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Influence of body weight and *UGT2B7* polymorphism on varenicline exposure in a cohort of smokers from the general population

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ABSTRACT

Purpose:

The abstinence rate to tobacco after varenicline treatment is moderate and might be partially affected by variability in varenicline concentrations. This study aimed at characterizing the sources of variability in varenicline pharmacokinetics and to relate varenicline exposure to abstinence.

Methods:

The population pharmacokinetic analysis (NONMEM®) included 121 varenicline concentrations from 82 individuals and tested the influence of genetic and non-genetic characteristics on apparent clearance (CL/F) and volume of distribution (V/F). Model-based average concentrations over 24 h (Cav) were used to test the impact of varenicline exposure on the input rate (Kin) expressed as a function of the number of cigarettes per day in a turnover model of 373 expired carbon monoxide levels.

Results:

A one-compartment model with first order absorption and elimination appropriately described varenicline concentrations. CL/F was 8.5 L/h (coefficient of variation, 26%), V/F was 228 L and the absorption rate (k_a) was fixed to 0.98 h^{-1}. CL/F increased by 46% in 100-kg individuals compared to 60-kg individuals and was found to be 21% higher in *UGT2B7* rs7439366 TT individuals. These covariates explained 14% and 9% of the inter-individual variability in CL/F, respectively. No influence of varenicline Cav was found on Kin in addition to the number of cigarettes.

Conclusions:

Body weight mostly and to a smaller extent genetic polymorphisms of *UGT2B7* can influence varenicline exposure. Dose adjustment based on body weight and, if available, on *UGT2B7* genotype might be useful to improve clinical efficacy and tolerability of varenicline.

Keywords: varenicline, pharmacokinetics, pharmacogenetics, dose individualization, variability

INTRODUCTION

Varenicline, a selective partial agonist of the $\alpha_4\beta_2$ nicotinic acetylcholine receptor, indicated as an aid to smoking cessation, has a moderate efficacy on smoking abstinence at best. In more than 160,000 treatment episodes of smokers from smoking cessation clinic, the reported 4-week success rate was 44% [1]. The continuous abstinence rate was 44% during the treatment period of week 9 to 12 and decreased to 30% between the week 9 to 24 in a randomized trial including 1000 smokers [2]. Based on dose-ranging studies, the manufacturer established an exposure-response relationship characterized by an increase of the probability of continuous abstinence during the treatment period from the week 9 to 12 (9-12 CAR) with increasing varenicline exposure. The probability of 9-12 CAR was estimated from 0.3 to 0.7 over the range of varenicline $AUC_{0\text{-}24,SS}$ from 60 to 450 ng.h/mL in individuals receiving the recommended dose 1 mg b.i.d. [3].

The drug is mainly eliminated in the form of the unchanged molecule (>90%) and in two pharmacologically inactive metabolites (<10%) of which one is obtained by glucuronidation via the UDP-glucuronosyltransferase 2B7 isoform (UGT2B7) [4,5]. Varenicline is excreted unchanged in urine mainly via glomerular filtration but active tubular secretion also occurs trough organic cation transporter 2 (OCT2) [5] . A variety of genetic polymorphisms of the *SLC22A2* gene coding for the OCT2 transporter and of the *UGT2B7* gene might have an influence on varenicline exposure. Expression of the genes coding for phase I and phase II drug-metabolizing enzymes and transporters, such as UGT2B7 and OCT2 are regulated by transcription factors such as: the constitutive androstane receptor (CAR, encoded by the *NR1I3* gene), the pregnane X receptor (PXR, encoded by the *NR1I2* gene), the estrogen receptor 1 (encoded by the *ESR1* gene), the farnesoid X receptor (FXR, encoded by the *NR1H4* gene), the peroxisome proliferator activated receptor gamma (PPARγ encoded by the *NR1C2* gene) and its coactivator PPAR coactivator 1-alpha (PPARGC1A) which all have genetic polymorphisms [6-14]. Finally, genetic variability in the $\alpha_4\beta_2$ nicotinic acetylcholine receptor (*CHRNA4* gene) where varenicline binds might also explain variability in the effectiveness of the drug. To date, a published population pharmacokinetic analysis of varenicline showed the influence of demographic and clinical variation on drug exposure but genetic characteristics were not studied [15].

