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ARTICLE

Pharmacokinetic/pharmacodynamic modeling of cortical dopamine concentrations after quetiapine lipid core nanocapsules administration to schizophrenia phenotyped rats

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Abstract

Schizophrenia (SCZ) response to pharmacological treatment is highly variable. Quetiapine (QTP) administered as QTP lipid core nanocapsules (QLNC) has been shown to modulate drug delivery to the brain of SCZ phenotyped rats (SPR). In the present study, we describe the brain concentration–effect relationship after administrations of QTP as a solution or QLNC to SPR and naïve animals. A semi-mechanistic pharmacokinetic (PK) model describing free QTP concentrations in the brain was linked to a pharmacodynamic (PD) model to correlate the drug kinetics to changes in dopamine (DA) medial prefrontal cortex extracellular concentrations determined by intracerebral microdialysis. Different structural models were investigated to fit DA concentrations after QTP dosing, and the final model describes the synthesis, release, and elimination of DA using a pool compartment. The results show that nanoparticles increase QTP brain concentrations and DA peak after drug dosing to SPR. To the best of our knowledge, this is the first study that combines microdialysis and PK/PD modeling in a neurodevelopmental model of SCZ to investigate how a nanocarrier can modulate drug PK and PD, contributing to the development of new treatment strategies for SCZ.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Schizophrenia (SCZ) treatment presents 30% of nonrespondent patients. The antipsychotic quetiapine (QTP) increases brain dopamine (DA) concentrations, and

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it is used to treat SCZ. Previously, we showed that QTP lipid core nanocapsules (QLNC) can increase the drug penetration through the blood–brain barrier of SCZ phenotyped rats (SPR), and we developed a population pharmacokinetic (PK) model to describe free plasma and medial prefrontal cortex (mPFC) QTP concentrations in naïve animals and SPR.

WHAT QUESTION DID THIS STUDY ADDRESS?

Is it possible to correlate the increase on free QTP concentrations in the brain of SPR with the changes in mPFC DA levels following QLNC intravenous dosing?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

This study shows that pharmacodynamic (PD) properties are altered in disease animals. A semimechanistic PK/PD model described the relationship between unbound QTP and DA concentrations following drug administration as solution or nanoencapsulated (QLNC) to naïve animals and SPR, shading light on the mechanisms involved on the increase in DA brain levels in SPR when the drug is nanoencapsulated.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

The PK/PD model allows a better understanding of the lack of response to antipsychotics in SCZ treatments and the role of the nanodelivery system to overcome QTP-reduced brain penetration and effect in the disease condition. This work also demonstrates the importance of evaluating the effect of unbound drug delivered by nanocarriers at the site of action in the disease condition.

INTRODUCTION

Schizophrenia (SCZ) is a severe mental disorder that affects how a person thinks, feels, and behaves, and in addition to presenting with the subjective experience of psychotic symptoms, it significantly shortens a patient's life expectancy in comparison with the general population.[1] A dysregulation in brain dopaminergic circuits with reduced dopaminergic signaling in the mesocortical pathway has been proposed as an underlying dysfunction in SCZ, especially related to negative and cognitive symptoms. Antipsychotic drugs used in SCZ treatment are based in blocking the D_2 dopamine (DA) receptors, modulating these neurotransmitter levels in the brain, and contributing to reduced psychotic symptoms.[2,3]

Quetiapine (QTP) is a second-generation antipsychotic that has an atypical profile against the positive, negative, and cognitive symptoms of SCZ with a low propensity to induce extrapyramidal adverse effects. Although its mechanism of action is not fully understood, QTP has the ability to increase catecholamine levels, such as DA, in the prefrontal cortex, which plays a role in its clinical effectiveness.[3–7]

Approximately 30% of SCZ patients do not respond to pharmacological treatment.[8,9] Pharmacokinetic (PK) and pharmacodynamic (PD) components can be associated with resistance to SCZ pharmacotherapy. The high therapeutic variability related to the PD component can be associated with alterations in antipsychotic drug-receptor binding or signal transduction caused by SCZ.[10] The disease can also affect biophase antipsychotic concentrations (PK) as a result of changes in the blood–brain barrier (BBB) transporter expression,[11,12] impacting drug penetration to the central nervous system (CNS).

Assuming that drug delivery to the CNS could be limited in SCZ patients, we developed QTP lipid core nanocapsules (QLNC) and investigated the drug unbound cortical and hippocampal concentrations in naïve rats and SCZ phenotyped rats (SPR) models of disease.[13,14] A semimechanistic population PK (popPK) model was used to understand the changes in plasma and brain PK after administration of QTP in solution (FQ) or nanoencapsulated (QLNC) to SPR and naïve animals.[10] We have shown that QTP unbound brain exposure is reduced in SPR in comparison with naïve animals, supporting the hypothesis that BBB dysfunction contributes to treatment failures. Furthermore, QTP nanoencapsulation returned drug penetration in SPR to the levels observed in naïve animals.

Preclinical PK/PD models described in the literature for antipsychotic drugs use in vivo PK (plasma or tissue drug concentration) and in vitro PD (dopaminergic or serotoninergic receptor occupancy) data to establish a temporal relationship between drug concentration and effect. Antipsychotic drugs such as risperidone and

olanzapine have been described by these models, which were used to perform simulations and predictions of effect in humans.[15,16] However, the in vivo temporal relationship between unbound drug brain concentration and neurotransmitter concentration in an SCZ animal model has not been established so far.

In the present work, we aimed to increase the understanding of the role of QTP and its nanoencapsulated form on SCZ pharmacotherapy. The novel contribution of the present analysis is the developing of a model relating free brain concentrations of QTP to the response (DA) profiles. We developed a PK/PD model merging the previously developed semimechanistic popPK model with medial prefrontal cortex (mPFC) extracellular DA levels measured by microdialysis in naïve rats and SPR following FQ and QLNC administration. The PK/PD model allows exploring the PD component of SCZ variability in response to treatment and the influence of QTP nanoencapsulation on these neurotransmitter levels.

