

## **Sex-dependent effects of progesterone on nicotine withdrawal and neural response to smoking cues during brief abstinence**

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### **Introduction:**

Although exogenous progesterone may hold promise as a treatment for nicotine use disorders, it is unclear whether it is similarly effective in males and females. This study examined the effects of progesterone on nicotine use disorder comprehensively using behavioral, psychological, and neural measures in male and female smokers exposed to brief abstinence.

### **Methods:**

Thirty-four male and 32 female non-treatment seeking smokers participated in a double-blind, randomized, placebo-controlled crossover study of 200mg of progesterone or placebo daily over a four-day abstinence period. Smoking behavior and subjective effects of nicotine were assessed at baseline and after final drug administration. Nicotine withdrawal, smoking urges, mood states, and neural response to smoking cues were measured at baseline, after the first drug administration, and after the final drug administration.

### **Results:**

No main effect of drug (progesterone vs. placebo) emerged for any outcome. Significant sex by drug interactions emerged for nicotine withdrawal ( $p = 0.016$ ), lingual gyrus response to smoking cues ( $p = 0.021$ ), and perceived strength of nicotine ( $p = 0.017$ ). Males receiving progesterone reported worse nicotine withdrawal ( $p = 0.039$ ) and experienced higher activation of the lingual gyrus in response to smoking cues ( $p = 0.012$ ). Females on progesterone perceived nicotine's effects as being stronger relative to placebo ( $p = 0.025$ ).

### **Conclusions:**

Progesterone causes sex-dependent effects on smoking-related outcomes during brief abstinence. Specifically, progesterone in males may increase rather than decrease nicotine withdrawal and salience to smoking cues, potentially hindering efforts to quit smoking.