The objectives of this study were to develop a population pharmacokinetic model to assess the influence of clinical and genetics factors on varenicline exposure, and to further explore the relationships between varenicline blood levels and treatment success measured by the expired carbon monoxide (CO) during a 3-month treatment period.

MATERIALS AND METHODS

Study population and design

Smokers from the general population wishing to participate in a smoking cessation program were recruited in the clinical and pharmacogenetic study. Details on the study population, inclusion and exclusion criteria and on the smoking cessation program are provided in the Supplemental material 1. Among the 194 smokers included in the study, 95 subjects chose to receive varenicline. Two blood samplings performed at the beginning and after one month of treatment were used to determine varenicline and cotinine plasma concentrations. Cotinine is the major metabolite of nicotine with a half-life of 16-17 hours. Subjects are biochemically confirmed abstinent from smoking if plasma cotinine ≤ 15 ng/mL [16-18]. At each visit, abstinence from smoking was assessed by self-declaration and by expired CO levels (Micro Smokerlyzer; Bedfont Scientific, Rochester, England) lower than 10 ppm [18,19]. Smoking withdrawal symptoms were also recorded by a self-administered questionnaire [20]. Each symptom was assessed by 3 or 4 questions and summarized with a score from a minimal to a maximal grade as follow: depression (min: 4 - max: 20), craving (4-20), irritation (4-20), concentration (3-15), appetite and weight gain (3-15), and insomnia (3-15). Co-medications were also registered. The study was approved by the Ethics Committee of the Lausanne University Medical School and by the Swiss Agency for Therapeutic Products (Swissmedic, Bern, Switzerland). Written informed consent was obtained from all participants.

Varenicline and cotinine concentration measurements

Briefly, all blood samples were collected in EDTA-containing tubes. After centrifugation, plasma samples were stored at -20°C until analysis. Varenicline and cotinine plasma concentrations were determined by ultra performance liquid chromatography coupled with tandem mass spectrometry as previously described [21]. Details of the analytical procedure are provided in the Supplemental material 1.

Genotyping

Genomic DNA was extracted from EDTA blood sample at the baseline visit using the FlexiGene DNA extraction kit (Qiagen Instruments AG, Hombrechtikon, Switzerland) according to the manufacturer's protocol. The following SNPs were selected based on previously published pharmacogenetic studies

and on their minor allele frequency (MAF) in the Caucasian population [22,23,7,8,24-36]: *SLC22A2* (rs316003), *SLC22A2* (rs316019), *SLC22A2* (rs2279463), *UGT2B7* 802T>C (rs7439366), *NR1|2* (rs1523130), *NR1|2* (rs2472677), *NR1|2* (rs7643645), *NR1|3* (rs2307424), *NR1|3* (rs4073054), *NR1|3* (rs2502815), *RXRA* (rs3132297), *RXRA* (rs3818740), *PPARG* (rs3856806), *PPARG* (rs1801282), *PPARGC1A* (rs8192678), *ESR1* (rs6902771), *ESR1* (rs9322336), *FXR* (rs4764980), *HNF1* (rs1169288), *CHRNA4* (rs1044396). GenomeStudio Data Analysis Software was used to export results generated by Illumina Cardio-MetaboChip. Details on genotyping are provided in the Supplemental material 1.

Pharmacokinetic-pharmacodynamic analysis

Non-linear mixed effect modelling was performed using NONMEM® version 7.3 program [37] with the PsN-Toolkit (version 3.2.4) [38].

Base model

A stepwise procedure was used to identify models that best fitted the data. Multi-compartment models with linear elimination were first fitted to the data to determine the appropriate structural model, which was finally identified as a one-compartment model. Since varenicline was administered orally, apparent clearance (CL/F) and volume of distribution (V/F) were estimated (where F is the absolute oral bioavailability). Exponential errors following a log-normal distribution were assumed for the description of inter-individual variability of the parameters. Proportional, additive and combined proportional-additive error models were finally compared to describe the residual variability.

Exposure-response analysis

Average varenicline concentration over 24 hours (Cav) at each visit day assuming a complete adherence to treatment were derived using:

$$Cav = AUC_{0\text{-}24}/24 \qquad (1)$$

where $AUC_{0\text{-}24}$ were computed analytically in NONMEM® based on the individual dose history and pharmacokinetic parameters.

Only data from visits during the period of effective dose (1 mg twice daily) were included. Whenever a cotinine measurement was available, cotinine and CO levels were compared based on the definition

of abstinence (≤ 15 ng/mL and < 10 ppm, respectively). If they were discordant, data of the visit were excluded from further analyses.