METHODS

A brief description of QLNC (1 mg/mL) preparation and characterization as well as the protocol for the neurodevelopmental animal model of SCZ are presented in Supplementary Material S1.

Experimental design

Animals

The effect of FQ and QLNC on mPFC extracellular DA concentrations on naïve animals and SPR was investigated using intracerebral microdialysis. Naïve rats and SPR offspring were divided into the following eight groups according to disease status, sex, and treatment type: $FQ_{naïve,male}$ ($n=7$); $FQ_{naïve,female}$ ($n=6$); $FQ_{SPR,male}$ ($n=5$); $FQ_{SPR,female}$ ($n=6$); $QLNC_{naïve,male}$ ($n=7$); $QLNC_{naïve,female}$ ($n=6$); $QLNC_{SPR,male}$ ($n=6$); and $QLNC_{SPR,female}$ ($n=6$).

Surgical procedure

Microdialysis methodology for assessing DA concentration in the brain was performed as detailed by Carreño et al.[17] Briefly, rats were anesthetized with ketamine, xylazine, and acepromazine (100, 10, and 2 mg/kg, respectively; i.p.), received preemptive analgesia with ketoprofen (5 mg/kg, s.c.) and local anesthesia with lidocaine (5 mg/kg s.c.) and bupivacaine (2 mg/kg s.c.). A guide cannula was surgically implanted in the rat mPFC (A, +3.2 mm; L, +0.8 mm; V, −5.2 mm relative to bregma) with a stereotaxic frame 2 days before the microdialysis experiment. On the day of the experiment, the guide cannula was carefully replaced by a CMA 12 microdialysis probe (3 mm, polyarylethersulfone (PAES) membrane, 20 kDa cutoff–CMA®, CMA Microdyalisis), which was perfused with an artificial cerebroespinal fluid (ACF) solution for equilibration at a flow rate of 1 µL/min. After 1 h, four dialysate samples were collected in 20 min intervals to determine DA basal levels. The animals then received a single 5 mg/kg of FQ or QLNC dose via the lateral caudal vein, and 15 microdialysate samples (20 min interval/sample), up to 280 min, were collected in iced amber microcentrifuge tubes containing an antioxidative mixture (1:4 parts mixture:sample) to prevent DA degradation. Samples were stored at − 80 ± 2°C until analysis.

Analytical determination

The quantification of DA in microdialysate samples was performed using a validated liquid chromatography–electrospray ionization–tandem mass spectrometry method.[17] Microdialysate samples were directly injected into the system without the need of an internal standard or clean-up process. No attempt to correct for in vitro probe recovery was made in the present study given that in vitro recovery cannot be directly extrapolated to in vivo samples. Therefore, DA extracellular concentrations were reported as directly measured in microdialysate samples.

PK/PD modeling

Data analysis was performed through the population approach using the software NONMEM (Version 7.4, ICON Development Solutions) with the first-order conditional estimation method and interaction. The Perl-speaks NONMEM toolkit Version 4.9.0 was used for the complementary analysis. Model management was done in PIRANA® Version 2.9.9 (Pirana Software and Consulting). Ggplot2 and xpose4 libraries for R Version 4.1.1 and RStudio Version 1.4.1717 (The R Foundation for Statistical Computing) were used for graphical analysis.

Interindividual variability (IIV) was modeled exponentially, and residual variability was described with an additive error model. DA microdialysate concentrations were described by the integral over each collection interval[18]; therefore, no assumptions regarding collection times were made.

Typical unbound brain QTP concentration profiles for each experimental group were generated from the semimechanistic PK model developed previously[19] (Figure S2) and were used as the drivers of the DA response.

The following mechanisms and assumptions were taken into consideration during model building: (i) in the absence of perturbation (i.e., lack of drug administration), the DA concentration remains constant as a result of the balance between the release and reuptake mechanisms and accounted for the zero- and first-order rate constants K_{in} for release and K_{out} for reuptake, respectively; (ii) QTP exerts its action exacerbating DA release mechanisms; (iii) delays in response with respect the free brain QTP concentration ($C_{u,brain}$) profiles can be present as a result of either further distribution processes and/or noninstantaneous receptor binding kinetics; (iv) the presence of acute autoregulation might have a role in the fast recovery of the baseline levels after treatment; and (v) an effect of the nanoparticles (NP) at the level of the target and beyond their implication in PK cannot be ruled out.

Covariate analysis was performed by the stepwise covariate model, considering a significant reduction of the objective function value (OFV) as described later. From the base model, we included each covariate one by one. The model with the covariate was compared with the base model, and a drop in 3.84 points in OFV was considered significant. The second step in the analysis was the elimination of each covariate included. Judiciously, when removing a covariate, the OFV increase in 6.64 points was considered a significant covariate. The variables evaluated were sex, type of formulation (FQ or QNLC), and the SCZ condition, which was addressed by the values of the prepulse inhibition (PPI) test. This test evaluates the startle reduction and the dysfunction in the sensorimotor gating present in SCZ animals, which was used to confirm the SCZ phenotype.

Model selection was guided by (i) changes in the minimum value of the objective function approximately equal to $-2\times\log(\text{likelihood})$ (-2LL) (For two nested models differing in one parameter, a decrease in 3.84 or 6.64 points in -2LL is significant at the 5% or 1% level, respectively.); (ii) visual exploration of goodness-of-fit (GOF) plots; and (iii) precision of model parameters reflected as the relative standard error computed as the ratio between the standard error and the parameter estimate.

The simulation-based diagnostic tool, visual predictive check, was generated to evaluate model performance. A total of 1000 data sets of the same characteristics as the original were simulated using the structure and the corresponding parameters of the selected model. For each simulated data set and sampling time, the 2.5th, 50th, and 97.5th percentiles were calculated. Then, the 95% prediction intervals of the aforementioned percentiles were obtained and displayed graphically together with the corresponding percentiles calculated from the raw data.

Parameter precision was further investigated analyzing 1000 bootstrap data sets, calculating for each model parameter the median value and the 95% confidence intervals.

