A Population Approach to Guide Amisulpride Dose Adjustments in Older Patients With Alzheimer's Disease

Suzanne Reeves, PhD[a,b,*]; Julie Bertrand, PhD[c]; Emma McLachlan, MBChB[b]; Fabrizia D'Antonio, MBBS[a,b]; Stuart Brownings, BSc[a]; Akshay Nair, MBBS[a]; Suki Greaves, MBBS[d]; Alan Smith, MBBS[d]; Joel T. Dunn, PhD[e]; Paul Marsden, PhD[e]; Robert Kessler, MD[f]; Hiroyuki Uchida, MD, PhD[g]; David Taylor, PhD[d]; and Robert Howard, MD[a,b]

ABSTRACT

Objective: We have previously reported high dopamine $D_{2/3}$ receptor occupancies at low amisulpride concentrations in older people with Alzheimer's disease (AD), during off-label treatment of AD-related psychosis. This post hoc analysis explored pharmacokinetic (concentration) and pharmacodynamic (prolactin, $D_{2/3}$ occupancy) contributions to symptom reduction and extrapyramidal side effects (EPS) to inform AD-specific dose adjustments.

Methods: Population pharmacokinetic-pharmacodynamic models were developed by combining pharmacokinetic data from a phase 1 study in 20 healthy older people with pharmacokinetic prolactin, [^{18}F]fallypride $D_{2/3}$ receptor imaging, and clinical outcome data from 28 older patients prescribed open amisulpride (25–75 mg/d) to treat AD-related psychosis. Model predictions were used to simulate dose-response and dose-EPS.

Results: Symptom reduction (delusions) was associated with amisulpride concentration ($P = 1.3e\text{-}05$) and $D_{2/3}$ occupancy ($P < .01$, caudate, putamen, thalamus). Model predictions suggested that across concentrations of 40–100 ng/mL, and occupancies of 40% to 70% in the caudate and thalamus and 30% to 60% in the putamen, there was a 50% to 90% probability of response and < 30% probability of EPS. Simulations, based on concentration-delusions and concentration-EPS model outputs, showed that 50 mg/d of amisulpride was the appropriate dose to achieve this target range in those aged > 75 years; increasing the dose to 75 mg/d increased the risk of EPS, particularly in those aged > 85 years of low body weight.

Conclusions: These findings argue strongly for the consideration of age- and weight-based dose adjustments in older patients with AD-related psychosis and indicate that 50 mg/d of amisulpride may be both the minimal clinically effective dose and, in those aged > 75 years, the maximally tolerated dose.

J Clin Psychiatry 2017;78(7):e844–e851
https://doi.org/10.4088/JCP.16m11216

[a]Division of Psychiatry, University College London, London, United Kingdom
[b]Department of Old Age Psychiatry, Kings College London, London, United Kingdom
[c]IAME, UMR 1137 INSERM, Paris, France, and Genetics Institute, University College London, London, United Kingdom
[d]South London and Maudsley NHS Foundation Trust, London, United Kingdom
[e]Division of Imaging Sciences, St Thomas Hospital, London, United Kingdom
[f]University of Alabama, Birmingham
[g]Department of Neuropsychiatry, Keoi University School of Medicine, Tokyo, Japan
**Corresponding author:* Suzanne Reeves, PhD, Division of Psychiatry, University College London, 6th Floor, Maple House, 149 Tottenham Court Rd, London W1T 7NF (suzanne.reeves@ucl.ac.uk).

Since the therapeutic window of striatal dopamine $D_{2/3}$ receptor occupancy was first described for antipsychotic drugs,[1,2] $D_{2/3}$ receptor imaging has played a key role in guiding antipsychotic prescribing in schizophrenia. Optimal dose-occupancy ranges have now been established for both typical and atypical drugs, and dosage strategies refined through statistical modeling of pharmacokinetic, $D_{2/3}$ occupancy, and clinical outcome data.[3–6] There is a relative absence of equivalent data in older people and a limited understanding of the relative importance of pharmacokinetic[7,8] and pharmacodynamic[9,10] contributions to response and side effect profiles. This issue is particularly relevant for older people with Alzheimer's disease (AD), in whom excessive antipsychotic-related morbidity and mortality and poorly understood efficacy in relation to the treatment of psychosis, agitation, and aggression have led to a restriction in antipsychotic drug use[11,12] and no clear guidance on minimum clinically effective dose or threshold sensitivity for extrapyramidal side effects (EPS).

The population approach has considerable utility in this respect, as it uses statistical modeling to identify sources of variability in dose-exposure and exposure-response relationships in order to predict dose requirements for a "typical person" in the population of interest.[13–16] We have recently developed population amisulpride pharmacokinetic and pharmacokinetic-$D_{2/3}$ occupancy models in older patients with AD by combining pharmacokinetic data from a richly sampled phase 1, single-dose (50 mg) study in healthy older people[17] with a sparsely sampled clinical dataset (pharmacokinetic, [^{18}F]fallypride $D_{2/3}$ receptor imaging, and clinical outcome data) of AD patients prescribed amisulpride (25–75 mg/d) off label to treat psychosis.[18,19] We found a 10-fold variability in amisulpride concentration (9–109 ng/mL) in patients with AD, which was partly accounted for by an effect of age on drug clearance.[20] Low concentrations, which in all but 1 participant were below the recommended therapeutic range (100–319 ng/mL) to treat psychosis in schizophrenia,[4,21,22] were associated with high $D_{2/3}$ receptor occupancies (43%–84%, caudate) and accompanied by clinically relevant responses and EPS.[19] However, these data were not analyzed or interpreted in terms of oral dosing, which would be more relevant in the real-world clinical setting.

In the current study, we aimed to provide clear guidance on optimum dose adjustments for older people with AD by extending the population analysis to include clinical

Clinical Points

- Empirical data to guide antipsychotic treatment of psychosis in Alzheimer's disease (AD) are lacking.
- Amisulpride 50 mg/d is the optimal dose to treat AD-related psychosis in those aged over 75 years due to high $D_{2/3}$ receptor occupancy.
- Dose increases above 50 mg/d of amisulpride should be made cautiously, particularly in those over 85 years or of low body weight, who are at greatest risk of EPS.

outcome data with the following objectives: (1) to investigate the relationship between pharmacokinetic (average steady-state concentration) and/or pharmacodynamic (prolactin, $D_{2/3}$ receptor occupancy) biomarkers with clinical outcome (symptom reduction, EPS) and (2) to use model outputs to simulate dose-response and dose-EPS across the prescribed dose range for patients aged 65 to 85 years and of average (70 kg) and low (50 kg) body weight.