CO observations were used as a clinical marker of response to varenicline and were described by an indirect response model using the following equations describing a basal turnover:

$$dCO/dt = Kin - Kout * CO$$
$$\text{initial condition: } CO(0) = Kin / Kout \quad (2)$$

$$Kin = A + EFFCPD * CPD \quad (3)$$

where Kin is a zero order input rate and Kout a first-order degradation rate. The effect (EFFCPD) of the number of cigarettes per day (CPD) on Kin was directly integrated in the model as a surrogate marker of varenicline therapy. Finally, A represents the contribution of all other sources of CO production (environmental sources and endogenous metabolism) to Kin [39].

Covariate analysis

Bayesian estimates of the pharmacokinetic parameters were derived and plotted against the available subject characteristics (body weight (BW), age, ethnicity, sex, height, glomerular filtration rate (GFR) estimated with the Modification of Diet in Renal Disease (MDRD) formula [40], smoking status, co-medications and several genetic polymorphisms (see Table 1)). Potentially influencing covariates were then incorporated sequentially in the model and tested for significance on the pharmacokinetic parameters. The covariate analysis was performed using a stepwise insertion/deletion approach testing linear or non-linear functions as appropriate (categorical covariates coded as 0 and 1, continuous covariates centered on their median value). Parameter values were estimated for each genotypic group (rich model), defined as the reference allele group (Ref) and alternative allele groups: heterozygote alternative (Het-Alt) and homozygous alternative (Hom-Alt) or for further regrouped (reduced model) subpopulations.

In the exposure-response analysis, several covariates (continuous: Cav, nicotine metabolite ratio, *i.e.* 3-hydroxycotinine/cotinine ratio during smoking ad libitum, BW, age, study duration and recorded scores of smoking withdrawal symptoms; categorical: sex, *UGT2B7* 802T>C (rs7439366) and *CHRNA4* (rs1044396) polymorphisms) were tested on EFFCPD. Influence of sex, age and BW on A parameter was also investigated.

Parameter estimation and model selection

The log likelihood ratio test, based on changes in the objective function value (ΔOFV) was employed to discriminate between hierarchical models. Since a ΔOFV between any two models approximates a χ^2 distribution, a 3.8- (p=0.05) and 6.4- (p=0.01) point change of OFV was considered statistically significant for one additional parameter in model building and backward deletion steps, respectively. The Akaike's information criterion (AIC) was instead employed to choose between non-hierarchical models. Diagnostic goodness-of-fit plots, precision and plausibility of the model parameters were also used to assess the reliability of the results. Details on estimation method are provided in the Supplemental material 1.

Model evaluation and simulation

For pharmacokinetic and exposure-response analyses, the final model stability was assessed by medians of the non-parametric bootstrap method implemented in PsN [38], generating 2000 datasets by re-sampling from the original dataset. Median parameters values with their 95%CI were thus derived and compared with the final model estimates. The predictive performance of the pharmacokinetic models was evaluated by calculation of the normalized prediction distribution errors (NPDEs) [41]. Visual predictive check (VPC) was finally performed with NONMEM® by simulations based on the final pharmacokinetic model with interpatient variability using 1000 *UGT2B7* TC (Het-Alt) or CC (Hom-Alt) individuals of 77 kg (median population BW) to calculate the average concentration time profile with 95% prediction intervals (95%PI).

The trough concentrations at steady-state ($Cmin_{SS}$) after administration of 1 mg b.i.d were calculated based on the final model in 500 individuals per strata of *UGT2B7* rs7439366 genotypes and BW values and then plotted with the trough concentrations range expected for the recommended dose of 1 mg b.i.d (4-5 ng/mL) reported in the clinical trials supporting the development of varenicline for comparison [42]. Figures were generated with GraphPad Prism® (Version 5.00 for Windows, GraphPad Software, San Diego California USA, http://www.graphpad.com/) and with R (v. 3.1.2, http://www.r-project.org).

RESULTS

Study population and data

Among the 95 subjects enrolled in the study and receiving varenicline, 8 subjects had early treatment discontinuation and 5 subjects had no detectable varenicline levels suggesting a poor treatment adherence. The remaining 82 subjects provided a total of 121 concentrations for the pharmacokinetic analysis: 70 samples were collected at treatment initiation (from days 1 to 10) and 51 samples were collected after one month of treatment (from days 35 to 88). Subject's characteristics are presented in Table 1. For the exposure-response analysis, a total of 373 CO measurements from 76 patients were available (median= 2 ppm, range= 0-45 ppm). Details on data are provided in the Supplemental material 1.