Statistical analysis

A Student *t*-test was performed to account the differences in PPI values between naïve rats and SPR considering a confidence level of 95% ($\alpha=0.05$). The significance of the parameters across the four experimental groups was evaluated through the analysis of variance statistic tests ($\alpha=0.05$) followed by Bonferroni tests. Statistical analyses were performed in the R program Version 4.2.1 and RStudio Version 2022.07.1+554 (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

A total of 924 DA microdialysate observations from 49 rats were used for the PK/PD model development for FQ and QLNC formulations. No data below the limit of quantification were reported, and missing data were excluded from the analysis because they represented less than 5% of the total. One animal was excluded from the analysis because it showed a PPI value discrepant of its experimental group (75.38%).

Figure 1 shows the median time course of DA in the experimental groups studied. Administration of QTP elicited a transient increase in DA levels. Maximum median DA change from baseline was 98.6, 21.4.0, 114.8, and 141.2% for the $FQ_{naïve}$, FQ_{SPR}, $QLNC_{naïve}$, and $QLNC_{SPR}$ groups, respectively. The time at which DA peaks occurred were 3, 2.3, 4, and 4.3 h, for the corresponding groups $FQ_{naïve}$, FQ_{SPR}, $QLNC_{naïve}$, and $QLNC_{SPR}$, respectively.

PK/PD model

A model considering the presence of a pool of precursors of DA behaved significantly better that the simple indirect response model ($p<0.001$). Equations (1) and (2) represent the core model for DA dynamics.

$$\frac{dPool}{dt} = K_{in} - K_{rel} \times \left[1 + f\left(C_{Qtp}\right) \times g(NP)\right] \times Pool \quad (1)$$

$$\frac{dDA}{dt} = K_{rel} \times \left[1 + f\left(C_{Qtp}\right) \times g(NP)\right] \times Pool - K_{out} \times DA \times MOD \quad (2)$$

where K_{in} and K_{rel} are the zero- and first-order rate constants governing the synthesis and release of DA precursors, respectively, and K_{out} represents the first-order rate

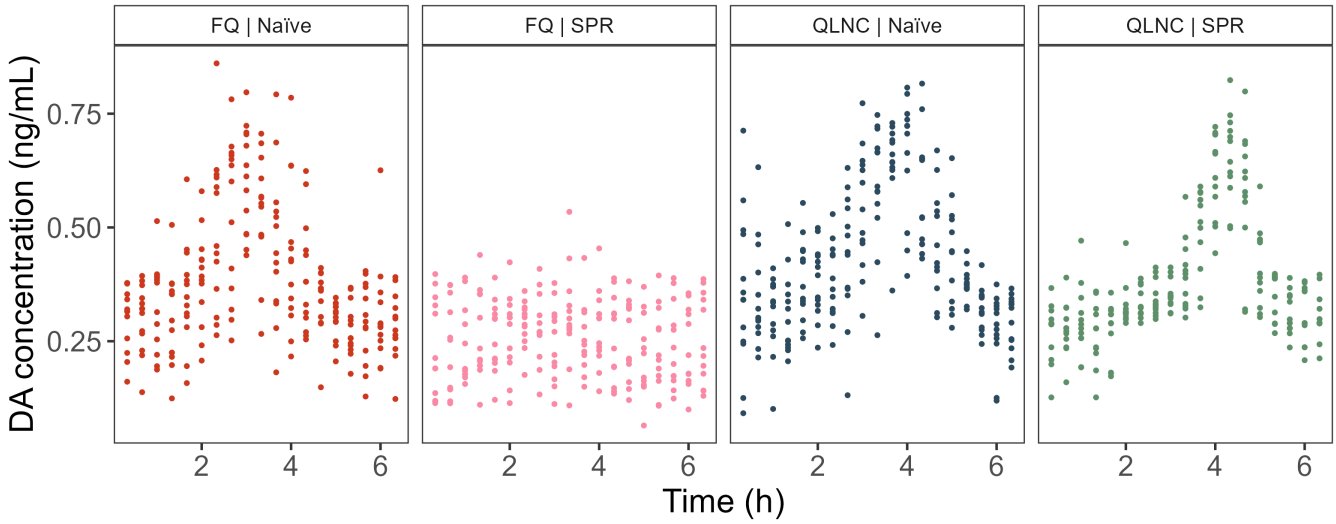

FIGURE 1 Dopamine concentrations in medial prefrontal cortex determined by microdialysis after FQ and QLNC 5 mg/kg i.v. dosing to male and female naïve rats and SPR: $FQ_{naïve}$ ($n = 13$), FQ_{SPR} ($n = 11$), $QLNC_{naïve}$ ($n = 13$), $QLNC_{SPR}$ ($n = 12$). FQ, solution; QLNC, quetiapine lipid core nanocapsules; SPR, schizophrenia phenotyped rats.

constant resembling DA reuptake. The terms $f(C_{Qtp})$, $g(NP)$, and MOD relate to the PD effects of QTP, impact of the NP, and the feedback (regulation) mechanisms, respectively. In the absence of treatment, $f(C_{Qtp}) \times g(NP)$ and MOD show the values of zero and 1, respectively, and the system is characterized by the initial conditions $Pool_0$ and DA_0, where the parameters K_{in} and K_{out} are derived from the expressions $K_{rel} \times Pool_0$, and $K_{rel} \times Pool_0/DA_0$, respectively.

With respect to the PD element of the model, it was found that the DA response was significantly better characterized with the use of an effect compartment model compared with the predicted $C_{u,brain}$ profiles or considering a nonequilibrium in receptor binding ($p < 0.001$). In addition, the maximum effect (E_{max}) or sigmoidal E_{max} model did not provide any improvement in the fit compared with the linear PD model ($p > 0.05$). Therefore, the term $f(C_{QTP})$ in Equations (1) and (2) takes the form $E_{QTP} \times C_{u,brain,e}$; the former is the parameter representing the slope of the K_{rel} versus $C_{u,brain,e}$, the predicted unbound concentration in the effect site according to Equation (3).

$$\frac{dC_{u,brain,e}}{dt} = K_{e0} \times \left(C_{u,brain} - C_{u,brain,e}\right) \quad (3)$$

where the parameter K_{e0} is the first-order rate constant governing the distribution equilibrium between the brain and the target site.

