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Effects of valerian on subjective sedation, field sobriety testing and driving simulator performance

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ABSTRACT

Introduction: The availability of herbal medicines over-the-counter (OTC) has increased the use of natural products for self-treatment. Valerian has been used to effectively treat generalized anxiety disorder and insomnia. Studies suggest that valerenic acid may increase gamma-aminobutyric acid (GABA) modulation in the brain. Benzodiazepines have a similar mechanism of action and have been linked to an increased risk of hospitalizations due to traffic accidents. Despite the risk of somnolence, the safety of driving while under the influence of valerian remains unknown.
Purpose: The purpose of the study was to determine the effects of a one-time valerian 1600 mg dose on subjective sedation effects, standardized field sobriety testing (SFST) and driving simulator performance parameters.
Methods: The study design was a randomized, placebo-controlled, double-blind, cross-over trial. For each session, participants received either a dose of valerian or placebo. The outcome measures included a simple visual reaction test (SVRT), subjective sleepiness scales, SFST performance scores, and driving simulator performance parameters.
Results: There were no significant differences in the SVRT or sleepiness scales between placebo and valerian exposures, but the study may have been underpowered. SFST total and individual test failure rates were not significantly different between the two exposures. The driving simulator performance parameters were equivalent between the two exposure conditions.
Conclusions: A one-time valerian 1600 mg dose, often used to treat insomnia, does not appear to impair driving simulator performance after acute ingestion.

1. Introduction

Valerian has been used to treat insomnia and generalized anxiety disorder. One research group has proposed that valerian's modulation of $GABA_A$ receptors in animal models may explain valerian's antianxiety and sedative effects (Yuan et al., 2004). In 2012, 23.6% of the U.S. population surveyed complained of insomnia (Kessler et al., 2012). GABA modulators, such as benzodiazepines and imidazopyridines, are common treatments for insomnia (Anderson et al., 2005). Since 2005, anxiety disorders affect 40 million American adults (18%) (Kessler et al., 2005). Benzodiazepines are also used to treat generalized anxiety disorder (GAD). The use of benzodiazepine hypnotics (OR 3.9) and anxiolytics (OR 2.5) has been associated with an increased risk of hospitalization due to traffic accidents (Neutel, 1995). One review suggests that driving and simulator studies have generally found evidence of benzodiazepine-induced impairment in driving performance, including measured outcomes such as lane position, speed control and reaction time (Kelly et al., 2004). Some patients may opt to use valerian for treating insomnia or GAD and expect to avoid benzodiazepine-induced impairment, but the safety of driving under the influence of valerian remains unknown.

The use of natural or herbal remedies has become increasingly popular. According to the National Health Interview Survey (NHIS), in 2012, 33.2% of U.S. adults use complementary health approaches. More specifically, 17.7% of U.S. adults use natural products as their chosen complementary health approach (NHIS, 2012). In 2013, valerian was the 9th top selling herb in the U.S. (Lindstrom et al., 2014). Valerian (*Valeriana officinalis*) root contains a variety of compounds (valepotriates, valerenic acid and its derivatives) and has been used for sleep-inducing, tranquilizing and anxiolytic effects (Houghton, 1999).

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Very few studies have attempted to determine the hypnotic or anxiolytic efficacy of valerian constituents. As a hypnotic, researchers determined that valerian reduced slow-wave sleep latency compared to placebo (21.3 min vs. 13.5 min, $p < 0.05$) (Donath et al., 2000). As an anxiolytic, both valepotriates and diazepam were shown to reduce the psychic symptoms of anxiety measured by the Hamilton Anxiety Scale ($p < 0.05$), while placebo had no effect (Andreatini et al., 2002). Another anxiolytic trial found that valerian extract 765 mg daily decreased Yale-Brown Obsessive-Compulsive Scale scores more than placebo ($p < 0.05$) and identified somnolence as the most common adverse effect ($p = 0.02$) (Pakseresht et al., 2011). While these few studies have demonstrated potential efficacy as a hypnotic or anxiolytic agent, valerian studies in healthy volunteers have demonstrated no cognitive impairment when evaluated by psychometric testing, specifically the digit symbol substitution test (DSST). In one small study, diazepam 10 mg impaired DSST performance of young healthy volunteers, while valerian extract (600 mg, 1200 mg, 1800 mg) over a range of doses did not affect DSST performance (Gutierrez et al., 2004). Another small study demonstrated that a different benzodiazepine, triazolam 0.25 mg, also impaired performance on the DSST, while valerian doses of 500 mg and 1000 mg demonstrated no effect on DSST performance 2 h after ingestion (Hallam et al., 2003). The relationship between DSST and driving performance parameters remains unclear since DSST has been excluded from regression models used to predict changes in standard deviation of lateral position (SDLP) due its lack of predictive validity (Verster and Roth, 2012). Therefore our study was designed to measure outcomes that more directly assess the effect of driving while under the influence of valerian.