Pharmacokinetic-pharmacodynamic analysis

Pharmacokinetic analysis

A one-compartment model with first-order absorption and elimination described adequately the data. No improvement to the fit was observed using a two-compartment model (ΔOFV = -0.3). Owing to very limited measurements at early time points after drug intake, the absorption parameter k_a could not be estimated and was thus fixed to 0.98 h^{-1} to achieve a peak concentration 3-4 hours after drug intake as reported in literature [15]. The association of an inter-individual variability to V/F or k_a in addition to CL/F did not improve the model fit (ΔOFV ≥ -0.3). Finally, residual variability was described by a proportional error model. The estimates of the base pharmacokinetic model were a CL/F of 9.6 L/h and a V/F of 211 L. The inter-individual variability for CL/F was 26% with a shrinkage of 22% which is not misleading for covariate analysis [43].

Univariate analyses showed that the effect of BW (ΔOFV = -14.5, p<0.001), height (ΔOFV = -11.1, p<0.001) and sex (ΔOFV = -7.4, p=0.007) on CL/F improved significantly the description of the data. In contrast, age, ethnicity, smoking status, co-medications and GFR were not associated to varenicline pharmacokinetics (ΔOFV > -2.2, p>0.14). Both linear and allometric power functions described adequately the relationship between CL/F and BW (ΔOFV ≤ -14.5). According to the AIC, the allometric power function was chosen to depict the BW impact on CL/F (AIC= 242 and AIC= 240 for the allometric and linear relationships, respectively).

Among all tested genetic covariates, only *UGT2B7* rs7439366 (ΔOFV = -9.0, p=0.003) and *NR1|2* rs1523130 (ΔOFV = -5.6, p=0.02) showed an influence on varenicline CL/F. No statistical significant differences in CL/F between *UGT2B7* rs7439366 Hom-Alt and Het-Alt individuals as well as between *NR1|2* rs1523130 Hom-Alt and Het-Alt individuals were observed compared to the rich model (ΔOFV > -0.03, p>0.87). A CL/F of 8.5 L/h was estimated for *UGT2B7* rs7439366 Hom-Alt and Het-Alt subjects and increased to 10.3 L/h for Ref individuals. *NR1|2* rs1523130 Hom-Alt and Het-Alt individuals were found to have a CL/F of 9.8 L/h, which decreased to 7.4 L/h for Ref subjects.

Multivariate analyses revealed that height and sex were correlated to BW, which was thus identified as the only significant non-genetic covariate influencing varenicline elimination. The inclusion of the *UGT2B7* rs7439366 polymorphism on CL/F further improved the description of the data (ΔOFV = -6.4, p=0.01). On the other hand *NR1|2* rs1523130 did not remain statistically significant (ΔOFV = 1.5, p=0.22). Our final results suggest that CL/F is increased by 46% in 100-kg individuals compared to 60-kg individuals and by 21% in *UGT2B7* rs7439366 Ref individuals with respect to Hom-Alt and Het-Alt individuals. BW and the *UGT2B7* rs7439366 polymorphism explained 14% and 9% of the inter-individual variability in CL/F, respectively.

Of 2000 replicates analyzed during the bootstrap analysis of the pharmacokinetic model, 1% failed to minimize successfully and were excluded. The bootstrap and the final model results are presented in Table 2. The model was considered reliable since the parameter estimates differed less than 10% from the bootstrap medians and lied within the bootstrap 95%CI. NPDE distribution was not found to be significantly different from a normal distribution and the goodness-of-fit plots were satisfactory meaning that the model adequately described the observed data (Supplemental Figure 1 and 2). The VPC of the observed dose-normalized concentrations versus time from the beginning of the treatment is shown in Figure 1 and the prediction- and variability-corrected VPC of the concentrations versus time after dose is shown in Supplemental Figure 3.

Major differences in varenicline exposure were observed with regard to BW and *UGT2B7* rs7439366 polymorphism in Figure 2. In patients with high BW, 31% and 72% of Ref and Hom-Alt/Het-Alt individuals, respectively are under the targeted range. Patients with very low BW and especially Hom-Alt/Het-Alt individuals are over the targeted range.