The negative feedback mechanism was incorporated in the model through a modulator with dynamics described by Equation (4) and controlled by the first-order rate constant, K_{mod}. The increase of DA levels over baseline triggers the increased of MOD, which exacerbates the reuptake mechanisms, allowing a faster recovery of baseline.

$$\frac{dMOD}{dt} = K_{mod} \times \left[\frac{DA}{DA_0} - MOD\right] \quad (4)$$

The model described by Equations (1) to (4) provided a fair description of the data except for the delay in DA increase observed in the groups receiving the drug nanoencapsulated. We postulate that NP at the target site compete reversibly with QTP and are degraded following a first-order process controlled by the first-order rate constant K_{NP} as shown in Equation (5).

$$\frac{dNP}{dt} = -K_{NP} \times NP \quad (5)$$

The expression $g(NP)$ in Equations (1) and (2) takes the form $1/(1 + NP)$, and the initial condition of the NP effect (NP_0) represents a parameter to be estimated.

IIV was found to be significant on the following model parameters: K_{in}, E_{QTP}, K_{e0}, K_{mod}, DA_0, and NP_0 ($p < 0.05$).

Figure 2 provides the schematic and mathematical representation of the selected model, identifying and defining all model parameters.

The covariate analysis shows that whereas sex and weight did not impact model parameters ($p > 0.05$), PPI (a surrogate marker of the disease) was associated with a greater drug effect and higher values of DA_0 ($p < 0.001$) as shown in Equations (6) and (7).

$$E_{QTP} = \theta_{QTP} \times \left[1 + \theta_{E_{QTP},SPR} \times \left(PPI - PPI_{md}\right)\right] \quad (6)$$

$$DA_0 = \theta_{DA,0} \bullet \left[1 + \theta_{DA_0,SPR} \times \left(PPI - PPI_{md}\right)\right] \quad (7)$$

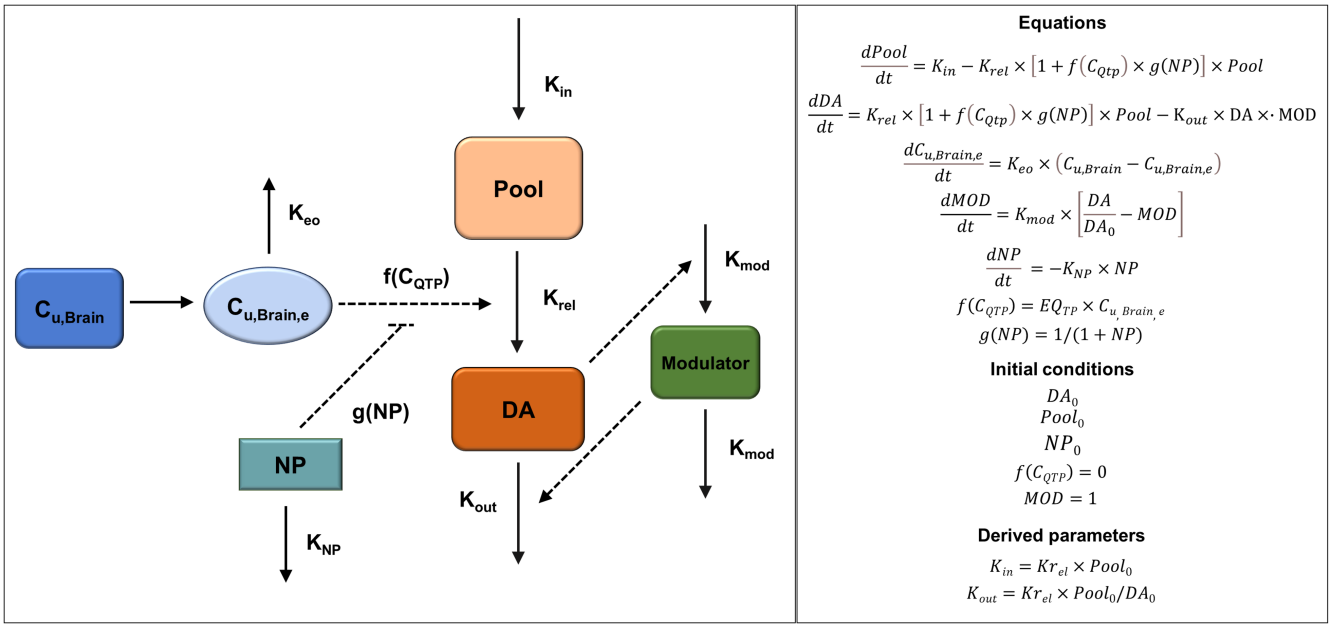

FIGURE 2 Schematic representation of the final pharmacokinetic/pharmacodynamic model developed for quetiapine. All parameters and terms are defined in the text. DA, dopamine; FQ, solution; QLNC, quetiapine lipid core nanocapsules; SPR, schizophrenia phenotyped rats. K_{in}, zero-order rate constant; K_{eo}, K_{rel}, K_{out}, K_{mod} and K_{NP} are first-order rate constants; $f(C_{QTP})$ and E_{QTP}, the effect of QTP; g(NP), the impact of NP on effect; Cu, brain, the free brain QTP concentrations.

TABLE 1 Parameters estimated for the semimechanistic pharmacokinetic/pharmacodynamic model for each group.

