

How safe is cytisinicline as a first-line smoking cessation treatment during pregnancy and lactation?

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Dear Editor,

Cytisinicline, also known as cytisine, is a plant-derived alkaloid whose molecular structure resembles that of nicotine. It represents a new pharmacological option for nicotine addiction and smoking cessation¹. Cytisinicline acts similarly to varenicline. It selectively binds to the $\alpha 4 \beta 2$ subtype of nicotinic acetylcholine receptors involved in nicotine dependence, acting as a partial agonist to alleviate withdrawal symptoms and block nicotine reinforcement during smoking¹.

Cytisinicline combined with behavioral support has demonstrated effectiveness for smoking cessation and for cessation of e-cigarette use compared with placebo^{2,3}. In a randomized clinical trial involving 810 smokers, cytisinicline significantly increased abstinence rates compared with placebo, with 25.3% abstinence after 6 weeks and 32.6% after 12 weeks versus 4.4% and 7% in the placebo group, respectively². Adverse effects such as nausea, insomnia, and abnormal dreams were reported, but treatment discontinuation was uncommon (2.9%), indicating generally good tolerability². Similarly, in a trial of 160 e-cigarette users, cytisinicline significantly improved cessation outcomes, with only 3.8% of participants discontinuing treatment due to adverse effects³. In a phase 2b trial, both 1.5 mg and 3 mg cytisinicline doses resulted in significantly higher continuous abstinence rates than placebo, with the 3 mg dose demonstrating greater efficacy and no significant safety concerns⁴.

In pregnancy, behavioral interventions remain the recommended first-line approach for smoking cessation, while evidence supporting pharmacological therapies is limited. Among available pharmacotherapies, nicotine replacement therapy (NRT) – which includes nicotine

patches, gum, or lozenges designed to reduce withdrawal symptoms – is the most commonly considered option. However, guideline bodies differ in their recommendations: some suggest that NRT may be used cautiously under medical supervision when behavioral strategies alone are insufficient, whereas others conclude that current evidence is insufficient to recommend for or against its routine use during pregnancy⁵. Against this backdrop, any consideration of cytisinicline for smoking cessation during pregnancy or lactation requires not only demonstrated efficacy in non-pregnant adults but also robust perinatal safety data, which are currently lacking.

Pregnancy and lactation have been exclusion criteria in clinical trials, resulting in a lack of human data regarding cytisinicline use during these critical periods. However, data from animal studies exist. For instance, Swiatkowski et al.⁵ evaluated the effects of cytisinicline on nicotine-induced embryotoxicity using zebrafish larvae. Their study examined teratogenicity, mortality, and delayed hatching due to nicotine and cytisinicline – both individually and combined⁵. Nicotine increased mortality and hatching delays, whereas cytisinicline alone did not affect mortality. Delayed hatching was observed only at high experimental cytisinicline concentrations in the zebrafish model⁶. When nicotine and cytisinicline were co-administered, teratogenic effects were reduced compared to nicotine alone⁵. The authors concluded that cytisinicline may offer protective effects against nicotine during the prenatal period in zebrafish, which could guide future studies on human prenatal nicotine exposure⁶. Human randomized trials support cytisinicline's efficacy for smoking cessation in adults, whereas the zebrafish findings suggest a possible protective effect against nicotine-related embryotoxicity that cannot be extrapolated to human

pregnancy without dedicated studies.

Pregnancy and lactation have been exclusion criteria in clinical trials, resulting in a lack of human data regarding cytisinicline use during these critical periods. However, the available preclinical and toxicological literature provides several points that should be considered when discussing safety. Experimental data comparing nicotine, varenicline and cytisine suggest that cytisine has a distinct pharmacological profile and does not fully reproduce the *in vivo* effects of nicotine or varenicline in models related to $\alpha 4\beta 2$ nicotinic receptor activation⁷.

Experimental toxicology data further suggest that biological vulnerability may influence cytisine-related effects. In spontaneously hypertensive rats, cytisine administration was associated with reduced brain glutathione and increased malondialdehyde, indicating oxidative-stress-related neurochemical vulnerability in this model⁸. These findings may be relevant to pregnancy because hypertensive disorders are common obstetric complications and pregnancy-specific cardiovascular and pharmacokinetic changes may alter drug exposure and biological response. In zebrafish embryos, cytisine alone did not increase mortality across a wide range of concentrations, whereas delayed hatching was observed only at the highest experimental concentrations⁶. When cytisine was co-administered with nicotine, some nicotine-induced embryotoxic effects appeared to be attenuated⁹.

Human toxicological evidence remains limited. A recent case report described cytisine overdose without consequent adverse effects, but isolated overdose observations cannot establish reproductive, fetal, neonatal or lactational safety⁹. Although animal models provide important preliminary safety signals, their translation to human pregnancy remains limited. Differences in placental structure, drug metabolism, developmental timing, and exposure levels mean that findings from experimental models such as zebrafish cannot be directly extrapolated to human fetal development. Moreover, many animal studies primarily assess early developmental outcomes such as mortality or gross malformations, while clinically relevant outcomes in humans – including neurodevelopmental effects, fetal growth, preterm birth, and long-term offspring health – are often not evaluated. Similar challenges exist in lactation research, where data on drug transfer into breast milk and potential neonatal exposure are lacking. These limitations highlight the broader difficulties of conducting pharmacological research during pregnancy and lactation, populations that are commonly excluded from clinical trials due to ethical and regulatory concerns. Future studies should therefore aim to incorporate pregnancy registries, pharmacokinetic analyses of placental and breast-milk transfer, and long-term offspring follow-up in order to better characterize the safety profile of cytisinicline in these populations.

In conclusion, available evidence indicates that cytisinicline is an effective and generally well-tolerated

smoking cessation therapy in non-pregnant adults^{1,2,4}. However, its safety profile during pregnancy and lactation remains largely unknown, as these populations have been excluded from clinical trials. Although animal studies have not demonstrated major teratogenic or embryotoxic effects, these findings cannot be directly extrapolated to humans. Consequently, current evidence is insufficient to support the use of cytisinicline as a first-line smoking cessation treatment during pregnancy or lactation. Well-designed clinical studies are needed to evaluate its safety, efficacy, and optimal dosing in these populations before clinical recommendations can be made.

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CONFLICTS OF INTEREST

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