Exposure-response analysis

The basal turnover model fitted the data correctly. The A parameter estimate was 5.8 ppm/d and the EFFCPD parameter 1.9 ppm/d, meaning that for one more cigarette smoked during the day, Kin is increased by 1.9 ppm. Kout could not be estimated and was thus fixed to 2.77 day^{-1} to achieve a CO

mean half-life of 6 hours [44]. Residual variability was described by an additive error model and estimated to 2.3 ppm. The inter-individual variability of the input rate Kin (IIV Kin) was 46%. All the parameters were correctly estimated (relative standard error, RSE< 15%).

Univariate analysis showed that sex (ΔOFV = -11.3, p<0.001), score of insomnia (ΔOFV=-15.7, p<0.001), score of depression (ΔOFV=-6.1, p=0.01) and score of irritation (ΔOFV=-5.4, p=0.02) had a significant impact on the EFFCPD parameter. All remaining covariates were not improving the basal model (ΔOFV > -3.70, p=0.054).

Multivariate analysis did not discard any of the identified influential covariates on EFFCPD (ΔOFV > 7.7, p=0.006). The model suggested a decrease in EFFCPD of 63% in female compared to male individuals, an increase in EFFCPD of 154% in individuals with the highest score on insomnia (15) compared to the lowest score (3), an increase of 96% in individuals with the highest score of depression (20) compared to the lowest score (4) and a decrease of 62% in individuals with the highest score of irritation (20) compared to the lowest score (4) (see Supplemental Table 1). The effects of sex, score of insomnia, depression and irritation were correctly estimated (RSE = 8%, 24%, 39% and 12%, respectively). The final model results are presented in Supplemental Table 1.

Of 2000 replicates analyzed during the bootstrap analysis of the exposure-response model, 1% failed to minimize successfully and were excluded. The parameter estimates of A, IIV Kin and the residual error differed less than 10% from the bootstrap medians and lied within the bootstrap 95%CI. However, the estimates of EFFCPD and of the effects of the sex, score of insomnia, depression and irritation differed more than 16% from the bootstrap medians. 95% CI of the bootstrap medians for the effect of the sex and the three scores were not significant.

DISCUSSION

This work presents the exposure to varenicline in a real setting of patients enrolled in a clinical and pharmacogenetic study. The pharmacokinetics of varenicline are in good accordance with reported values. The CL/F estimate for a 70-kg individual with normal creatinine clearance was 8.5 L/h (95%CI=7.9-9.2) in Hom-Alt/Het-Alt individuals and increased by 21% in Ref individuals (10.3 L/h, 95%CI=8.5-12.2). This range is in accordance with the clearance reported for a 70-kg individual with a creatinine clearance of 100 mL/min (10.4 L/h, 95%CI=10.2-10.6) [15]. The V/F estimated in the present study (228 L, 95%CI=192-275) was significantly lower than the steady-state volume of distribution published for a two-compartment model (Vss=415 L, 95%CI=371-463) and so was our estimation of the elimination half-life (19h vs 24h). Since 95% of the drug concentrations available in our study population were collected less than 12 hours after dose administration, the characterization of the profound compartment could not be done. Nevertheless, it is in agreement with the central volume estimated in adolescents by a one-compartment model (V =215 L, 95%CI=204-238) [45]. Only 10% of the study population had a mildly reduced kidney function (defined as GFR estimated with MDRD formula < 90 mL/min). The absence of subjects with severe impaired renal function might explain the absence of effect of this variable on varenicline elimination, previously described in adults [15]. The IIV CL/F (26%) estimated in the base one-compartment model was found to be explained in part by the BW and the genetic polymorphism of *UGT2B7* rs7439366 resulting in a decreased of IIV CL/F to 19% close to the reported value of 25% [15].

The originality of our work is in the analysis of the influence of genetic factors (i.e. *OCT2*, *UGT2B7* and nuclear factors) on varenicline clearance. *UGT2B7* rs7439366 Hom-Alt/Het-Alt individuals had a decrease of varenicline clearance compared to Ref subjects. This is in accordance with a reported reduced morphine-6-glucuronide/morphine ratio in Hom-Alt individuals compared to Ref individuals in a study involving 86 patients [46] although contradictory results have been published [47,48]. Of note, it has been showed that PXR is not involved in *UGT2B7* expression [49,50] but could regulate the OCT2 expression as suggested in rats [51].