METHODS

Post hoc analysis was carried out on data from 3 clinical studies.[17,18,19] The sample included pharmacokinetic data on 20 healthy older people (10 men, mean ± SD age = 68.7 ± 4.1 years; 14 samples per person), sampled over 72 hours following 50 mg of amisulpride[17] and data from 38 patients diagnosed with probable AD,[23] which included (1) pharmacokinetic, prolactin, imaging, and clinical outcome data on 28 patients with AD-related psychosis[24] who were prescribed open amisulpride[18,19] and (2) imaging and prolactin data on 10 antipsychotic-free (control) AD patients, included to provide additional "pretreatment" data to inform the model.[19]

Patients with AD were recruited from the South London and Maudsley NHS Foundation Trust (SLaM).[18,19] All were antipsychotic naive and included on the basis of having no previous history of psychiatric illness, traumatic brain injury, epilepsy, significant cardiorespiratory disease, needle phobia, any contraindication to amisulpride prescribing, or features suggestive of Lewy body dementia.[25] Verbal and written informed consent was obtained from participants, or an appropriate caregiver if a participant lacked capacity. Studies were approved by Berkshire (11/SC/0486)[19] and Joint SLaM and Institute of Psychiatry NHS (10/H0807/75)[18] Research Ethics Committees. Clinical assessment, carried out at baseline and every 2 to 4 weeks during dose titration, included (1) frequency × severity ratings for 3 Neuropsychiatric Inventory domains (delusions, hallucinations, agitation)[26] and (2) EPS rating: Simpson-Angus Scale (SAS; total score > 3).[27] [^{18}F]fallypride imaging was carried out at the PET Centre at St Thomas Hospital, London, United Kingdom, at baseline (all patients) and at "optimum" dose, defined as > 25% symptom reduction (treated patients), using an interrupted (3 × 20 minute sessions) scanning protocol.[18,28] Patients commenced amisulpride at 25 or 50 mg/d (based on clinician preference) and increased to an optimum dose.[18,19] Amisulpride (racemate) concentration was determined using a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) method (detection limit, 9 ng/mL). Prolactin was measured using chemiluminescence immune assay (Siemens Advia Centaur XP assay), with a detection limit of 6.4 mIU/L (0.29 ng/mL).[19]

Statistical Analysis

Demographic and clinical data were analyzed using SPSS (version 22.0). Group differences were explored using independent samples *t* tests (*P* values shown) and correlations (Spearman correlation coefficient *r*). Values are shown as mean ± SD. For the population analysis, nonlinear mixed-effects modeling (NLME) was implemented using Monolix software (version 4.33; www.lixoft.eu). NLME simultaneously estimates fixed effects (parameters which describe pharmacokinetic-pharmacodynamic relationships) and random effects, comprised of interindividual variability and residual unexplained variability (system noise, dosage history errors, and/or model misspecifications). Parameters were estimated using the stochastic approximation expectation minimization (SAEM) algorithm.[29] Appropriateness of models was evaluated using goodness-of-fit criteria: diagnostic scatter plots, visual predictive checks, shrinkage, change in interindividual variability, model precision, and likelihood ratio tests. A change in log-likelihood estimate was considered significant if ≥ 3.84 (equivalent to $P < .05$, 1 degree of freedom). Diagnostic graphics, tests for covariate screening, and estimation of statistical significance of model outputs were performed in R.

Population Model Development

Pharmacokinetic model. A pharmacokinetic model for amisulpride was developed by combining pharmacokinetic data on healthy older people[17] and older patients with AD,[18,19] informed by pharmacokinetic studies[17,30,31] that describe a double peak in plasma levels (1 and 3 hours post dose) suggestive of hepatobiliary elimination, no interaction with cytochrome P450, and predominantly renal elimination (excretion and additional secretion). On covariate testing (age, creatinine clearance,[32] height, weight, gender, serum creatinine), the model that best described the data incorporated age and allometric scaling based on standard 70-kg body weight[33] on drug clearance[20] and showed no additional contribution of creatinine clearance (Supplementary eTable 1).

Pharmacokinetic-pharmacodynamic model. The pharmacokinetic model was combined with (1) an E_{max} model to describe serial prolactin data[34] (Supplementary eTable 1, Supplementary eFigure 1) and (2) an inhibitory E_{max} (I_{max}) model to describe serial [^{18}F]fallypride imaging data (Supplementary eTable 2, Supplementary eFigure 2), expressed as binding potential (BP_{ND}).[35] Individual parameter estimates derived from pharmacokinetic-prolactin and pharmacokinetic-occupancy models were used to calculate average steady state concentration ($C_{average}$),

Table 1. Demographic and Clinical Characteristics of Treated Patients (n = 28, 11 men)[a]

Characteristic	Mean ± SD
Age, y	82.1 ± 6.6
CrCL, mL/min	67.7 ± 17.3
Weight, kg	68.0 ± 15.2
BMI, kg/m^2	26.5 ± 5.4
MMSE	17.7 ± 5.4
Number of days treatment	56.9 ± 58.0
Daily dose (mg)	49.4 ± 11.2
Amisulpride concentration, ng/mL	40.9 ± 27.1
Time since last dose, h	16.2 ± 3.1
Posttreatment PRL, ng/mL	87.9 ± 72.0
Men[b]	44.9 ± 22.0**
Women	110.9 ± 79.0
$C_{average}$, ng/mL[c]	71.0 ± 30.3
% $D_{2/3}$ receptor occupancy[d]	
Caudate	62.5 ± 9.2
Putamen	48.5 ± 12.3
Thalamus	66.2 ± 10.5
% Reduction in symptom scores[e]	
Delusions	80 ± 27
Hallucinations	95 ± 15
Agitation	84 ± 28
SAS total score	3.1 ± 5.2

[a]Data from clinical studies.[18,19]
[b]**$P < .01$ gender differences in PRL.
[c]$C_{average}$: Individual model predictions for steady state exposure across the dosing interval.
[d]Individual model predictions for $D_{2/3}$ occupancies, across the $C_{average}$ range.
[e]Scores reflect frequency × severity ratings for individual Neuropsychiatric Inventory (NPI) symptom domains.
Abbreviations: BMI = body mass index; CrCL = estimated creatinine clearance (Cockcroft and Gault); MMSE = Mini-Mental State Examination; PRL = prolactin hormone; SAS = Simpson Angus Scale, used to rate extrapyramidal side effects: 0–2 = nil, 3–5 = subclinical; ≥ 6 = clinically significant.

corresponding regional occupancies, and prolactin levels across the prescribed dose range. Each model-derived biomarker was then considered as independent variable (regressor) to explain treatment response and EPS. The model-derived biomarker-response relationship was evaluated using an ordered categorical response logistic model, describing the logit function of the probability (P) of being in any of 3 symptom categories as a linear function of response-specific parameters, and the regressor effect coefficient.

Neuropsychiatric Inventory symptom domain scores were categorized as follows: category 1 (score 0–4) indicated mild, infrequent (or no) symptoms; category 2 (score 6–9) moderate; and category 3 (score > 9) very frequent and severe symptoms. Random effects (interindividual variability) were incorporated on response-specific parameters. For each model, the regressor effect coefficient β (standard error [SE]) value was used to calculate a Wald statistic, and its P value, based on the χ^2 statistic. Prolactin models were tested with and without an effect of gender. Motor side effects were evaluated in a binary model (fixed effects only), which described the probability (P) of any EPS (SAS total score > 3) being present, taking into account the predictor variable.

Model Simulations

Model-based simulations were performed to predict the probability of response or EPS for 100 individuals per combination of the following categories: 65, 75, or 85 years; standard (70 kg) or low (50 kg) body weight; and prescribed dose of 25 mg, 50 mg, or 75 mg daily.

