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A review of the clinical pharmacokinetics and pharmacodynamics of varenicline for smoking cessation.

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Varenicline tartrate (Chantix®/Champix®) is a selective partial agonist of the α(4)β(2) nicotinic acetylcholine receptor and is approved as an aid to smoking cessation. The usual oral dosage in adults is 1 mg twice daily for 12 weeks, with an initial titration week. Several clinical pharmacology studies have characterized the pharmacokinetics of varenicline in adult smokers aged 18-55 years, elderly smokers and nonsmokers aged ≥65 years, adolescent smokers aged 12-17 years and subjects with impaired renal function. Varenicline exhibits linear pharmacokinetics following single- and multiple-dose administration of up to 3 mg/day. After oral administration absorption is virtually complete and systemic availability is high. Oral bioavailability is not affected by food or time-of-day dosing; maximum plasma drug concentrations typically occur within 3-4 hours after dosing. Protein binding of varenicline is low (≤20%) and independent of age and renal function. Varenicline is almost exclusively excreted unchanged in urine, primarily through glomerular filtration, with some component of active tubular secretion via human organic cation transporter, hOCT-2. Varenicline does not undergo significant metabolism and is not metabolized by hepatic microsomal cytochrome P450 (CYP) enzymes. Consistent with an elimination half-life of ~24 hours, steady-state conditions are reached within 4 days of repeat dosing. There are no remarkable differences between smokers and nonsmokers in metabolism or excretion of varenicline. In vitro, varenicline does not inhibit nor induce the activity of the major CYP enzymes. No clinically meaningful pharmacokinetic drug interactions are observed when varenicline is coadministered with the narrow therapeutic index drugs warfarin or digoxin, the smoking cessation therapies bupropion or transdermal nicotine, and the renally secreted drugs cimetidine or metformin. An integrated model-based analysis of varenicline pharmacokinetics across several studies in adult smokers further showed that renal function was the clinically important factor leading to interindividual variability in systemic exposure to varenicline. Although no dose adjustment is required for subjects with mild to moderate renal impairment, a dose reduction to 1 mg/day is indicated for subjects with severe renal insufficiency. After accounting for renal

function, there was no apparent effect of age, sex or race on varenicline pharmacokinetics. Varenicline pharmacokinetics in adolescents were generally comparable to those in adults; the bodyweight effect, which resulted in greater exposure in individuals of smaller body size (weighing ≤55 kg), was adequately offset by administration of half the dose recommended in adults. **(It is, however, important to note that varenicline is currently not approved for use in smokers aged under 18 years).** Exposure-response analyses relating individual-specific drug exposure to clinical responses consistently showed that the end-of-treatment abstinence rate in adult smokers increased linearly with increasing varenicline exposure; the 1 mg twice-daily dose regimen was reliably associated with greater exposure and an increased probability of achieving a stable quit within 1 year from the start of treatment. Nausea was the single most frequently reported adverse event in varenicline clinical trials, with an incidence that was sex-related and increased with varenicline exposure. In all, the predictable pharmacokinetic properties and straightforward dispositional profile of varenicline simplify its use in clinical practice.