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Neuropsychological functioning in military pesticide applicators from the Gulf War: Effects on information processing speed, attention and visual memory

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ABSTRACT

1991 Gulf War (GW) veterans continue to experience debilitating cognitive and mood problems more than two decades following their return from deployment. Suspected causes for these cognitive complaints include additive and/or synergistic effects of the varying combinations of exposures to chemicals in theater, including pesticides and pyridostigmine bromide (PB) pills. This study was undertaken to address one of the key recommendations of the US Department of Defense Environmental Exposure Report on Pesticides, which was to conduct an epidemiological study to further evaluate the role of neurotoxicant exposures in the expression of central nervous system symptoms reported by GW veterans. This study evaluated the role of pesticides and/or PB in the development of chronic neuropsychological dysfunction in GW veterans. We examined the associations between self-reported measures of pesticide and PB exposures and performance on neuropsychological tests in a group of 159 GW-deployed preventative medicine personnel who had varying levels of pesticide exposures during their work as pesticide applicators or other preventative medicine roles. These veterans had a unique knowledge of pesticides and their usage during the war. It was hypothesized that pesticide applicator personnel with higher exposures would perform significantly worse on objective cognitive measures than lower-exposed personnel and that multiple chemical exposures (pesticide and PB) would further diminish cognitive functioning and increase mood complaints. Study results showed that the participants with both high pesticide and high PB exposure performed worse on specific measures than the groups with high single exposures or low exposures to both toxicants. High combined exposure was associated with significantly slower information processing reaction times, attentional errors, worse visual memory functioning, and increased mood complaints. In addition, stepwise regression analyses of individual pesticide exposures found that pest strip exposure was associated with slower reaction times and attentional errors, and that fly bait and delouser exposures predicted greater mood complaints.

1. Introduction

After returning home from deployment, many 1990–1991 Gulf War veterans reported debilitating health complaints including problems with short-term memory and fatigue (Iowa Persian Gulf Study Group, 1997; Fukuda et al., 1998; Proctor et al., 1998; Unwin et al., 1999; Steele, 2000; White et al., 2001; Sullivan et al., 2003; White et al., 2016). It was noted early on that potential causes for these complaints included effects of varying combinations of exposures to neurotoxicants, including pesticides, that were used widely in the Gulf region to protect soldiers from insect-borne illnesses (White et al., 2016; RAC, 2008; Kang et al., 2009; Golomb, 2008; Abdel-Rahman et al., 2004;

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Sullivan et al., 2003; Wolfe et al., 2002; White et al., 2001; Moss, 2001; Abdel-Rahman et al., 2001; Fricker et al., 2000, Proctor et al., 1998; Haley and Kurt, 1997; Abou-Donia et al., 1996). In 1997–98, the Department of Defense (DOD) conducted pesticide health risk assessments by telephone in an effort to understand the extent to which service men and women were exposed to pesticides. Nearly 300 GW veteran pesticide applicators and preventative medicine personnel were interviewed. This cohort was collectively known as pest-control interviewees (PCIs) and the interview results were summarized in the Environmental Exposure Report – Pesticides (EER) (Winkenwerder, 2003).

The report estimated that 41,000 GW veterans were likely overexposed to organophosphate (OP) and carbamate pesticides during the war (Winkenwerder, 2003). The report also suggested that exposures in some general military personnel exceeded levels of concern for toxicity as established by EPA guidelines at that time. Fly baits, pest strips, sprayed liquids, and sprayed powders were cited as sources of concern for general military personnel, and also pesticide fogs and prisoner delousing for some military pesticide applicators. Of the twelve pesticides of potential concern (POPC) identified in the report, 8 were either OP or carbamate pesticides. The study did not include questions about multiple exposure scenarios in the health risk calculations nor did it assess potential cognitive and health effects at the individual veteran level (Winkenwerder, 2003). One of the key recommendations from the health risk assessment was to conduct an epidemiological study with this cohort that included individual cognitive and health assessments to aid in determining potential causes for Gulf War Illness (GWI) symptoms experienced by these and other groups of GW veterans (Winkenwerder, 2003).

In addition to sprays and powders, another significant exposure to carbamates occurred when deployed GW veterans were given pills containing pyridostigmine bromide (PB). These were administered during the war as a prophylactic against possible nerve agent attack (Golomb, 2008; Sullivan et al., 2003; Cook et al., 2002; White et al., 2001; Golomb, 1999). PB usage in GW veterans has been associated with cognitive decrements in executive system functioning and with meeting criteria for GWI in particular groups of GW veterans (Steele et al., 2012; Sullivan et al., 2003).