RESULTS

Demographic and Clinical Characteristics of Amisulpride-Treated Patients

There were 28 patients in the treated group (age 82 ± 6.6 years; 11 [39%] men; Mini-Mental State Examination [MMSE] 17.7 ± 5.4), all of whom were experiencing psychosis symptoms at baseline (26 [92.8%] delusions, 19 [67.8%] hallucinations) and 20 (71.4%) associated agitation, and 10 antipsychotic-free patients (age 83.6 ± 3.8 years, 4 [40%] men, MMSE 20.3 ± 6.1). Demographic, physiological, and clinical characteristics of treated patients are described in Table 1. Across the 25- to 75-mg/d dose titration range, symptom scores were reduced by 80% ± 27% (delusions), 95% ± 15% (hallucinations), and 84% ± 28% (agitation), and 7 patients (25%) were withdrawn due to EPS (n = 5), falls (n = 1), or unrelated health problems (n = 1). All who completed the study (n = 21) were prescribed 50 mg/d of amisulpride.

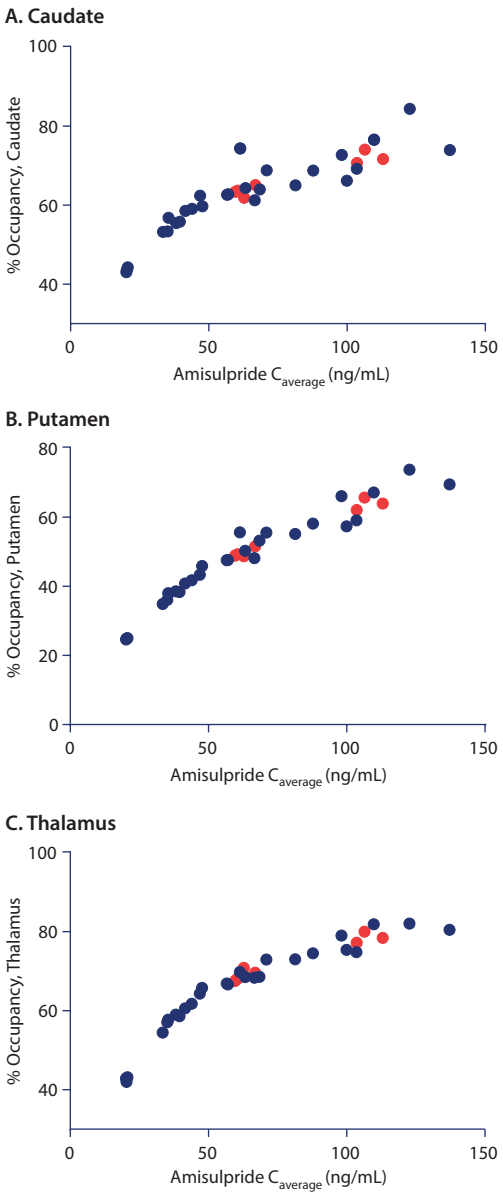
Pharmacokinetic-Prolactin

Prolactin was modeled with good precision (Supplementary eTable 1, eFigure 1) for all parameters apart from EC_{50} (relative standard error [RSE] = 74%) and random effect standard deviation (interindividual variability) on $prolactin_{base}$ (RSE = 92%) and EC_{50} (not estimated). Covariate testing identified a significant contribution of gender to explain interindividual variability in E_{max} ($P = 9.7e-005$; interindividual variability reduced from 60% to 48%) and weight ($P = .03$; interindividual variability further reduced to 43%). Model estimates suggested that, for a typical older person with AD of standard (70 kg) weight, there was a 2-fold difference in E_{max} between men (52 ng/mL) and women (124 ng/mL).

Pharmacokinetic-$D_{2/3}$ Occupancy

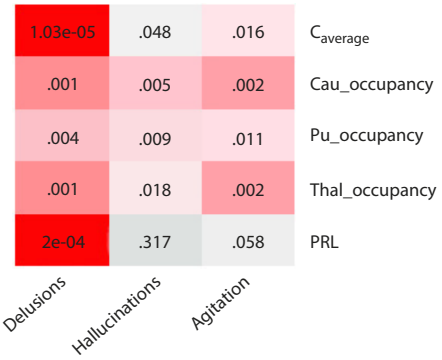
Pharmacokinetic-occupancy model parameters are detailed in Supplementary eTable 2. I_{max} was estimated as 84.3% for the caudate (IC_{50} 19.1 ng/mL; residual variability, 15.3%), 98.7% for the putamen (IC_{50} 61.3 ng/mL; residual variability, 14.4%), and 100% for the thalamus (IC_{50} 29.5 ng/mL; residual variability, 17.2%). Fixed effects were estimated with good precision, apart from IC_{50} for the putamen (RSE = 70%). Random effects were estimated on all parameters apart from IC_{50} (not estimated in any model) and I_{max} (only estimated with precision for the caudate). Residual variability was estimated with better precision for pharmacokinetic (RSE = 5%) than I_{max} (RSE = 58%, 40%, and 48% for caudate, putamen, and thalamus, respectively). Individual model predictions for $C_{average}$ and corresponding occupancies across the dose titration range are described in Table 1 and plotted in Figure 1, separated on the basis of EPS.

Figure 1. Model Estimated $C_{average}$ and $D_{2/3}$ Corresponding Occupancy[a]



[a]Model estimates for $C_{average}$ across the dose titration range are plotted against corresponding $D_{2/3}$ receptor occupancy, separated on the basis of extrapyramidal side effects, present (red) or absent (blue).

Figure 2. Significance Heat Map[a]



[a]Wald *P* values for each response-regressor model, based on the magnitude and standard error of the β coefficient, are shown for each regressor: $C_{average}$; corresponding $D_{2/3}$ occupancies in caudate (Cau), putamen (Pu), and thalamus (Thal); and prolactin (PRL). Color coding: gray ($P > .05$) to red ($P < .001$).

Table 2. Effect Size Estimates of the Association Between the Regressor and Response and Extrapyramidal Side Effects (EPS)

Variable	β Coefficient	SE (%)	*P*
Delusions[a]			
$C_{average}$	0.0397	0.9	1.03e-05
Cau_occupancy	0.0582	1.8	.001
Pu_occupancy	0.0766	2.7	.004
Thal_occupancy	0.0580	1.8	.001
PRL[b]	0.0809	2.2	2e-04
Hallucinations[a]			
$C_{average}$	0.0691	3.5	.048
Cau_occupancy	0.0755	2.7	.005
Pu_occupancy	0.122	4.7	.009
Thal_occupancy	0.083	3.5	.018
PRL	0.13	13.0	.317
Agitation[a]			
$C_{average}$	0.0479	2.0	.016
Cau_occupancy	0.0658	2.2	.002
Pu_occupancy	0.0765	3.0	.011
Thal_occupancy	0.061	2.0	.002
PRL	0.0606	3.2	.058
EPS[c]			
$C_{average}$	0.037	1.3	.004
Cau_occupancy	0.081	4.4	.076
Pu_occupancy	0.075	3.4	.025
Thal_occupancy	0.113	5.9	.061
PRL	0.004	4.0	.315

[a]Response models were defined by: [logit (P(category ≤ =1)) = $\theta_1 + \beta X$; logit (P(category ≤ =2)) = $\theta_1 + \theta_2 + \beta X$; P(category ≤ =3) = 1 – P(category ≤ =2)]; *P*, probability; θ_1 and θ_2 parameters of the logistic function; β, coefficient of the predictor variable X: interindividual variability (IIV) on θ_1.