	Individual estimates, median (SD)			
Parameters	**FQ–näive**	**FQ–SPR**	**QLNC–naïve**	**QLNC–SPR**
$Pool_0$ (ng/mL)	2.19 (2.97)	2.07 (2.79)	2.57 (1.54)	3.19 (1.21)
K_{in} (ng/mL * h)	0.299 (0.134)	0.853 (0.902)	0.609 (0.245)	0.913 (0.683)
DA_0 (ng/mL)	0.298 (0.062)	0.222 (0.068)[a]	0.340 (0.057)	0.294 (0.032)[a]
E_{QTP}	37.3 (10.9)	33.6 (18.4)	50.8 (21.5)	100.7 (38.3)[a,b,c]
K_{eo} (h^{-1})	0.450 (0.131)	0.500 (0.188)	0.568 (0.238)	1.01 (0.323)[a,b,c]
K_{mod} (h^{-1})	0.529 (0.304)	0.910 (0.869)	0.772 (0.646)	1.27 (0.91)
K_{NP} (h^{-1})	–	–	3.79 (0.78)	2.56 (0.42)[d]
NP_0 (ng/mL)	–	–	8.4×10^4 (2.4×10^4)	6.3×10^4 (1.7×10^4)[d]

Abbreviations: DA, dopamine; FQ, solution; QLNC, quetiapine lipid core nanocapsules; SPR, schizophrenia phenotyped rats; K_{in}, zero-order rate constant; K_{eo}, K_{mod} and K_{NP} are first-order rate constants.

[a]Statistically different from group FQ–naïve.

[b]Statistically different from group FQ–SPR.

[c]Statistically different from group QLNC–naïve; one-way analysis of variance followed by Bonferroni test, $p < 0.05$.

[d]Statistically different from group QLNC–näive; t-test, $p < 0.05$.

where PPI_{md} is the median PPI value across the entire animal study population (33.4%).

The population PK/PD parameters estimated for the final model are shown in Table S1, where it can be observed that the point estimates of both fixed and random effects were obtained precisely (the NMTRAN code corresponding to the selected model is available in Supplementary Material S1). Visual inspection of the different GOF plots (Figure S3a) revealed the absence of tendencies, suggesting the lack of major model misspecifications. However, the results of the visual predictive checks (Figure S3b) showed that maximum DA levels were underpredicted for the case of the animals administered with NP despite the NP effects incorporated into the model. Such deviation was investigated in detailed following a two-stage approach. Table 1 lists the model parameter estimates for each experimental group expressed as mean and SD. DA baseline values presented differences between naïve rats and SPR groups as

expected, accounting for the disease ($p < 0.05$). E_{QTP} and K_{e0} were different for the animals who were schizophrenic and received the drug nanoencapsulated. The NP influence was also different for the naïve and schizophrenic animals, indicating that the NP interaction is different in the presence of disease.

Figure 3 shows the individual observed and model predicted profiles obtained from the two-stage approach for each experimental scenario together with the typical profiles generated using the mean estimates listed in Table 1. The agreement between observations and predictions is remarkable. The individual model predictions obtained from the population and two-stage approaches are shown in Figure S4, indicating very similar performance.

The dynamics of the main elements of the selected model are showed in Figure 4. Upper panels (Figure 4a) describe the time course of QTP-free concentrations in the brain and effect compartments in each experimental group. Note that the peak of QTP in the effect compartment is agreeing with the peak of DA, as shown in Figure 4b. Concentrations decrease in the pool compartment across time, whereas DA increases. Figure 4c shows the time course of NP and the modulator across groups, in which both have higher effects when using NP in schizophrenic groups.

DISCUSSION

In the present study, we describe the in vivo concentration–effect relationship after administrations of QTP as a solution or nanoencapsulated into lipid core nanocapsules to SPR and naïve animals seeking to explore the PK and PD components of variability in schizophrenic patient response to pharmacological treatment. We proposed a semimechanistic PK/PD model to describe the observed increase in DA concentrations in SPR following the administration of a nanocarrier containing QTP.

Preclinical PK/PD models for antipsychotic drugs normally combine the drug transport across the BBB and the time course of D_2 receptor occupancy, which later can be used for translating PK/PD information from animals to human.[15] Although such models have a greater value on antipsychotic drug development, they do not consider drug-related alterations on PK and PD caused by SCZ status on active influx and efflux transporters as well as on the D_2 receptors.

The model published by Movin-Osswald and Hammarlund-Udeneas[20] to describe prolactin release after remoxipride administration to healthy human volunteers was found adequate to describe the time course of DA in the current investigation and from a mechanistic point of view resembles the synthesis, release, and reuptake DA processes.[20]

Previously, we demonstrated that SPR did not respond to the FQ formulation, in the dose investigated, on the PPI test.[21] Although the neurological pathway that governs PPI response and changes in DA levels in the mPFC might not be correlated, one can infer that alterations in other neurotransmitter receptors as a result of SCZ can be expected. The PK/PD model considers that DA baseline levels in the rats before QTP administration and the $DA_{baseline}$ estimated for naïve rats and SPR were significantly different, confirming that SCZ alters DA pathways[2,3] (DA_0 [ng/mL]: $0.288 * [1 + 0.0095 * PPI - PPI_{md}]$) in this animal model.

