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A PHARMACOKINETIC SIMULATION-BASED COMPARISON OF VARYING ADHERENCE RATES FOR PALIPERIDONE ER AND RISPERIDONE IN PATIENTS WITH SCHIZOPHRENIA

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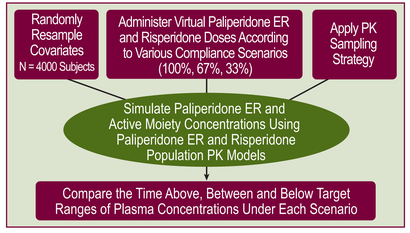
BACKGROUND

- Medication adherence is important to successful management of patients with schizophrenia and related psychotic disorders; patient nonadherence is documented in numerous studies (e.g., 30%-35% patient noncompliance).[1,2]
- Drug formulation affects the pharmacokinetic (PK) profile and plays an important role in maintaining therapeutic plasma concentrations.
- Paliperidone extended-release (ER) and risperidone have similar pharmacologic effects with regard to D_2 receptor occupancy.[3,4] Compared with risperidone, however, paliperidone ER formulation has a longer elimination half-life[5] and less peak-to-trough fluctuations at steady state.
- PK simulations using clinical study population data provide a novel methodology to compare drug plasma concentrations following different adherence rates.
- PK simulations were performed to examine the impact of various adherence rates during chronic therapy with paliperidone ER and risperidone.

METHODS

- Data utilized were from three Phase 3 studies of paliperidone ER[6-8] and four Phase 1 and three Phase 3 trials for risperidone.[9]
- PK parameter estimates for paliperidone ER and risperidone were obtained from population models developed previously with the mixed-effects computer modeling algorithm NONMEM (Nonlinear Mixed Effects Modeling Software)[10] using pooled clinical trial data.
- The PK simulation process is outlined in **Figure 1**.

Figure 1. PK Simulation Flow Chart.



PK Models

- **Risperidone:** two-compartment model (developed using 5359 plasma drug concentrations) with zero- and first-order absorption; a mixed model that accounted for CYP2D6 polymorphic metabolism and covariate effect of carbamazepine comedication (CYP3A4 induction)
- **Paliperidone ER:** two-compartment model (developed using 21,183 plasma drug concentrations) with zero-order input, first-order absorption and elimination, and covariate effects for renal function (creatinine clearance) and lean body weight

Target Concentration Ranges

- Steady-state dosing interval was defined for each medication to correspond to 70%-80% dopamine D_2 receptor occupancy.
  - Paliperidone: 10-17 ng/mL[11]
  - Risperidone: 26-46 ng/mL[12]
- Impact of missed doses on the time above, within and below the targeted concentration ranges was assessed using model-based simulations.

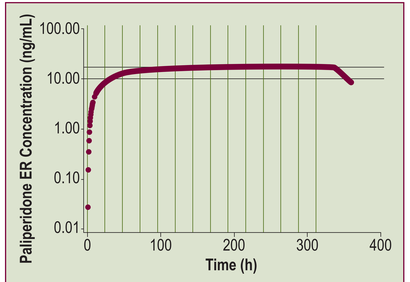
Compliance Analysis

- Population PK models and parameter estimates were used to simulate paliperidone ER concentrations following paliperidone ER dosing and risperidone and 9-hydroxy-risperidone concentrations following risperidone dosing for virtual patients.
- Plasma drug concentrations were simulated for approximately 4000 virtual patients.
  - Assumed all virtual paliperidone ER patients received 6 mg daily for 12 weeks
  - Assumed all virtual risperidone patients received 4 mg daily for 12 weeks
- Initial simulations assumed 100% compliance for both paliperidone ER and risperidone; subsequent simulations assumed 67% (two doses deleted) and 33% (four doses deleted) compliance within a window of 6 days prior to the concentration-time profile to be evaluated.