[b]β values represent men only.

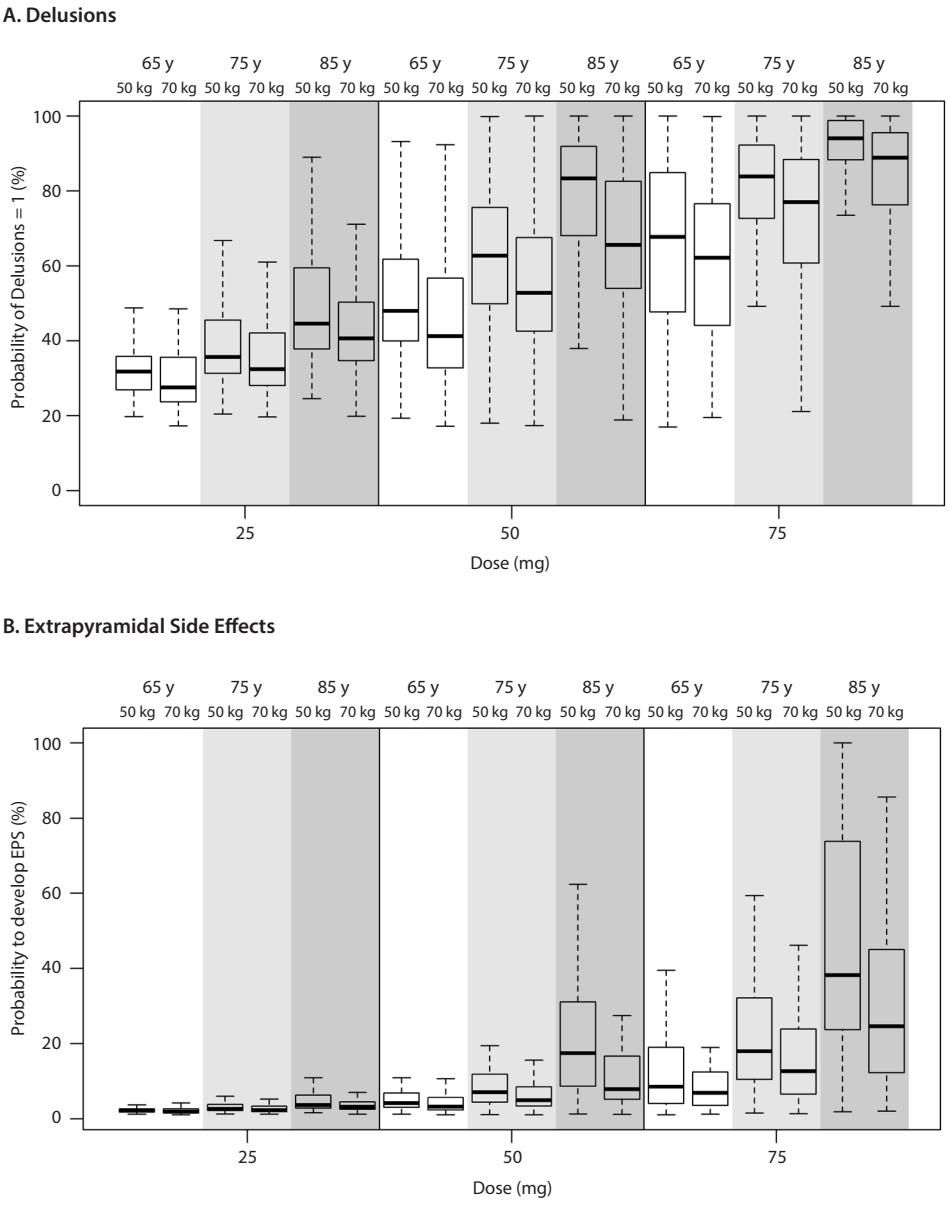
[c]EPS models were defined by: $P(Y = 1) = p + \beta X$; *P*, probability; p, parameter of the binomial function; β, coefficient of the predictor variable X. Fixed effects included only.

Abbreviations: $C_{average}$ = steady state concentration across the dosing interval, Cau = caudate, EPS = extrapyramidal side effects, Pu = putamen, Thal = thalamus, PRL = prolactin.

Response and EPS

Associations between regressor variables, response, and EPS are described as a heat map in Figure 2 and detailed in Table 2. $C_{average}$ was significantly associated with scores on the delusions domain ($P = 1.03e\text{-}05$), and more modestly with hallucinations ($P = .04$) and agitation ($P = .016$). Model predictions suggested that, across a 40–100 ng/mL $C_{average}$ range, the probability of response (delusions score ≤ 4) increased from 50% to 92%. $D_{2/3}$ occupancies were associated with response across all symptom domains ($P < .05$), achieving greatest significance in relation to delusions (caudate, $P = .001$; putamen, $P = .004$; thalamus, $P = .001$). Model predictions suggested that the probability of response increased from 50% to 90% across occupancy ranges of 40% to 70% (caudate, thalamus), and 30% to 60% (putamen). Prolactin concentration was associated with delusions scores alone, and only in men ($P = 2e\text{-}04$).

Figure 3. Model Based Simulations[a]



[a]Simulated probability of (A) being in category 1 (score of 4 or less) on the delusions domain of the Neuropsychiatric Inventory (NPI) and (B) emergent extrapyramidal side effects (EPS) (score of 3 or more on the Simpson Angus Scale), in a population of 100 people in each of the combinations of the following categories: 65, 75, or 85 years old; average (70 kg) or low (50 kg) body weight; prescribed dose of 25, 50, 75 mg daily. Boxes represent 25th, 50th, and 75th percentile of simulated probabilities; the upper error bar represents 75th percentile plus (1.5 × interquartile range [IQR]) and the lower error bar represents 25th percentile minus (1.5 × IQR), where IQR is the interquartile range (75th minus 25th percentile).

$C_{average}$ was the most powerful predictor of EPS ($P = .004$), with $D_{2/3}$ occupancy in the putamen achieving modest levels of significance ($P = .025$) and occupancy in other regions showing a similar trend (Table 2). Model predictions suggested that the probability of developing EPS increased from 4% to 30% across the 40- to 100-ng/mL range, and from 2% to 26% across a 20% to 60% occupancy range in the putamen. Model simulations for dose-response (delusions) and dose-EPS, accounting for age and body weight, are shown across the dose titration range in Figure 3.