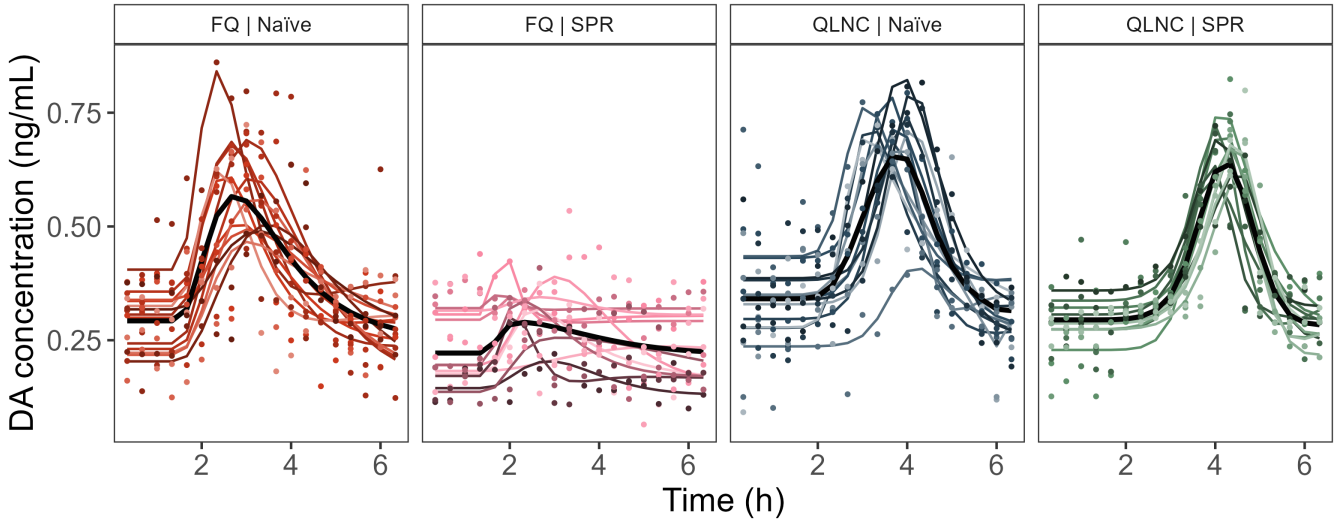

FIGURE 3 Individual observed and model-predicted profiles obtained from the two stages approach for each group. Points are observations, colored lines are individual predictions, and black line is the typical profile of each experimental group. DA, dopamine; FQ, solution; NP, nanoparticles; QLNC, quetiapine lipid core nanocapsules; SPR, schizophrenia phenotyped rats.

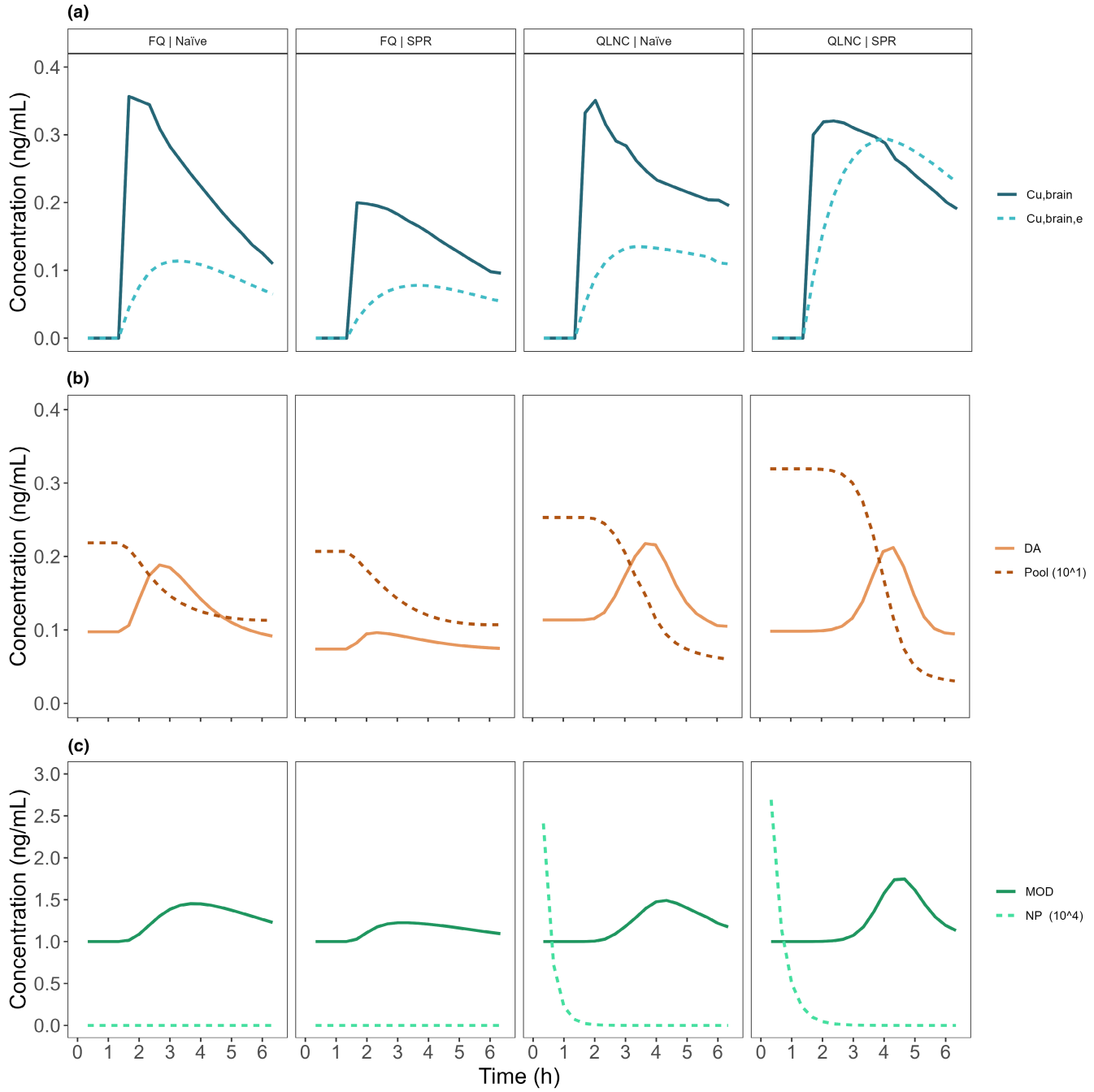

FIGURE 4 Time course of quetiapine-free concentrations in (a) the brain and effect compartment, (b) DA and pool concentrations, and (c) MOD and NP for the different experimental groups. DA, dopamine; FQ, solution; NP, nanoparticles; QLNC, quetiapine lipid core nanocapsules; SPR, schizophrenia phenotyped rats.

In the selected model, the DA precursor is synthesized in a rate described by K_{in} (0.313 ng/mL · h). Catecholamines, such as DA, norepinephrine, and epinephrine, are produced from the precursor amino acid tyrosine by a hydroxylation in the meta-position and a sequential L-decarboxylation.[22] Those processes are accounted for by the pool compartment, in which the precursor is transformed in DA that is released from the pool in a rate determined by K_{rel}. When the unbound QTP concentration binds to D_2 receptors[10,23] in the brain, it stimulates the formation and release of DA from the pool. QTP also presents affinity to cerebral serotonergic 2A receptores ($5HT_{2A}$), histaminergic (H1), and dopaminergic receptors.[4,5,23] The inclusion of the effect compartment was necessary to account for the time delay between QTP binding to receptors and DA release, despite the fact that we are already using free-QTP concentrations in the mPFC interstitial space as PK input. A similar situation

was encountered by Bouw et al.,[24] when the unbound morphine-6-glucuronide brain concentrations was used as the driver of the antinociceptive effect. In that case the estimate of K_{eo} was $1.17 \times 10^{-4} h^{-1}$.