The standardized field sobriety test (SFST) is a validated method for predicting if a person has a blood alcohol concentration (BAC) of 0.04% (the legal limit for commercial Class A drivers) and 0.08% (the legal limit for Class C drivers) (DMV Vehicle Code, 2012; DOT/NHTSA, 2012; Stuster and Burns, 1998; Ronen et al., 2010). The SFST has a sensitivity of 98% and specificity of 71% of tested subjects for driving while impaired with alcohol (detecting a BAC $\geq$ 0.08%) (Ronen et al., 2010). However, the SFST has only been studied on a limited number of drugs or illicit substances. Since valerian is one of the top selling natural remedies in the U.S. (Lindstrom et al., 2014), the objective of this study was to utilize the SFST and a driving simulator to establish the effects of valerian on driving performance. A second objective of the study was to determine a simple visual reaction test (SVRT) time along with the subjective sedative effects of valerian by using the Karolinska Sleepiness Scale (KSS) and Stanford Sleepiness Scale (SSS).

2. Methods

2.1. Study design

40 healthy adult participants were recruited for this randomized, placebo-controlled, double-blind, cross-over trial of valerian versus placebo. The study consisted of two separate 2–3 h sessions. In each session, participants were given a dose of either valerian 1600 mg or placebo and waited 1 h for absorption. The product used was Nature's Way Valerian Standardized®, which was standardized to contain 0.8% valerenic acid and was manufactured in Wisconsin, USA (lot numbers 20026532 and 20007247). The placebo was prepared by taking the same size gelatin capsule and filling it with brown sugar. The placebo capsules were stored in an empty Nature's Way Valerian Standardized® bottle to have similar smell characteristics. The order of administration was randomized based on a random number chart. The participants were then required to complete a simple visual reaction time test (SVRT) after a practice demonstration, the Karolinska Sleepiness Scale (KSS), and the Stanford Sleepiness Scale (SSS). Next, the SFST was conducted to determine if the participants would be presumed "under the influence." After SFST, a 10-min practice scenario allowed the participants to become familiar with the driving simulator. Once the participants were confident in handling the wheel, participants began the main scenario for approximately 40 min (Fig. 1). Participants completed these tasks individually during the same time of day for each of their sessions and used the same computer.

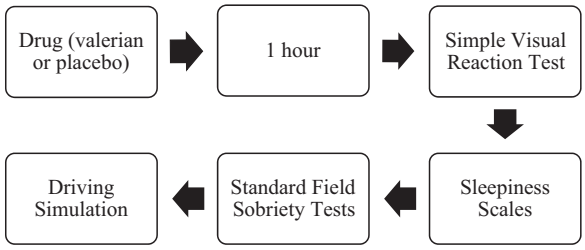

Fig. 1. Experimental session flow chart.

2.2. Inclusion and exclusion criteria

The study recruited healthy females and males who were at least 21 years of age. Participants were recruited using on-campus paper advertisements and an email sent through a campus-wide listserv. Participants were eligible if they were willing to take a dose of study medication (valerian or placebo) on two separate occasions, would test negative on a saliva drug screen test and were able to comply with instructions for testing.

The exclusion criteria included individuals with (1) a history of brain tumor, (2) any recent inner ear infection or vestibular/balance problems within the past 12 months, (3) pregnant or breastfeeding, (4) any known hypersensitivity to the experimental drug (valerian), (5) unwilling to undergo any risks associated with the adverse effects of the study drug, (6) currently taking prescription or over-the-counter medications that are known to cause psychomotor changes on a chronic basis (7) currently taking any psychiatric or psychotropic medications, (8) consumed alcohol or alcohol-containing beverages 24 h prior to the study sessions, (9) consumed caffeine or other stimulant-containing beverages 24 h prior to the study sessions, and (10) participant is blind, color blind, and/or deaf.

2.3. Saliva drug screen

A saliva sample was obtained at the beginning of each experimental session. A Rapid Detect saliva drug screen (SDS) was used to determine if each subject tested negative for drugs of abuse affecting cognition, including alcohol, amphetamine, methamphetamine, cocaine, opiates, oxycodone, phencyclidine, benzodiazepines, barbiturates, and cannabis (Rapid Detect, Inc., Poteau, OK). Participants were only included if all substances tested were negative on the SDS.

2.4. Sleepiness scales

Excessive daytime sleepiness (EDS) occurs when an individual is expected to be awake and alert but experiences sleepiness (Johns, 2009). EDS is a common symptom when under the influence of sedatives. Daytime sleepiness or moments of sudden sleep onset can have a major impact on everyday function and may cause motor vehicle accidents (Högl et al., 2010). Sleep scales are applied as an outcome measure to evaluate the response of a specific treatment (Högl et al., 2010). Two commonly used sleepiness scales were administered before the main driving scenario in our study.