DISCUSSION

This study extended our investigation of low-dose amisulpride prescribing in older patients with AD psychosis, by exploring the associations of pharmacokinetic and pharmacodynamic biomarkers with symptoms and EPS. We found that amisulpride concentration predicted both the degree of reduction in delusional symptoms and emergent EPS. Simulations based on $C_{average}$ model predictions showed that, in those aged >75 years, 50 mg/d of amisulpride was

associated with a 50% to 90% probability of response and <30% probability of EPS. Increasing the dose to 75 mg/d increased the risk of EPS with minimal additional benefit, particularly in those aged >85 years and of low body weight. This very low dose requirement is explained by high occupancies at low amisulpride concentrations in AD, which overlapped with the 40% to 70% window of striatal occupancy described for amisulpride in schizophrenia[4,5] and were associated with response across all symptom domains. We also demonstrated a cumulative probability of response with increasing occupancy, consistent with the schizophrenia literature and suggestive of a continuum of clinical effectiveness within the therapeutic window.[3]

The fact that we observed the anticipated occupancy gradients—thalamus > striatum[36,37] and caudate > putamen[38]—in older patients with AD suggests that there is a global increase in occupancy for a given plasma concentration, relative to young adults. These findings strongly implicate age and/or AD-specific disruption of the blood-brain barrier (permeability, expression of transporters), which controls central drug access.[39,40] However, we cannot rule out a contribution of other central mechanisms, including reduced amisulpride clearance *within* the central nervous system[41] and/or reduced competition by endogenous dopamine.[42] The emergence of EPS at lower than anticipated occupancies, particularly in the putamen, is broadly consistent with data on older adults with schizophrenia[9,10,43] and suggests that pharmacodynamic changes, which reduce $D_{2/3}$ receptor reserve, are increasing the functional outcome for a given occupancy in older patients with AD and lowering the threshold sensitivity for EPS.

Differences in imaging (tracer, timing of scan relative to dose, scan duration) and statistical (use of $C_{average}$) methodology between the current study and published occupancy data in schizophrenia[4,5] mean that it is not possible to make direct comparisons. As discussed previously,[19] choice of tracer is highly relevant, as in vitro studies have shown that tracers with a high affinity (low dissociation constant) such as [^{18}F]fallypride[44] require higher concentrations of competing drug to displace them from $D_{2/3}$ receptor sites than those with lower affinity, resulting in lower apparent occupancies.[45–47] In vivo, underestimation of occupancy is most pronounced when occupancy is calculated prior to transient equilibrium and is more likely to occur in striatal regions, as time to equilibrium is dependent on number of receptor sites.[37,48,49] Although sampling times for the current study were guided by the above studies and previous [^{18}F]fallypride protocols,[50,51] it remains possible that we are underestimating the true extent of the differences between older patients with AD and young adults.

The study was limited by small sample size, sparse sampling, and the absence of pretreatment imaging and prolactin data in a proportion of individuals. It was therefore necessary to combine the clinical dataset[18,19] with data from a richly sampled phase 1 study,[17] to fully parameterize the pharmacokinetic model and further inform pharmacokinetic-prolactin and pharmacokinetic-occupancy profiles, by incorporating age and weight into the model development process. Use of a population approach allowed estimation of typical values for $C_{average}$, prolactin, and corresponding occupancy[52] across the dose titration range for each individual, including those withdrawn from the study due to emergent EPS. The fact that associations between pharmacokinetic and pharmacodynamic indices and delusions achieved greater significance than those for hallucinations or agitation reflects the fact that delusional beliefs were the predominant presenting complaint, and baseline scores were higher for delusions than other symptom domains.

Sample size limitations meant that it was not possible to estimate all model parameters with precision or to fully examine covariate effects. Model-based predictions should therefore be interpreted cautiously. This is particularly important in relation to prolactin response models, which require further investigation in a sample large enough to evaluate the impact of gender and weight. Neither was it possible to model random effects for EPS, and this reduced the predictive power of the models. Nevertheless, it was possible to demonstrate a clear relationship between EPS and both $C_{average}$ and occupancy in the putamen, the striatal region which has greatest functional connectivity with the motor cortex.[53] The impact of concomitant medication on safety and efficacy of amisulpride is unclear, as patients who were prescribed drugs known to interact with amisulpride[54] were excluded from participation in the study. Diagnostic issues need to be considered when psychosis is present in the context of dementia, and careful screening (case note review, clinical assessment, dopamine transporter imaging) was therefore carried out to exclude patients with suspected Lewy body dementia.[25] While we cannot completely rule out the possibility that Lewy body pathology may have contributed to the observed drug sensitivity, emergent EPS in patients with AD are sufficiently explained by higher than anticipated occupancies.

Despite the limitations of the clinical dataset, this study is important, as it represents the first pharmacokinetic-pharmacodynamic analysis of amisulpride within the context of off-label prescribing for the treatment of psychosis in AD, a population at the extreme end of the age spectrum. We have shown that, similar to young adults with schizophrenia, amisulpride concentration is a reliable predictor of both response and EPS in older patients with AD and, furthermore, have found no overlap with the target concentration recommended for the treatment of schizophrenia.[4,21] These findings argue strongly for the consideration of age- and weight-based dose adjustments in older patients with AD and suggest that 50 mg/d of amisulpride may be both the minimal clinically effective and maximally tolerated dose in those aged >75 years. Further dose increases should be made with caution, particularly in patients aged >85 years and/or of low body weight, as these factors are likely to result in blood concentrations beyond

100 ng/mL and occupancies of > 60% in the putamen. It should be noted that this dose requirement does not apply to those with severe renal impairment and may not universally apply to all patients, given the residual unexplained variability in pharmacokinetic and pharmacodynamic parameters in this population. Further therapeutic drug monitoring studies are required in AD, to identify factors that contribute to interindividual variability in EPS. It will also be important to investigate and compare pharmacokinetic-pharmacodynamic relationships across other older clinical populations, to establish age- and disease-specific target therapeutic drug concentrations as well as oral doses.

Submitted: September 13, 2016; accepted January 3, 2017.

Potential conflicts of interest: None.

Funding/support: Funded by the UK National Institute for Health Research (NIHR) (PCDKBRA). Dr Reeves and Prof Howard are also supported by the NIHR University College of London Hospital Biomedical Research Centres.

Role of the sponsor: The sponsors had no role in the design, analysis, interpretation, or publication of this study.

Acknowledgments: We acknowledge participants, caregivers, and clinical teams in Mental Health for Older Adult services in the South London and Maudsley NHS Foundation Trust (SLaM) who made this study possible; the research team; the Central Research Network (CRN) who facilitated recruitment; radiographers and radiochemists at St Thomas PET Centre (KCL); and the London Pharmacometric Interest Group (UCL). Demographic and pharmacokinetic data obtained in 20 elderly healthy volunteers were provided by Sanofi-Aventis R&D, from the report "Amisulpride: Study of Pharmacokinetics and Safety Following a Single Oral Administration (50 mg tablets) in the Elderly" (Synthelabo report no. 95-00596-EN-00). These data were supplied by Sanofi-Aventis R&D in the interest of supporting medical research in very elderly patients. Sanofi does not support any use of the medicine outside the locally approved labeling.

Supplementary material: See accompanying pages.

