**Towards safer risperidone prescribing in Alzheimer's disease**

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**Abstract**

**Background**

In the treatment of psychosis, agitation and aggression in Alzheimer's disease (AD), guidelines emphasise the need to 'use the lowest possible dose' of antipsychotic drugs, but provide no information on optimal dosing.

**Aims**

This analysis investigated the pharmacokinetic profiles of risperidone and 9-hydroxy (OH)-risperidone, and how this related to treatment emergent extrapyramidal side effects (EPS), using data from The Clinical Antipsychotic Trials of Intervention Effectiveness-AD study.

**Method**

A statistical model, which described the concentration-time course of risperidone and 9-OH-risperidone, was used to predict peak, trough and average concentrations of risperidone, 9-OH-risperidone and 'active moiety' (combined concentrations) (108 participants). Logistic regression was used to investigate the associations of pharmacokinetic biomarkers with EPS. Model based predictions were used to simulate the dose adjustments needed to avoid EPS.

**Results**

The model showed an age-related reduction in risperidone clearance ($p<0.0001$), reduced renal elimination of 9-OH-risperidone ($t_{1/2}$ 27 hours), and slower active moiety clearance in 22% of patients, (concentration-to-dose ratio (C/D) 20.2±7.2 versus 7.6±4.9 ng/mL per mg/day, Mann Whitney U, $p<0.0001$). Higher trough 9-OH-risperidone and active moiety concentrations ($p<0.0001$), and lower Mini-Mental State Examination (MMSE) scores ($p<0.0001$), were associated with EPS. Model based predictions suggest the optimum dose ranged from 0.25mg/day (85 years, MMSE of 5), to 1mg/day (75 years, MMSE of 15), with alternate day dosing required for those with slower drug clearance.

**Conclusions**

Our findings argue for age- and MMSE -related dose adjustments and suggest that a single measure of C/D ratio could be used to identify those with slower drug clearance.

## Introduction

### Antipsychotic drug use in Alzheimer's disease

Alzheimer's disease affects around 35 million people worldwide, fifty percent of whom will experience psychosis symptoms (delusions and hallucinations). Psychosis symptoms are often distressing, increase the risk of aggression towards caregivers, predict faster cognitive and functional decline, and reduce ability to live independently (1). Although symptoms sometimes respond to psychosocial interventions, for those with severe persistent symptoms, antipsychotic medication is required to reduce distress and associated risks. (2) The best evidence of efficacy is for second generation antipsychotic drugs. (3) However, concerns about side-effects (sedation, falls, parkinsonism, and stroke) and increased mortality in people with dementia, , particularly in those aged over 80 years, (4) has led to a restriction in prescribing. In England, National Institute for Clinical Excellence (NICE) guidance emphasises the need to treat with 'the lowest effective dose for the shortest possible time' but provides little practical information on the optimal dose range for individual drugs.

We have shown that amisulpride therapeutic plasma concentrations for the treatment of AD psychosis (40-100 ng/mL), are lower than those recommended for the treatment of schizophrenia (100-320 ng/mL), due to a leftwards shift in the dopamine $D_{2/3}$ receptor concentration-occupancy curve. (5) These findings raise questions regarding the mechanisms of antipsychotic sensitivity in AD and suggest that, for amisulpride at least, 50 mg/day (compared to 400-800mg/day in young adults), may optimally balance the risks and benefits of treatment. (6) It is, however, not clear how far we can extrapolate this approach to other antipsychotic drugs.

### Pharmacokinetics and consensus guidance on risperidone prescribing

Risperidone, an antipsychotic drug with high affinity for dopamine $D_{2/3}$ and serotonin $5HT_{2A}$ receptors, is the only drug licensed for short-term use in the treatment of aggression and psychosis in dementia in the European Union, and is typically prescribed across a 0.5-2 mg/day dose range in this indication. (7) Oral risperidone has high (70-85%) bioavailability and is extensively metabolized by cytochrome P450 (CYP 2D6 and to a lesser extent CYP3A4) to the active metabolite 9-hydroxy(OH)-risperidone. (8) Peak concentrations of risperidone and 9-OH-risperidone are reached after 1 and 3 hours respectively. The elimination half-life ($t_{1/2}$) of risperidone is dependent on multiple factors: Genetic variation in CYP2D6 genotype, which leads to non-functional, decreased and increased enzyme activity in poor, intermediate and extensive metabolisers respectively, accounts for around 50% of the

variability in risperidone concentrations ($t_{1/2}$ 4.7 hours in extensive and 22 hours in poor metabolisers); with age, hepatobiliary dysfunction, and use of CYP (2D6 inhibitors, 3A4 inducers) further contributing to variability (9, 10). The metabolite is predominantly renally excreted (glomerular filtration and tubular secretion by an unknown transporter) with a $t_{1/2}$ of 20 hours; increased to 25 hours in the over-65s and in moderate renal failure. The time taken to achieve steady state concentrations of the active moiety (combined concentrations of risperidone and 9-OH-risperidone) is dependent on $t_{1/2}$ and estimated as 4-5 days in young adults who are normal metabolisers.