Despite the weak proportion of variability in the varenicline concentrations separately explained by BW (14%) or *UGT2B7* rs7439366 polymorphism (9%), Figure 2 highlighted a 4-times variation in varenicline exposure between the two extreme groups of BW and *UGT2B7* rs7439366 polymorphism ($Cmin_{SS}$ = 12 ng/mL and 3.4 ng/mL in the group of 45 kg/Hom-Alt/Het-Alt and 130 kg/Ref individuals, respectively). The variation in varenicline exposure decreased to 2.6 if only the two extreme groups of BW are considered ($Cmin_{SS}$ = 12 ng/mL and 4.6 ng/mL in the group of 45 kg and 130 kg with the same *UGT2B7* rs7439366 genotype, respectively). Moreover, a positive association between varenicline

exposure and probability of abstinence or nausea incidence has been shown at the dose 1 mg b.i.d [3]. Subjects with very low BW and especially the Hom-Alt/Het-Alt subjects are overexposed to varenicline and nausea could be more frequent and could affect the patient adherence to the treatment. In contrary, overweight smokers and Ref individuals in particular might have a lower probability of abstinence at this dose due to underexposition to the drug. Thus, dose adjustment according to BW values and *UGT2B7* genotype if known should be considered to maximize the probability of abstinence while limiting the apparition of nausea, the most prevalent side-effect of varenicline. For overweight subjects and especially *UGT2B7* Ref individuals, this work suggests to increase the dose as it has been already proposed for nonresponders to the standard dose in a clinical experience [52]. We acknowledge that in the present study the effect of *UGT2B7* rs7439366 polymorphism observed on varenicline concentrations is more important than expected based on the data published by Obach et al. [4]. It is indeed reported that varenicline N-carbamoylglucuronide represent in excreta 3.6% of the dose but the study included only 6 subjects with unknown metabolizer status for UGT2B7. In the present study, the genotypes *UGT2B7* rs7439366 CC/TC corresponded to the majority of the study sample (77%, table 1) which is in good agreement with the reported genotype distribution in the European population and excluded a selection bias [53]. In the present study, the effect of *UGT2B7* rs7439366 polymorphism on varenicline pharmacokinetics is of limited clinical relevance and however lower than the body weight effect.

In this study, the exposure-response analysis did not show any influence of varenicline concentrations on CO levels contrary to the study from Ravva et al. [3]. Here, most of the patients (92%) were abstinent (expired CO measurements below 10 ppm) thus preventing the estimation of any positive relationship between varenicline exposure and abstinence. In contrast in the study from Ravva et al. positive relationship was characterized in a study population with almost 50% of abstinent individuals. The bootstrap analysis revealed that the effect of the covariates were not statistically significant possibly due to the right-skewed distribution of the covariates in our analyzed population.

Limitations of the present work should be noted. First, the limited amount of pharmacokinetic data in early and late times after dose prevented the estimation of the absorption constant and of the second volume of distribution of varenicline, respectively. A second major limitation of the work resides in the assumption that the participants had good adherence to the treatment and that all doses were taken by the participants. It must be mentioned that, although adherence cannot be ascertained, all participants were asked about the actual intake of varenicline at each visit. Third, in this analyzed population most of the participants were abstinent after a 3-month treatment period.

Despite these limitations, our study is the first to analyze the genetically-based variability of varenicline pharmacokinetic. This work showed that *UGT2B7* polymorphism and BW can influence varenicline concentrations. During smoking cessation program, in case of lack of abstinence in overweight individuals or apparition of side-effects in underweight individuals, dose adjustment based on BW and, if available, on *UGT2B7* genotype, might be useful to improve clinical efficacy and tolerability of varenicline.

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Author contribution

Anaïs Glatard wrote manuscript, analyzed data.

Monia Guidi wrote manuscript, analyzed data.

Maria Dobrinas wrote manuscript, designed research, performed research.

Jacques Cornuz wrote manuscript, designed research.

Chantal Csajka wrote manuscript, analyzed data.

Chin B. Eap wrote manuscript, designed research, obtained fundings.

Compliance with Ethical Standards

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Anaïs Glatard, Monia Guidi, Maria Dobrinas, Jacques Cornuz, Chantal Csajka and Chin B. Eap declare that they have no conflict of interest.

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