NP did not cause alterations in PD parameter values in naïve groups because the values for E_{QTP} are similar to those observed after FQ dosing (37.3 ± 10.9 and 50.8 ± 21.5 for FQ and QLNC, respectively). However, because lipid core nanocapsules were able to modulate QTP delivery to the brain, an increase in DA levels in the mPFC was observed, and this effect was included in the model by the "nano effect," necessary to describe the QLNC group. Some researchers have suggested the intrinsic NP impact on drug response,[25] and even though we did not find any study that describes the effect of blank NP in neurotransmitter receptors in the brain, our results suggest that NP administered as drug carriers penetrate the brain space and interfere in its receptors, as previously demonstrated by Carreño et al.[26] The molecular mechanism of this interaction remains to be investigated.

The lack of ability of the population parameter estimates to describe the typical tendency of the DA versus time profiles (Figure S3) can be attributed to several aspects, such as nonsymmetrical distribution of the random effects around zero and certain model misspecifications derived by the lack of a control group receiving blank nanocapsules, hampering a better characterization of the aforementioned formulation effect.

The biggest limitation of this work is related to SCZ, which is a very complex disease and difficult to mimic in an animal model, although the animal model used presents face, predictive, and construct validity.[27,28] It is also important to point out that DA concentrations were investigated only in mPFC, which is not the brain region where the QTP effect is more pronounced,[29] although previous work from our group has demonstrated that QTP levels in the hippocampus and mPFC did not differ after FQ and QLNC administration.[19] From a translational point of view, the current contribution untangles drug effects into disease status, PK, and PD, allowing an in silico investigation integrating human PK and drug PD properties. Also, we highlight the importance in evaluating PK and PD in a disease animal model. When translating these findings to humans, it should be considered that the disease can have different progress in each individual, as well as the treatments used by the patient and the resistant and tolerance developed.

To the best of our knowledge, this is the first study that combines microdialysis and PK/PD modeling in a neurodevelopmental model of SCZ to investigate nanocarrier's modulation of antipsychotic drug delivery, contributing to the development of new treatment strategies for SCZ. This study should be seen as a starting point for a new approach for preclinical antipsychotic evaluation using mathematical modeling and simulation by correlating in vivo PK and PD data obtained from a predictive animal model of SCZ. The findings of this work can provide important information about QTP PD and the effect of its nanoencapsulation into lipid core nanocapsules, contributing to the improvement of this drug for use in treating SCZ patients.

AUTHOR CONTRIBUTIONS

B.B.D., F.C., I.F.T., and T.D.C. wrote the manuscript. F.C., S.M.K.R., A.P.H., S.S.G., and T.D.C. designed the research. B.B.D., F.C., V.E.H., L.B.O., K.J.S., K.P., F.S.M. and F.B. performed the research. F.B. contributed with analytical tools. B.B.D., F.C., B.V.A., I.F.T., and T.D.C. analyzed the data.

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CONFLICT OF INTEREST STATEMENT

The authors declared no competing interests for this work.

