Abstract: Progesterone is a steroid hormone that is important for reproductive function. Progesterone is used in a number of clinical applications and has been investigated as a possible novel approach for treatment of stimulant drug abuse. Extensive clinical studies have been conducted to examine the subjective and physiological effects of exogenous progesterone administration and to evaluate its side effects. This review summarizes the safety and side effects of acute and chronic administration of 3 progesterone formulations (synthetic, natural, and micronized natural), several routes of administration (oral, intramuscular, intravenous, intravaginal, intranasal, transdermal, and rectal), and dosing regimens. Synthetic progestins marketed as Provera, PremPro, and Cycin are widely used but may produce a number of significant side effects, such as fatigue, fluid retention, lipid level alterations, dysphoria, hypercoagulant states, and increased androgenicity. Natural progesterones are reported to have milder adverse effects, depending on the route of administration. Micronized natural progesterone is available for oral administration, has better bioavailability and fewer side effects than natural progesterone, and is convenient to administer. Therefore, micronized natural progesterone appears to be a safe and effective alternative to synthetic and natural progesterone formulations for variety of clinical and research applications. PMID: 17924777