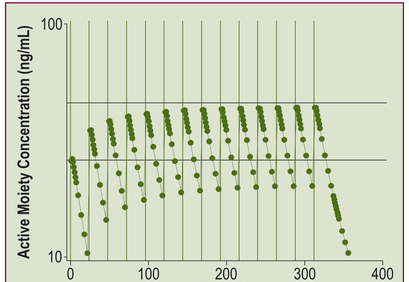
RESULTS

- Plasma concentrations representative of 100% adherence are outlined in **Figure 2**.

Figure 2. Predicted Paliperidone ER and Risperidone Concentrations Following 100% Adherence.



Approximate C(ss) = 17 ng/mL
The vertical lines represent paliperidone ER OROS doses of 6 mg QD.
The horizontal lines represent the target bounds of 10-17 ng/mL.



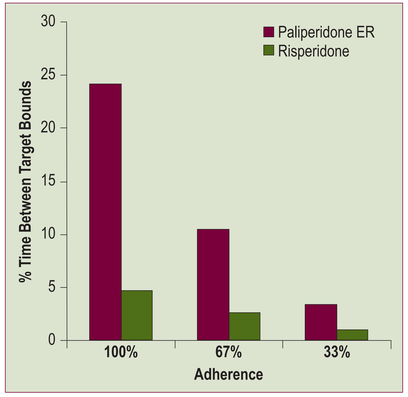
The vertical lines represent risperidone IR doses of 4 mg QD.
The horizontal lines represent the target bounds of 26-46 ng/mL.

- With 100% adherence, approximately 24% of the virtual paliperidone ER patients showed consistent plasma concentration levels in the target range compared with 5% of virtual risperidone patients (**Table 3, Figure 3**).
- With adherence rates of 67% and 33%, the effects on paliperidone ER plasma concentrations were less extensive compared with those of risperidone plasma concentrations; paliperidone ER demonstrated longer time within the target range.
- With 67% adherence rate, approximately 10% (virtual paliperidone ER patients) and 3% (virtual risperidone patients) were consistently within the target ranges (**Table 3, Figure 3**).

Table 3. Comparison of the Grouped Percent Time Between the Target Bounds for Paliperidone ER and Risperidone, Stratified by Adherence Rate.

	Paliperidone ER 10-17 ng/mL			Risperidone 26-46 ng/mL		
	Adherence			Adherence		
% Time Between Bounds	100%	67%	33%	100%	67%	33%
Always, N (%)	967 (24.2)	417 (10.4)	135 (3.4)	188 (4.7)	105 (2.6)	39 (1.0)
Sometimes, N (%)	10 (0.2)	1222 (30.6)	1322 (33.2)	2524 (63.1)	1827 (45.7)	870 (21.8)
Never, N (%)	3023 (75.6)	2361 (59.0)	2526 (63.4)	1288 (32.2)	2067 (51.7)	3086 (77.2)
Total	4000	4000	3983	4000	3999	3995

Figure 3. Percentage of Time Subjects Always Remained Within Target Bounds for Paliperidone ER and Risperidone, Stratified by Adherence Rate.



DISCUSSION AND LIMITATIONS

- Adherence rates altered the drug plasma concentration levels and altered the amount of time during a dosage interval that either risperidone or paliperidone ER concentration was completely within a range associated with desirable dopamine receptor occupancy.
- Although the effects of drug dosage regimens that produce plasma concentrations outside of these occupancy ranges have not been extensively studied regarding their clinical consequences, available data suggest that formulation modifications (e.g., ER) should minimize wide fluctuations in drug concentration.
- The effects of decreased adherence rates had less influence on maintaining plasma drug concentrations within a target range for paliperidone ER than for risperidone.
- Although this study used a PK simulation-based approach to analyze the effects of adherence rates on plasma drug concentrations, a variety of patient factors also are likely to influence outcomes in clinical practice.