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REFERENCES

1. Hjorthøj C, Stürup AE, McGrath JJ, Nordentoft M. Years of potential life lost and life expectancy in schizophrenia: a systematic review and meta-analysis. *Lancet Psychiatry*. 2017;4(4):295-301. doi:10.1016/S2215-0366(17)30078-0
2. Grace AA. Dysregulation of the dopamine system in the pathophysiology of schizophrenia and depression. *Nat Rev Neurosci*. 2016;17(8):524-532. doi:10.1038/nrn.2016.57
3. Ichikawa J, Li Z, Dai J, Meltzer HY. Atypical antipsychotic drugs, quetiapine, iloperidone, and Melperone, preferentially increase dopamine and acetylcholine release in rat medial prefrontal cortex: role of 5-HT1A receptor agonism. *Brain Res*. 2002;956(2):349-357. doi:10.1016/S0006-8993(02)03570-9
4. Pira L, Mongeau R, Pani L. The atypical antipsychotic quetiapine increases both noradrenaline and dopamine release in the rat prefrontal cortex. *Eur J Pharmacol*. 2004;504(1–2):61-64. doi:10.1016/j.ejphar.2004.09.053
5. Yamamura S, Ohoyama K, Hamaguchi T, et al. Effects of quetiapine on monoamine, GABA, and glutamate release in rat prefrontal cortex. *Psychopharmacology*. 2009;206(2):243-258. doi:10.1007/s00213-009-1601-9
6. Krause M, Zhu Y, Huhn M, et al. Antipsychotic drugs for patients with schizophrenia and predominant or prominent negative symptoms: a systematic review and meta-analysis. *Eur Arch Psychiatry Clin Neurosci*. 2018;268(7):625-639. doi:10.1007/s00406-018-0869-3
7. Martel JC, Gatti McArthur S. Dopamine receptor subtypes, physiology and pharmacology: new ligands and concepts in schizophrenia. *Front Pharmacol*. 2020;11(July):1-17. doi:10.3389/fphar.2020.01003
8. Meltzer HY. Treatment-resistant schizophrenia – the role of clozapine. *Curr Med Res Opin*. 1997;14:1-20. doi:10.1185/03007999709113338
9. Kennedy JL, Altar CA, Taylor DL, Degtiar I, Hornberger JC. The social and economic burden of treatment-resistant schizophrenia: a systematic literature review. *Int Clin Psychopharmacol*. 2012;29:63-76. doi:10.1097/YIC.0b013e32836508e6
10. Riedel M, Müller N, Stradding M, Spellmann I, Severus E, Möller HJ. Quetiapine in the treatment of schizophrenia and related Disordes. *Neuropsychiatr Dis Treat*. 2007;3(2):219-235. doi:10.2147/nedt.2007.3.2.219
11. Abbott NJ, Patabendige AAK, Dolman DEM, Yusof SR, Begley DJ. Neurobiology of disease structure and function of the blood – brain barrier. *Neurobiol Dis*. 2010;37(1):13-25. doi:10.1016/j.nbd.2009.07.030
12. Klerk OL, Willemsen ATM, Bosker FJ, et al. Psychiatry research: neuroimaging regional increase in P-glycoprotein function in the blood-brain barrier of patients with chronic schizophrenia: a PET study with [11 C] verapamil as a probe for P-glycoprotein function. *Psychiatry Res Neuroimaging*. 2010;183(2):151-156. doi:10.1016/j.pscychresns.2010.05.002
13. Carreño F, Paese K, Silva CM, Guterres SS, Dalla Costa T. Pre-clinical investigation of the modulation of quetiapine plasma pharmacokinetics and tissues biodistribution by lipid-Core Nanocapsules. *J Pharm Biomed Anal*. 2016;119:152-158. doi:10.1016/j.jpba.2015.11.027
14. Carreño F, Paese K, Silva CDM, Guterres SS, Costa TD. Characterizing the mechanism of quetiapine distribution in lipid-core nanocapsules pseudo-phares using a validated LC/UV method. *Quím. Nova*. 2015;38(9):1181-1186. doi:10.5935/0100-4042.20150137
15. Kozielska M, Johnson M, Pilla Reddy V, et al. Pharmacokinetic-pharmacodynamic modeling of the D 2 and 5-HT 2A receptor occupancy of risperidone and paliperidone in rats. *Pharm Res*. 2012;29(7):1932-1948. doi:10.1007/s11095-012-0722-8
16. Johnson M, Kozielska M, Pilla Reddy V, et al. Mechanism-based pharmacokinetic-pharmacodynamic modeling of the dopamine D 2 receptor occupancy of olanzapine in rats. *Pharm Res*. 2011;28(10):2490-2504. doi:10.1007/s11095-011-0477-7
17. Carreño F, Helfer VE, Staudt KJ, et al. Quantification of neurotransmitters in microdialysate samples following quetiapine dosing to schizophrenia Phenotyped rats using a validated LC-MS/MS method. *J Chromatogr B Anal Technol Biomed Life Sci*. 2020;1155:122282. doi:10.1016/j.jchromb.2020.122282
18. Tunblad K, Hammarlund-Udenaes M, Jonsson EN. An integrated model for the analysis of pharmacokinetic data from microdialysis experiments. *Pharm Res*. 2004;21(9):1698-1707. doi:10.1023/B:PHAM.0000041468.00587.c6
19. Carreño F, Helfer VE, Staudt KJ, et al. Semi-mechanistic pharmacokinetic modeling of lipid Core Nanocapsules: understanding quetiapine plasma and brain disposition in a neurodevelopmental animal model of schizophrenia. *J Pharmacol Exp Ther*. 2020;375(1):49-58. doi:10.1124/JPET.120.000109
20. Movin-Osswald G, Hammarlund-Udenaes M. Prolactin release after Remoxipride by an integrated pharmacokinetic - pharmacodynamic model with intra- and interindividual aspects. *J Pharmacol Exp Ther*. 1995;274(2):921-927.
21. Carreño F, Helfer VE, Staudt KJ, et al. Quetiapine lipid Core Nanocapsules restore Prepulse inhibition deficits in a neurodevelopmental model of schizophrenia in male and female rats. *Schizophr Res*. 2020;218:173-179. doi:10.1016/j.schres.2020.01.007
22. Vardanyan RS, Hruby VJ. *Adrenergic (sympathomimetic) drugs at Synthesis of Essential Drugs*. Elsevier Sciences; 2006;1:143-159. doi:10.1016/B978-0-444-52166-8X5000-6
23. Gefvert O, Bergström M, Långström B, Lundberg T, Lindström L, Yates R. Time course of central nervous dopamine-D2 and 5-HT2 receptor blockade and plasma Drug concentrations after discontinuation of quetiapine (Seroquel®) in patients with schizophrenia. *Psychopharmacology*. 1998;135(2):119-126. doi:10.1007/s002130050492
24. Bouw MR, Xie R, Tunblad K, Hammarlund-Udenaes M. Blood-brain barrier transport and brain distribution of Morphine-6-glucuronide in relation to the antinociceptive effect in rats – pharmacokinetic/pharmacodynamic modelling. *Br J Pharmacol*. 2001;134(8):1796-1804. doi:10.1038/sj.bjp.0704406
25. Mohammad Jafari R, Ala M, Goodarzi N, Dehpour AR. Does pharmacodynamics of drugs change after presenting them as nanoparticles like their pharmacokinetics? *Curr Drug Targets*. 2020;21(8):807-818. doi:10.2174/1389450121666620012811354

26. Carreño F, Paese K, Silva CM, Guterres SS, Dalla Costa T. Pharmacokinetic investigation of quetiapine transport across blood-brain barrier mediated by lipid Core Nanocapsules using brain microdialysis in rats. *Mol Pharm*. 2016;13(4):1289-1297. doi:10.1021/acs.molpharmaceut.5b00875
27. Białoń M, Wąsik A. Advantages and limitations of animal schizophrenia models. *Int J Mol Sci*. 2022;23(11):1-32. doi:10.3390/ijms23115968
28. Wilson C, Terry AV. Neurodevelopmental animal models of schizophrenia: role in novel Drug discovery and Development. *Clin Schizophr Relat Psychoses*. 2010;4(2):124-137. doi:10.3371/CSRP.4.2.4
29. Jerzemowska G. Hypothalamic and midbrain cells, tyrosine hydroxylase, and implications for Drug addiction. *Neuropathology of Drug Addictions and Substance Missue*. 2016;3:71-81. doi:10.1016/B978-0-12-800634-4.00007-X

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