REFERENCES

1. Farde L, Nordström AL, Wiesel FA, et al. Positron emission tomographic analysis of central D1 and D2 dopamine receptor occupancy in patients treated with classical neuroleptics and clozapine: relation to extrapyramidal side effects. *Arch Gen Psychiatry*. 1992;49(7):538–544.
2. Kapur S, Remington G, Zipursky RB, et al. The D2 dopamine receptor occupancy of risperidone and its relationship to extrapyramidal symptoms: a PET study. *Life Sci*. 1995;57(10):PL103–PL107.
3. Uchida H, Takeuchi H, Graff-Guerrero A, et al. Dopamine D2 receptor occupancy and clinical effects: a systematic review and pooled analysis. *J Clin Psychopharmacol*. 2011;31(4):497–502.
4. Sparshatt A, Taylor D, Patel MX, et al. Amisulpride - dose, plasma concentration, occupancy and response: implications for therapeutic drug monitoring. *Acta Psychiatr Scand*. 2009;120(6):416–428.
5. Lako IM, van den Heuvel ER, Knegtering H, et al. Estimating dopamine D_2 receptor occupancy for doses of 8 antipsychotics: a meta-analysis. *J Clin Psychopharmacol*. 2013;33(5):675–681.
6. Stone JM, Bressan RA, Erlandsson K, et al. Non-uniform blockade of intrastriatal D2/D3 receptors by risperidone and amisulpride. *Psychopharmacology (Berl)*. 2005;180(4):664–669.
7. Bigos KL, Pollock BG, Coley KC, et al. Sex, race, and smoking impact olanzapine exposure. *J Clin Pharmacol*. 2008;48(2):157–165.
8. Feng Y, Pollock BG, Coley K, et al. Population pharmacokinetic analysis for risperidone using highly sparse sampling measurements from the CATIE study. *Br J Clin Pharmacol*. 2008;66(5):629–639.
9. Uchida H, Kapur S, Mulsant BH, et al. Sensitivity of older patients to antipsychotic motor side effects: a PET study examining potential mechanisms. *Am J Geriatr Psychiatry*. 2009;17(3):255–263.
10. Graff-Guerrero A, Rajji TK, Mulsant BH, et al. Evaluation of antipsychotic dose reduction in late-life schizophrenia: a prospective Dopamine D2/3 receptor occupancy study. *JAMA Psychiatry*. 2015;72(9):927–934.
11. Jennum P, Baandrup L, Ibsen R, et al. Increased all-cause mortality with use of psychotropic medication in dementia patients and controls: a population-based register study. *Eur Neuropsychopharmacol*. 2015;25(11):1906–1913.
12. Maust DT, Kim HM, Seyfried LS, et al. Antipsychotics, other psychotropics, and the risk of death in patients with dementia: number needed to harm. *JAMA Psychiatry*. 2015;72(5):438–445.
13. Ette EI, Williams PJ, Lane JR. Population pharmacokinetics III: design, analysis, and application of population pharmacokinetic studies. *Ann Pharmacother*. 2004;38(12):2136–2144.
14. Duffull SB, Wright DF, Winter HR. Interpreting population pharmacokinetic-pharmacodynamic analyses — a clinical viewpoint. *Br J Clin Pharmacol*. 2011;71(6):807–814.
15. Bigos KL, Chew ML, Bies RR. Pharmacokinetics in geriatric psychiatry. *Curr Psychiatry Rep*. 2008;10(1):30–36.
16. Lotrich FE, Bies RR, Smith GS, et al. Relevance of assessing drug concentration exposure in pharmacogenetic and imaging studies. *J Psychopharmacol*. 2006;20(suppl):33–40.
17. Hamon-Vilcot B, Chaufour S, Deschamps C, et al. Safety and pharmacokinetics of a single oral dose of amisulpride in healthy elderly volunteers. *Eur J Clin Pharmacol*. 1998;54(5):405–409.
18. Clark-Papasavas C, Dunn JT, Greaves S, et al. Towards a therapeutic window of D2/3 occupancy for treatment of psychosis in Alzheimer's disease, with [18F]fallypride positron emission tomography. *Int J Geriatr Psychiatry*. 2014;29(10):1001–1009.
19. Reeves S, McLachlan E, Bertrand J, et al. Therapeutic window of dopamine D2/3 receptor occupancy to treat psychosis in Alzheimer's disease. *Brain*. 2016;140(4):1117–1127.
20. Reeves S, Bertrand J, D'Antonio F, et al. A population approach to characterise amisulpride pharmacokinetics in older people and Alzheimer's disease. *Psychopharmacology (Berl)*. 2016;233(18):3371–3381.
21. Hiemke C, Baumann P, Bergemann N, et al. AGNP consensus guidelines for therapeutic drug monitoring in psychiatry: update 2011. *Pharmacopsychiatry*. 2011;44(6):195–235.
22. Mauri MC, Paletta S, Maffini M, et al. Clinical pharmacology of atypical antipsychotics: an update. *EXCLI J*. 2014;13:1163–1191.
23. McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*. 1984;34(7):939–944.
24. Jeste DV, Finkel SI. Psychosis of Alzheimer's disease and related dementias: diagnostic criteria for a distinct syndrome. *Am J Geriatr Psychiatry*. 2000;8(1):29–34.
25. McKeith IG, Galasko D, Kosaka K, et al. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. *Neurology*. 1996;47(5):1113–1124.
26. Cummings JL, Mega M, Gray K, et al. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology*. 1994;44(12):2308–2314.
27. Simpson GM, Angus JW. A rating scale for extrapyramidal side effects. *Acta Psychiatr Scand suppl*. 1970;45(212):11–19.
28. Dunn JT, Clark-Papasavas C, Marsden P, et al. Establishing test-retest reliability of an adapted [(18)F]fallypride imaging protocol in older people. *J Cereb Blood Flow Metab*. 2013;33(7):1098–1103.
29. Kuhn ELM. Maximum likelihood estimation in non-linear mixed effects models. *Comput Stat Data Anal*. 2005;49(4):1020–1038.
30. Rosenzweig P, Canal M, Patat A, et al. A review of the pharmacokinetics, tolerability and pharmacodynamics of amisulpride in healthy volunteers. *Hum Psychopharmacol*. 2002;17(1):1–13.
31. Coukell ALSC, Benfield P. Amisulpride: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy in the management of schizophrenia. *CNS Drugs*. 1996;6(3):237–256.
32. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16(1):31–41.
33. Mould DR, Holford NH, Schellens JH, et al. Population pharmacokinetic and adverse event analysis of topotecan in patients with solid tumors. *Clin Pharmacol Ther*. 2002;71(5):334–348.
34. Gomeni R, Heidbreder C, Fudala PJ, et al. A model-based approach to characterize the population pharmacokinetics and the relationship between the pharmacokinetic and safety profiles of RBP-7000, a new, long-acting, sustained-released formulation of risperidone. *J Clin Pharmacol*. 2013;53(10):1010–1019.
35. Innis RB, Cunningham VJ, Delforge J, et al. Consensus nomenclature for in vivo imaging of reversibly binding radioligands. *J Cereb Blood Flow Metab*. 2007;27(9):1533–1539.
36. Bressan RA, Erlandsson K, Jones HM, et al. Is regionally selective D2/D3 dopamine occupancy sufficient for atypical antipsychotic effect? an in vivo quantitative [123I]epidepride SPET study of amisulpride-treated patients. *Am J Psychiatry*. 2003;160(8):1413–1420.
37. Xiberas X, Martinot JL, Mallet L, et al. In vivo