OPs and carbamates, two subsets of pesticides used during the GW, act by inhibiting the enzyme acetylcholinesterase (AChE) and are known to produce chronic health and cognitive symptoms at sufficient exposure levels (Golomb, 2008; Cecchine et al., 2000). Examples of lasting dysfunction in neuropsychological capabilities associated with exposures to AChE inhibiting (AChEi) pesticides include decreased processing speed and increased mood complaints in agricultural workers and professional pesticide applicators (Bazylewicz-Walczak et al., 1999; Kamel et al., 2007; Mackenzie Ross, 2008; Mackenzie Ross et al., 2010, 2007; Roldan-Tapia et al., 2005; Steenland et al., 1994; Stephens et al., 1995; Toomey et al., 2009). Furthermore, recent studies employing animal models in which rodents are exposed to GW-relevant pesticides have identified non-AChEi pathways of OP effects that are characterized by neuronal cell death or dysfunction through oxidative stress, neuroinflammation, metabolic and dopaminergic effects, and altered axonal transport of cellular organelles. These physiological changes are associated in the animal models with slower information processing speeds, sustained attention alterations and mood decrements on behavioral testing (Terry, 2012; Terry et al., 2007; Grigoryan et al., 2009, 2008; Laetz et al., 2009; Middlemore-Risher et al., 2010; Jiang et al., 2010; Parihar et al., 2013; O'Callaghan et al., 2015; Abdullah et al., 2016; Torres-Altoro et al., 2011; Abou-Donia et al., 2004).

The goal of the current study was to further evaluate the role of OP and other classes of pesticides in the expression of CNS symptoms reported by GW veterans and to assess the effects of combinations of neurotoxicant exposures on neuropsychological functioning and mood. This was accomplished by carrying out comprehensive individual assessments in a unique group of GW military pesticide applicators, some of whom bought, applied, and disposed of the pesticides used during the GW. This cohort is a subgroup of the larger preventative medicine and pest-management group interviewed by the DOD for the compilation of the health risk assessment (Winkenwerder, 2003) and to our knowledge is the only report of objective cognitive functioning in military pesticide applicators from the 1991 GW.

We hypothesized that GW military pesticide applicators with the highest exposures to pesticides would perform the worst among the participants on measures assessing processing speed, memory and mood. It was also hypothesized that high co-exposure to PB would further diminish functioning in these behavioral domains. Therefore, the aims of this study were to determine the cognitive effects of pesticide exposure in specific exposed groups of GW veterans, to determine the cognitive effects of PB exposure in specific groups of pesticide-exposed GW veterans, and to assess for combined effects in GW veterans with multiple chemical exposures (PB, pesticides).

2. Methods

2.1. Study population

For inclusion in the study, veterans were selected from a larger cohort of PCIs.

The DOD interviewed 293 GW veterans with military occupational specialties or designation including preventative medicine or delousing as part of the DOD's EER– Pesticides (Winkenwerder, 2003). PCIs were a uniquely knowledgeable cohort who bought, applied, and disposed of all of the pesticides that were used during the GW deployment. This cohort included physicians, entomologists, environmental science officers, preventive medicine specialists, field sanitation team members, military police, and other pest controllers representing every branch of military service and including both active duty and reservists. These individuals were chosen for interview because it was believed that they would be the most likely to have knowledge of pesticide products used in the Army, Navy, Air Force and Marines.

The PCIs comprise specific groups of GW veterans likely to fall into high and low categories of pesticide exposure based on their military occupational specialty or designation. PCI contact information and interview data were provided to the current study investigators by the DOD Force Health Protection and Readiness Programs (previously known as the Office of the Special Assistant for Gulf War Illnesses and Deployment Health Support Directorate). The VA Boston Healthcare System, Boston University and the Department of Defense institutional review boards (IRB) approved the study protocol and informed consent was obtained from all participants.

2.2. Subjects for analysis and inclusion/exclusion criteria

To minimize project cost, 160 of the original 293 PCIs were targeted for this study based on locations where the most veterans resided at the time of the study to minimize the number of study recruitment trips. 159 of the targeted 160 PCIs, from recruitment trips to 28 states, were recruited and completed a full neuropsychological, mood and health symptom assessment. Study participants represented all military branches and included male and female GW veterans (Table 2). The major inclusion criteria for study participation were that the veteran was considered preventative medicine personnel during the war and they had previously participated in the DOD EER-pesticides telephone interviews (1997–1998) regarding pesticide usage during the war. The exclusion criteria for this study included current substance abuse, and/or substantial traumatic brain injury or other documented neurological illness precluding the use of a computer. Screening for exclusion criteria occurred during the telephone recruitment phase of the study and was confirmed during the study enrollment. Prior substance abuse and current medications were recorded but did not constitute exclusion criteria. The exclusion criteria screened out participants with conditions