CONCLUSIONS

- These results suggest that decreased adherence rates may have less of an effect on drug plasma concentrations of paliperidone ER versus risperidone.
- This novel approach links medication adherence rates to comparative drug pharmacokinetics and potentially may be applied to other antipsychotic agents.

REFERENCES

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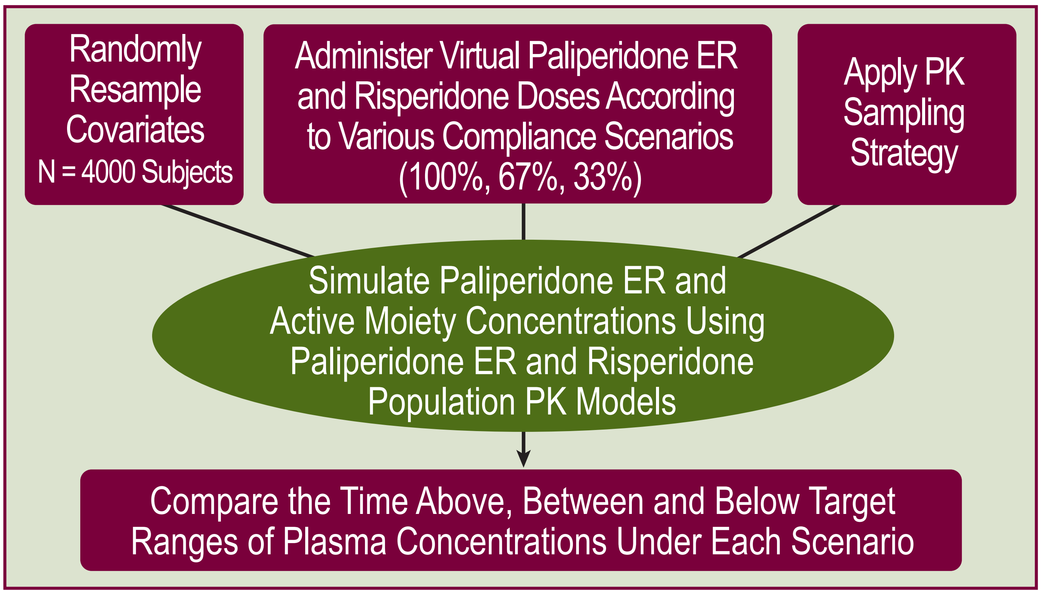

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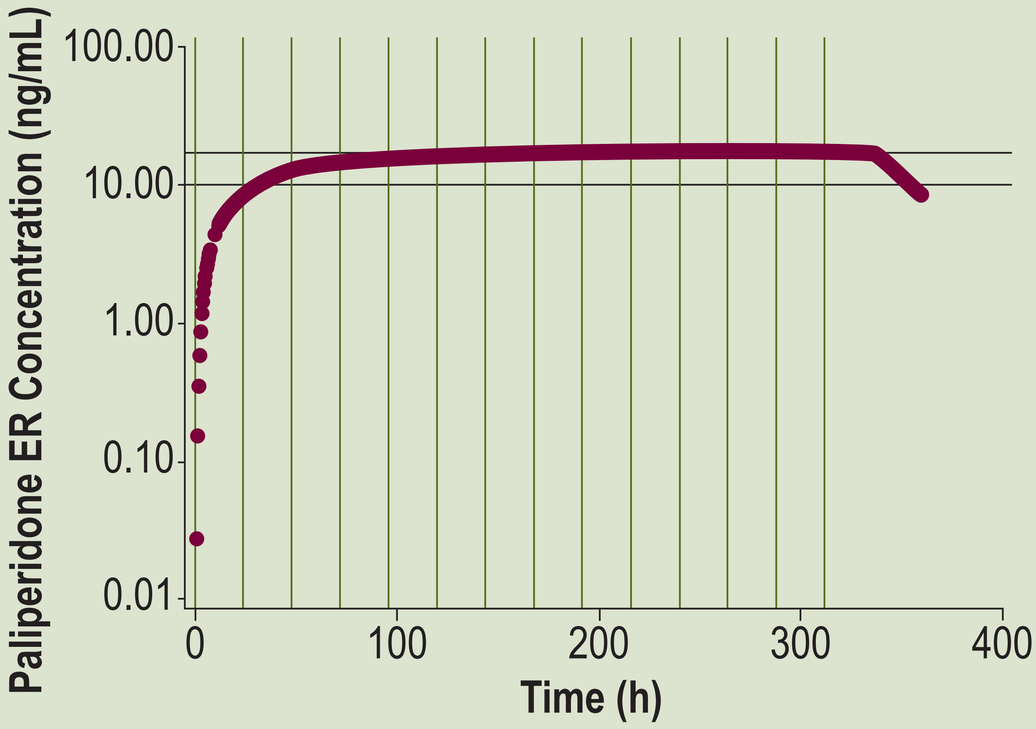