extrastriatal and striatal D2 dopamine receptor blockade by amisulpride in schizophrenia. *J Clin Psychopharmacol*. 2001;21(2):207–214.
38. Vernaleken I, Siessmeier T, Buchholz HG, et al. High striatal occupancy of D2-like dopamine receptors by amisulpride in the brain of patients with schizophrenia. *Int J Neuropsychopharmacol*. 2004;7(4):421–430.
39. Zeevi N, Pachter J, McCullough LD, et al. The blood-brain barrier: geriatric relevance of a critical brain-body interface. *J Am Geriatr Soc*. 2010;58(9):1749–1757.
40. Mehta DC, Short JL, Hilmer SN, et al. Drug access to the central nervous system in Alzheimer's disease: preclinical and clinical insights. *Pharm Res*. 2015;32(3):819–839.
41. Uchida H, Mamo DC, Mulsant BH, et al. Increased antipsychotic sensitivity in elderly patients: evidence and mechanisms. *J Clin Psychiatry*. 2009;70(3):397–405.
42. Volkow ND, Wang GJ, Fowler JS, et al. Imaging endogenous dopamine competition with [11C]raclopride in the human brain. *Synapse*. 1994;16(4):255–262.
43. Uchida H, Suzuki T, Graff-Guerrero A, et al. Therapeutic window for striatal dopamine D(2/3) receptor occupancy in older patients with schizophrenia: a pilot PET study. *Am J Geriatr Psychiatry*. 2014;22(10):1007–1016.
44. Mukherjee J, Yang ZY, Brown T, et al. 18F-desmethoxyfallypride: a fluorine-18 labeled radiotracer with properties similar to carbon-11 raclopride for PET imaging studies of dopamine D2 receptors. *Life Sci*. 1996;59(8):669–678.
45. Seeman P. All roads to schizophrenia lead to dopamine supersensitivity and elevated dopamine D2(high) receptors. *CNS Neurosci Ther*. 2011;17(2):118–132.
46. Seeman P. Therapeutic occupation of dopamine D2 antipsychotic receptors in Alzheimer's disease. *Int J Geriatr Psychiatry*. 2014;29(10):1096.
47. Seeman P, Van Tol HH. Deriving the therapeutic concentrations for clozapine and haloperidol: the apparent dissociation constant of a neuroleptic at the dopamine D2 or D4 receptor varies with the affinity of the competing radioligand. *Eur J Pharmacol*. 1995;291(2):59–66.
48. Olsson H, Farde L. Potentials and pitfalls using high affinity radioligands in PET and SPET determinations on regional drug induced D2 receptor occupancy–a simulation study based on experimental data. *Neuroimage*. 2001;14(4):936–945.
49. Vernaleken I, Peters L, Raptis M, et al. The applicability of SRTM in [(18)F]fallypride PET investigations: impact of scan durations. *J Cereb Blood Flow Metab*. 2011;31(9):1958–1966.
50. Kegeles LS, Slifstein M, Frankle WG, et al. Dose-occupancy study of striatal and extrastriatal dopamine D2 receptors by aripiprazole in schizophrenia with PET and [18F]fallypride. *Neuropsychopharmacology*. 2008;33(13):3111–3125.
51. Kessler RM, Ansari MS, Riccardi P, et al. Occupancy of striatal and extrastriatal dopamine D2 receptors by clozapine and quetiapine. *Neuropsychopharmacology*. 2006;31(9):1991–2001.
52. Nakajima S, Uchida H, Bies RR, et al. Dopamine D2/3 receptor occupancy following dose reduction is predictable with minimal plasma antipsychotic concentrations: an open-label clinical trial. *Schizophr Bull*. 2016;42(1):212–219.
53. Joel D, Weiner I. The connections of the dopaminergic system with the striatum in rats and primates: an analysis with respect to the functional and compartmental organization of the striatum. *Neuroscience*. 2000;96(3):451–474.
54. Bowskill SV, Patel MX, Handley SA, et al. Plasma amisulpride in relation to prescribed dose, clozapine augmentation, and other factors: data from a therapeutic drug monitoring service, 2002–2010. *Hum Psychopharmacol*. 2012;27(5):507–513.

Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Geriatric Psychiatry section. Please contact Helen Lavretsky, MD, MS, at hlavretsky@psychiatrist.com, or Gary W. Small, MD, at gsmall@psychiatrist.com.

Supplementary material follows this article.

THE JOURNAL OF CLINICAL PSYCHIATRY
THE OFFICIAL JOURNAL OF THE AMERICAN SOCIETY OF CLINICAL PSYCHOPHARMACOLOGY

Supplementary Material

Article Title: A Population Approach to Guide Amisulpride Dose Adjustments in Older Patients With Alzheimer's Disease

Author(s): Suzanne Reeves, PhD; Julie Bertrand, PhD; Emma McLachlan, MBChB; Fabrizia D'Antonio, MBBS; Stuart Brownings, BSc; Akshay Nair, MBBS; Suki Greaves, MBBS; Alan Smith, MBBS; Joel T. Dunn, PhD; Paul Marsden, PhD; Robert Kessler, MD; Hiroyuki Uchida, MD, PhD; David Taylor, PhD; and Robert Howard, MD

DOI Number: 10.4088/JCP.16m11216

List of Supplementary Material for the article

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplementary eTable 1. Amisulpride Pharmacokinetic (PK) - prolactin (PRL) Model			
Parameter	**Estimate (RSE%), p value**	**IIV% (RSE%)**	**RUV% (RSE%)**
PK			
ka (/hr)	0.83 (19)	45 (25)	
Cl (L/hr) [a, b]	51.5 (8)	50 (11)	18.2 (5)
V1 (L)	424 (15)	49 (22)	
Q (L/hr)	108 (16)	67 (19)	
V2 (L)	706 (12)	53 (16)	
PRL Emax			
PRL_{base}	5.9 (8)	15 (92)	
E_{max}	52 (26) Men 124 (26) Women	43 (21)	28.9 (18)
β-E_{max}, weight	-0.95 (46), p=0.03	ne	
β-E_{max},Gender	0.86 (26), p=9.7e-005	ne	
EC_{50} (ng/ml)	18.0 (74)	ne	

[a] *Covariate testing was restricted to CL and included weight, height, age, gender, creatinine clearance (CrCL). To address co--linearity between CrCL and other covariates (weight, age), serum creatinine was included as a separate covariate. Allometric scaling (power 0.75) was fixed for weight on CL as an initial step, and weight centred at 70kg.*

[b] *Best fit model estimated a power effect of -2.62 for age on CL; age centred at 77 years*

ka - absorption constant; Cl - apparent clearance from central compartment; V1- central volume of distribution; Q - intercompartmental clearance; V2- peripheral volume of distribution

