

On April 24, 2013, Dr. Richard Friedman presented the series' inaugural lecture, "Medicating Our Soldiers: Use or Misuse of Psychotropic Drugs by the Military?" to a large audience of practitioners, scholars, and friends. A regular contributor to the New York Times' *Science Times*, Dr. Friedman is an observer of trends in patient care and medical practice, which are often the subjects of his column. His lecture in April presented his thoughts on several months' inquiry into the use of psychiatric drugs by the military, the unusual prescribing trends he noted, and their thought provoking implications for patient well-being.

Friedman's interest became piqued when he learned that the suicide rate of active-duty American troops in the first half of 2012 surpassed the rate of soldiers dying in combat. Curious about this rate, Friedman lodged a series of Freedom of Information Act inquiries to investigate the nature of mental health care in the military. The picture that developed – though skeletal – was telling. In an attempt to stem the attrition of active-duty troops, he found that the military has been treating soldiers at risk for combat stress disorders with off-label applications of several potent psychoactive drugs. Unorthodox combinations of sedatives and stimulants have probably been effective at keeping soldiers functioning in the field, but their long-term effects are unstudied and likely to be extremely hazardous to patients. Taken together, the experiences of the military may be both disturbing and informative.

The information obtained through Dr. Friedman's inquiry made clear that the military is engaged in a pitched and growing battle against psychiatric illness. From 2005 to 2011, military prescribing of multiple psychoactive drugs per individual increased nearly 700%. The prescribing trends showed a steady and vast increase in the use of antipsychotics, anxiolytics, and anticonvulsants in a manner that is outside the usual bounds of accepted medical or psychiatric practice. At the same time, the use of antidepressants – the drugs demonstrated to have the greatest efficacy for depression -- dropped 48% between 2006 and 2009. Perhaps most startlingly, the increase in stimulant prescribing outpaced that of any other class of drug, increasing fifteen-fold. Though fragmentary, these data obtained from the Department of Defense raised some important questions: What is the military doing to mitigate combat-related stress? And what are the mental health care policy implications of these prescribing trends?

The key to the patterns of military prescribing, suggested Dr. Friedman, may have to do with the off-label use of many of the medications. The number of antipsychotic drug prescriptions, for instance, increased 1083% for active-duty troops from 2005-2011. The primary indications for antipsychotic drugs are the treatment of schizophrenia, bipolar disorder, and severe major depression. Since the military screens out prospective enlistees for these disorders, the use of these powerful drugs is clearly off-label. But in addition to their primary effects, antipsychotics are powerful sedatives, and are likely to be calming in stressful combat situations. Such a feature can be of great utility to enlisted men and women -- particularly under the pressure of repeated deployments -- and the increase in military prescriptions suggests that their potential has been noted. Indeed, the possibility was confirmed to Dr. Friedman by a psychiatrist in the department of defense, who acknowledged that insomnia, aggressive behavior, and anxiety have been treated by the military with antipsychotic drugs.

The rationale behind such treatment is not difficult to understand. Maintaining troop strength in a long and expensive war is no easy feat. In the absence of a draft, the Bush administration initiated "stop-loss" policies designed to keep boots on the ground, such as the automatic extension of soldiers' tours of duty. Yet the high-profile (and heavily criticized) deployment extensions were only one of the efforts to

stem attrition in the military; off-label uses of psychoactive drugs were another. Offering antipsychotics, sedatives, and sedating mood stabilizers to soldiers who had been recently traumatized could help ensure that such individuals slept through the night, and that they would be able to report for duty the following day. Soldiers made drowsy by the off-label cocktail could be revived with a stimulant. By contrast, the antidepressants clinically approved for treating PTSD could take several weeks to show an effect. Evidence gathered by Friedman has suggested that the application of sedatives and stimulants might be difficult to resist given the slow-acting alternatives, and that it has been administered quite often.

But the sedative/stimulant mix can have secondary effects, which Dr. Friedman warned may aggravate and even extend the trauma experienced by soldiers. PTSD, he noted, is at base a form of fear conditioning, which occurs when previously neutral stimuli become linked to traumatic situations. In troops, the fear response experienced in combat trauma elicits a surge of norepinephrine, which burns the memory of the event into the brain. It is that increase of noradrenergic function – accompanied by the burning of memory -- that is of concern. When soldiers are prescribed stimulants to counteract the effects of sedatives, they experience a rise in noradrenergic function that predisposes them toward PTSD should they experience a traumatic event. Between 2002 and 2009, the prevalence of PTSD increased from 0.2% to 22% in the U.S. military. At the same time, the failure to prescribe SSRI antidepressants as a first line treatment has deprived service men and women of one of the most effective medications to treat the disorder.

The development of stress disorders aside, antipsychotic, anxiolytic, and anticonvulsant drugs carry risks of their own. Difficulties with short term memory and fine motor coordination may accompany the use of anticonvulsants which, Friedman pointed out, “could adversely affect combat performance.” Anxiolytic medications such as Valium and Klonopin can be habit-forming, and antipsychotics can cause remarkable weight gain, elevate blood lipids and glucose, and cause the potentially irreversible disorder tardive dyskinesia, characterized by repetitive and involuntary movements such as grimacing and lip smacking. There is but weak evidence that these drugs are effective in treating PTSD, and even the military’s own treatment guidelines indicate that there is no evidence to support the use of antipsychotic drugs either alone or as adjuncts in PTSD. The guidelines explicitly state that SSRI antidepressants are the treatment of choice.

Friedman made clear that his findings were limited without more specific, patient-level data. Nevertheless, certain facts are in powerful evidence. The steady rise in nearly all classes of psychotropic drugs reflects a growing psychiatric burden of the nation’s war -- particularly depression and PTSD. Much of this is treated with off-label uses of psychoactive drugs, which can be strongly effective in reducing pain, stress, insomnia, and aggression, but which also carry potent risks and are at odds with accepted standards of care. The interdiction toward caution is clear, but the importance of follow-up may be just as strong. Care of troops affected by the psychic violence of war is of necessity our responsibility, but longitudinal study of soldiers who have been placed on off-label drug regimens is important, too. If the military were to monitor and study patient-level prescription trends for psychotropic drugs, physicians could develop better indications for their use. Such studies would help in development of new treatment guidelines for combat-related syndromes, some of which might benefit not just soldiers but the general population.