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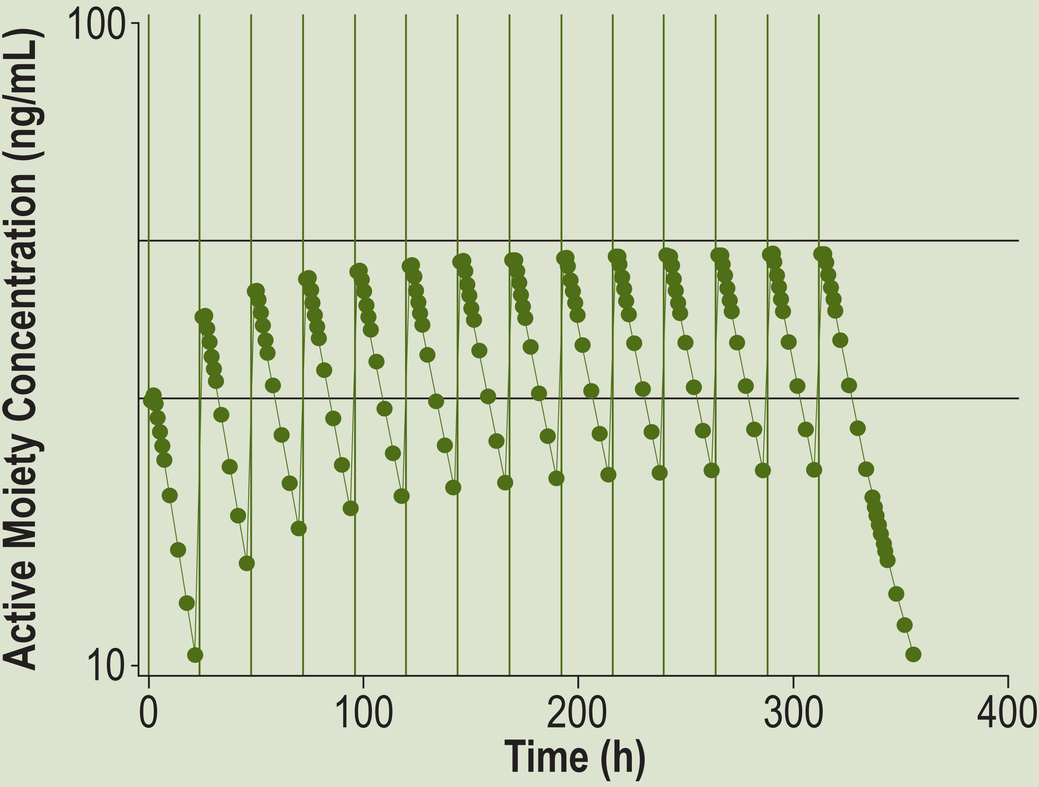