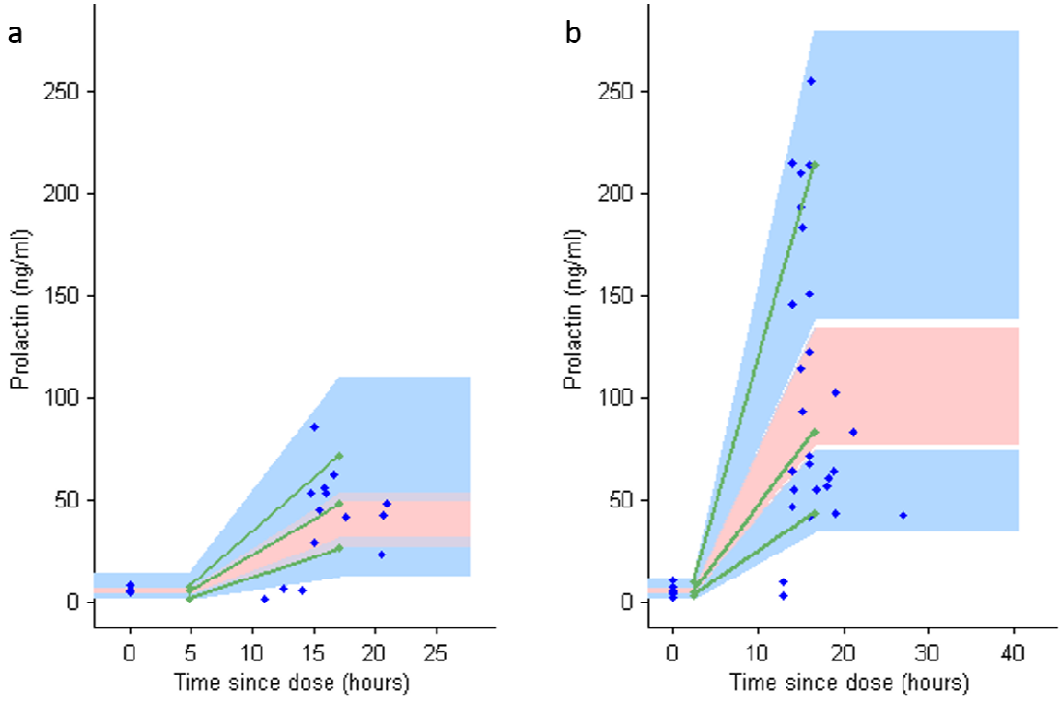
PRL = PRL_{base} + (E_{max} Cc) / (EC_{50} + Cc): PRL_{base} baseline PRL; E_{max}, maximum PRL concentration achieved; Cc, amisulpride blood concentration; and EC_{50}, amisulpride concentration required to achieve 50% Emax*

IIV- inter-individual variability for amisulpride PK and PRL related parameters was estimated using an exponential model $P_i = P_{TV} \times e^{\eta p}$ where P_i is the parameter estimate for the ith individual, and P_{TV} is the typical value for the parameter at the population level. Random effects between ith individual and population parameter values (eta, η_p), was assumed to be normally distributed (mean of 0, variance ω_η^2)

RUV - residual unexplained variability, described using a proportional residual error model ($y_{ij} = \hat{y}_{ij} (1+ \varepsilon_{ij})$, where y_{ij} and $\hat{y}_{ij}$ represents the jth observed PRL of the ith subject and corresponding model-predicted PRL; and ε_{ij} was assumed to be normally distributed (mean of 0, variance σ^2)

Other abbreviations:
RSE - relative standard error; ne - not estimated

Supplementary eFigure 1. Visual predictive checks (VPC): 95% prediction intervals around 5th (blue), 50th (pink) and 95th (blue) model predicted percentiles, overlaid to baseline (time=0) and post-treatment (time since last amisulpride dose) observed prolactin values and 5th, 50th and 90th observed percentiles (green) in a) men and b) women



Supplementary eTable 2. Pharmacokinetic-$D_{2/3}$ Receptor Occupancy Models			
Parameter	**Estimate (RSE%)**	**IIV% (RSE%)**	**RUV% (RSE%)**
Pharmacokinetic model			17.6 (5)
ka (/hr)	0.84 (18)	46.8 (23)	
Cl (L/hr) [a,b]	49.2 (7)	49.5 (10)	
V1 (L)	452 (15)	46.2 (22)	
Q (L/hr)	112 (16)	65.2 (19)	
V2 (L)	759 (11)	48.7 (17)	
PK- Caudate Imax model			15.3 (58)
BP_{PRE}	17.3 (5)	13.5 (40)	
Imax (%)	83.4 (11)	8.9 (36)	
IC_{50} (ng/ml)	19.1 (40)	ne	
PK- Putamen Imax model			14.4 (50)
BP_{PRE}	23.0 (5)	12.1 (41)	
I_{max} (%)	98.7 (33)	9.6 (67)	
IC_{50} (ng/ml)	61.3 (70)	ne	
PK-Thalamus Imax model			17.2 (48)
BP_{PRE}	1.54 (6)	17.5 (33)	
Imax %	100 (13)	ne	
IC_{50} (ng/ml)	29.5 (42)	ne	

[a] allometric scaling (power 0.75) fixed for weight on CL; weight centred at 70kg
[b] power effect of -3.21 estimated for age on CL.; age centred at 77 years

ka - absorption constant; Cl - apparent clearance from central compartment; V1- central volume of distribution; Q - intercompartmental clearance; V2- peripheral volume of distribution

$BP_{POST} = BP_{PRE} *[(1-I_{max}*Cc)/(Cc+IC50)]$: BP_{PRE} and BP_{POST} represent [^{18}F]fallypride binding potential pre- and post-treatment respectively; I_{max}, maximum inhibitory effect of amisulpride at $D_{2/3}$ receptors; Cc, amisulpride blood concentration; and IC50, amisulpride concentration required to achieve 50% Imax.

IIV- inter-individual variability for PK and BP_{ND} was estimated using an exponential model $P_i = P_{TV} \times e^{\eta p}$ where P_i is the parameter estimate for the ith individual, and P_{TV} is the typical value for the parameter at the population level. Variability between ith individual and population parameter values (eta, η_p), was assumed to be normally distributed (mean of 0, variance ω_η^2)

RUV - residual unexplained variability, described using a proportional residual error model ($y_{ij} = \hat{y}_{ij} (1+ \varepsilon_{ij})$, where y_{ij} and $\hat{y}_{ij}$ represents the jth observed BP of the ith subject and corresponding model-predicted BP; and ε_{ij} was assumed to be normally distributed (mean of 0, variance σ^2)

Other abbreviations:
RSE - relative standard error; ne - not estimated

Supplementary eFigure 2. PK- $D_{2/3}$ receptor occupancy model

[^{18}F]fallypride binding in 15 patients pre-treatment (10 'antipsychotic free' control AD patients, and 5 subsequently treated); and 19 patients post 80 ± 58 days of treatment (lines connect paired scans) (top); and visual predictive checks (VPC), 95% prediction intervals around 5th (blue), 50th (pink) and 90th (blue) model predicted percentiles, overlaid to observed [^{18}F]fallypride binding values and 5th, 50th and 95th percentiles (bottom) are shown, in a) caudate b) putamen and c) thalamus