhibition about saying hurtful things to people we love.

Memory loss: All of the benzos weaken the ability to remember what happened a short time ago, including things you yourself did or said. The more potent the benzo, the more it wipes out short-term memory—this is probably why Halcion (generic name: triazolam) has been such a bad actor, it's one of the most potent. Here's a little scene that everyone has experienced one way or another: “I'm going out for cigarettes—want anything?” “Quart of orange juice and a box of Pampers.” “OK” Half hour later you're back—with your cigarettes! No one is 100% on things like this, but people on benzos are sometimes close to zero.

Short-term memory is something that everyone needs to make relationships work, at home, at work, or anywhere. There's the additional stress that combat vets have when they find themselves forgetting—they have been in real situations where people died because someone forgot. The tension and guilt that this creates in everyday life can be unbearable, and veterans often do not know that their benzodiazepines are responsible for memory lapses.

Confusion of pleasant side-effects with main effect: The pleasant, couple-of-drinks, or drowsy feeling that you get when you first take a benzo (especially the ones that are rapidly absorbed into the blood) is a side-effect that most (not all) people get tolerant to. Because it comes on at the same time as the anti-anxiety effect, it is natural for patients to think that this pleasant feeling is the anti-anxiety effect. One of the strengths of the benzos is that people do not get tolerant to the therapeutic anti-anxiety effect. A very common problem is that people feel the drug is quitting on them when they become tolerant to the pleasant side-effect, and become very afraid that their anxiety symptoms will return. Often out of fear of fear, they double up on their meds and pressure their doctors to increase their dose. This natural confusion of a gradually weakening, pleasant side-effect with the main effect is responsible for some addictive properties of the benzos.

Mini-withdrawal syndrome between doses: Benzos differ from each other mainly in their pharmacokinetics, that is, how fast they go into the body and how fast they leave. Mini-withdrawal reactions are particularly likely to happen with the benzos that leave the body quickly, such as Halcyon (generic name: triazolam). This is why people who take this drug for sleep often wake up in the middle of the night because they are in the withdrawal phase. Though Xanax does not leave the body quite as fast as Halcyon, it is particularly prone to giving mini-withdrawals between doses. My observation has been that many combat vets on Xanax have periods of anxiety and irritability during each day that do them great harm, and which, in my view are mostly mini-withdrawal reactions between doses. Possible dangerous peculiarities of Xanax in PTSD during withdrawal: The staff of the in-patient PTSD unit at the American Lake VA in Washington State have published a paper reporting extreme violence by combat vets treated for long periods with Xanax and then taken off of it. This was apparently more frequent and more severe than what they found taking their patients off of other benzos, such as Valium. Several Vietnam combat veteran peer counselors whom I respect very highly, feel that Xanax has done a lot of harm. Xanax has some unique properties among its cousins in the benzodiazepine family. In lab tests Xanax acts the opposite at low blood levels of how it acts in the larger amounts actually used in medical practice. When you think about it, everybody passes through a low blood level twice when they take a pill—once when the pill is just being absorbed in the body and once when the body is almost done getting rid of it (unless, of course, the person takes the same pill again, before the first one is completely gone). Whether this is what causes the problems with Xanax is not clear right now.

## -Caffeine

The pharmacology of caffeine is horribly complicated: it's not just one drug, it's really three, each of which can have a different effect on different people. The way it's three drugs is that it's the original caffeine, then the body converts it into theobromin, which the body then converts into theophyllin. The peak effects of these three successive drugs are roughly two hours for caffeine, four hours for theobromin and six hours for theophyllin. The good effects that any of these three drugs can have is feeling more awake, energetic, and optimistic. The bad psychological effects that any of these three drugs can have are anxiety and depression. A given person does not necessarily react to all three the same way. (I'm not talking here about the well-known effects of caffeine on sleep—this is another important topic in itself. What many people are unaware of is that at very high doses—like 15+ cups of coffee a day—caffeine can reverse on you and it can be impossible to stay awake, unless the caffeine is stopped.)

Someone who reacts badly to caffeine itself has usually found that out long ago, because the anxiety and/or depression hits them soon after the big mug of coffee. These people know it's not for them. But there are literally millions of people who feel good after caffeine itself but have bad reactions to either theobromin or theophyllin (four or six hours after that big mug of coffee) and just think it's their life that's out of whack, not their brain chemistry. THERE IS NO WAY TO TELL WHETHER CAFFEINE AND ITS METABOLITES ARE RESPONSIBLE FOR YOUR ANXIETY AND/OR DEPRESSION UNLESS YOU TAKE YOURSELF OFF IT COMPLETELY FOR SEVERAL WEEKS. This means coffee, tea, Coke, Pepsi, Mountain Dew, Jolt, headache pills with caffeine. Some people are so sensitive to it that even the small amount of caffeine in decaffeinated coffee and in chocolate causes psychiatric symptoms. If you decide to take yourself off caffeine to see what your life is like, don't go cold turkey. Taper yourself off over a week or so, or you are likely to get severe withdrawal headaches.

## -Yohimbine

Yohimbine (brand names: Actibine, Aphrodyne, Yocon, Yohimex) is absolutely contraindicated in combat PTSD. It causes flashbacks and panic attacks. This drug is sometimes used to treat impotence.

## -Any illegal drug

The problems and appeals of specific illegal drugs in combat PTSD is a very big subject that can't be covered here, but all illegal drugs cause the following problems for combat vets with PTSD. Expense is the first problem—I know there are Vietnam vets who have been very successful financially, but the men I know who have severe, chronic PTSD have a heroic struggle to make ends meet. I know it's stating the obvious, but the first problem of illegal drugs is the expense.

The second problem is much more subtle—Getting illegal drugs involves you in relationships with and obligations to people you normally wouldn't let within a mile. Most of the combat vets I know have a very sharp eye for quality in human beings, and feel constantly tainted by the people they get involved with to support their habits.

The third problem is that situations of real danger and the presence of weapons gets in the way of healing from PTSD. In this country and time it's not possible to sustain a drug habit over a period of years without running into situations that rekindle PTSD because of their real combat elements.

The fourth problem is the worst—using illegal drugs often puts veterans in situations where they bring down other vets. Calling for rescue is a very common way of bringing down other vets, even if the rescue is “successful.” Users need to be rescued from the medical complications of their habits, from the pressure of debts to dealers, and so on. Vets who have been on rescue missions are put back into combat-mode and are wired for weeks after a rescue. Sometimes users bring down other vets by asking them for dangerous favors (e.g., “hold this for me till I come for it” where “this” is a parcel of drugs or drug-related weapons or money). And finally—this is really obvious but it needs to be said—if a fellow vet is trying to stay clean and you're using, this amounts to a standing invitation to break out.