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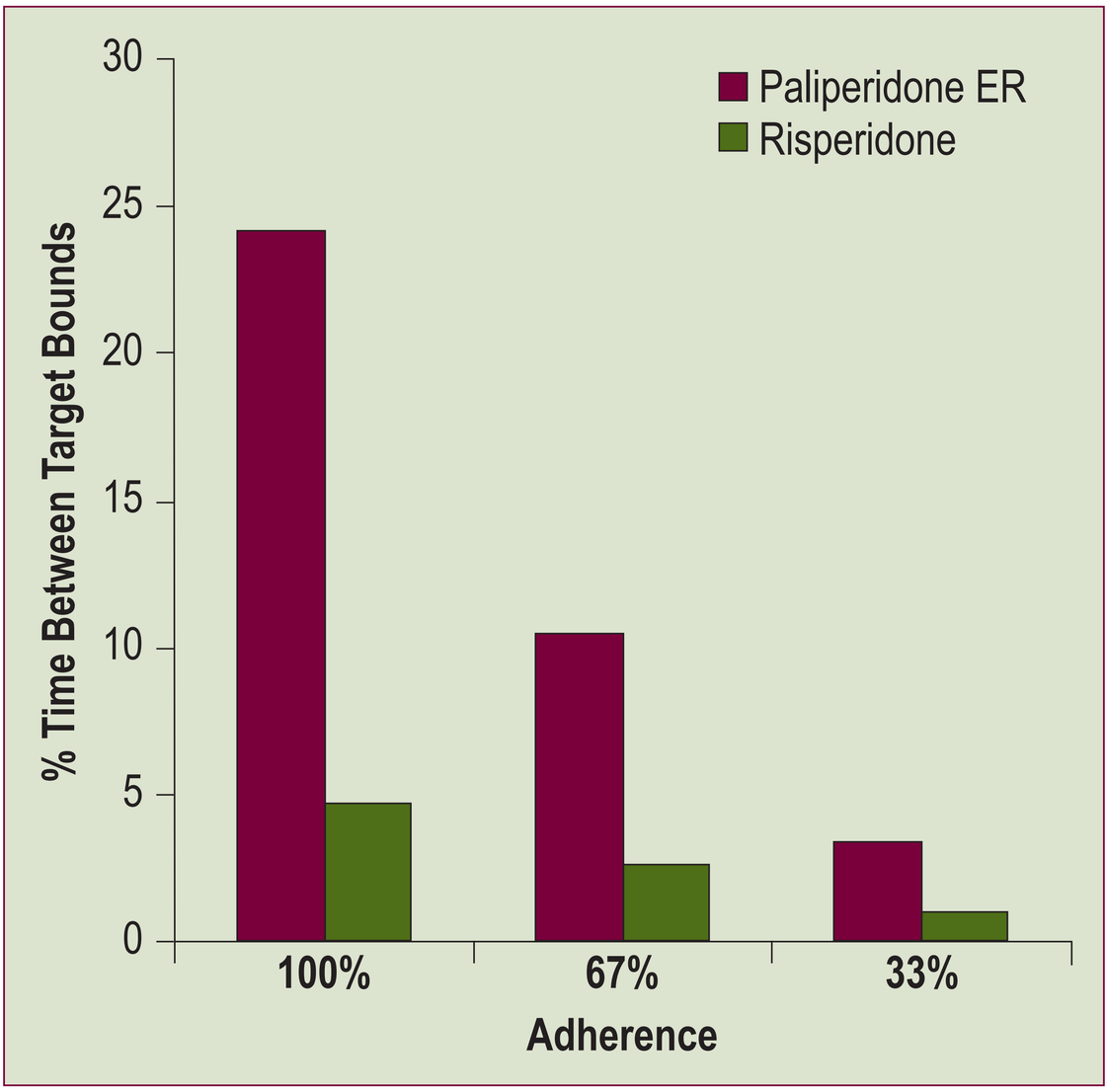

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