Consensus guidelines, based on therapeutic drug monitoring, (8, 11) pharmacokinetic modelling, (12) and imaging of striatal $D_{2/3}$ receptor occupancy (13) in risperidone treated patients with schizophrenia, recommend active moiety concentrations of 20–40 ng/mL (3-6 mg/day), (12) as higher concentrations increase occupancy beyond 80% and increase the risk of extrapyramidal side-effects (EPS). For those with glomerular filtration rates below 60 mL/min, due to age or other cause of renal impairment, a 50% dose reduction is advised to avoid excessive exposure (14). Recent guidance on personalised risperidone prescribing advocates dose reductions for those with concentration to dose (C/D) ratios of the active moiety over 14 ng/mL per mg/day, indicating slower clearance, due to the combined effect of CYP2D6, CYP3A4 *and* renal clearance. (15). There is a lack of empirical data from people with AD.

**Aims**

This analysis aimed to combine pharmacokinetic and clinical outcome data from The Clinical Trials of Intervention Effectiveness in Alzheimer's disease (CATIE-AD) study, (16) with the following objectives:

1) To investigate sources of variability in plasma concentration-time profiles of risperidone and 9-OH-risperidone, using an approach that allowed estimation of risperidone clearance (metabolism) in distinct subpopulations.
2) To estimate pharmacokinetic indices (peak, trough and average concentrations of risperidone, 9-OH-risperidone and active moiety) for each individual, across the prescribed dose range.
3) To investigate the relationship between the above pharmacokinetic indices with EPS.

**Method**

**Data source**

CATIE-AD was a randomized, double-blind, parallel group study comparing olanzapine, quetiapine, risperidone and placebo in the treatment of psychosis and aggression in AD (Clinicaltrials.gov identifier: NCT00015548). In phase 1, participants were randomized to receive risperidone, olanzapine, quetiapine, or placebo (1:1:1:1 ratio), with study physicians having a choice of two capsule strengths (0.5mg, 1.0 mg). Dose adjustments and treatment discontinuation (possible after 2 weeks, with a further decision point at 12 weeks) were at the discretion of study physicians. Patients with an adequate response continued treatment for up to 36 weeks. Patients whose initial treatment was discontinued during phase 1 could be enrolled in phase 2 and randomly assigned to receive one of the antipsychotic drugs to which they were not initially assigned, or to receive citalopram. In phase 3, treatment was prescribed in an open manner. Within each phase, plasma drug concentration was measured at 2, 4 and 12 weeks, or when a medication switch was made (16, 17).

Clinical assessment (Baseline, every 2-4 weeks during dose titration) included the Simpson Angus Scale (SAS), and Barnes Akathisia Scale (BAS). (16) Plasma concentrations of risperidone and the active metabolite 9-OH-risperidone were determined using a liquid chromatography-tandem mass spectrometry method with a detection limit of 0.1 ng/mL. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. Written informed consent was obtained from all patients. A comprehensive plan was developed to ensure that all institutional, National Institute for Health, and federal regulations concerning informed consent were fulfilled. The plan included careful assessment of risks and benefits, review by the CATIE protocol and ethics committees, and re-view by the National Institute of Mental Health Data Safety and Monitoring Board.

**Data Extraction**

Data available from risperidone treated participants included study identification number, phase, visit, dose (mg), timing of blood draw (hours post dose), number of days of treatment, dosage interval (daily), physiological characteristics (age, gender, height, weight, ethnicity (coded as white/other), and smoking (currently smoking or not), Mini-Mental State Examination (MMSE) scores, and plasma concentrations of risperidone and 9-OH-risperidone (ng/mL). Treatment emergent EPS were coded as present if SAS total scores were six or more, or BAS global scores were two or more at follow-up, in individuals with Baseline SAS ratings less than six and BAS scores less than two. Only participants without

Baseline EPS were included in our analysis of outcome data. Data extracted on other adverse events (AE) included sedation, postural hypotension, and ECG abnormalities were extracted from the AE log. Rating scales and AEs were checked for consistency with pharmacokinetic data, using phase, number of days treatment, and the timing of blood sampling. The concomitant mediation log was used to confirm that no participant was prescribed CYP2D6 inhibitors (fluoxetine, paroxetine, duloxetine, bupropion) or CYP3A4 inducers (carbamazepine).

**Statistical Analysis**

**Demographics**

Demographic data were analysed using statistical package for social sciences version 22.0. Mann Whitney U tests were used to describe group comparisons. Chi- squared tests were used to compare frequencies between groups.

**Pharmacokinetic model development**

Plasma concentration-time profiles of risperidone and 9-OH-risperidone were evaluated using a statistical model that linked parent risperidone and metabolite 9-OH-risperidone via a metabolism rate constant (*km*), with the following parameters: Risperidone clearance ($CL_{RISP}$); Risperidone volume of distribution ($V_{RISP}$); Absorption rate constant (*ka*); 9-OH risperidone volume of distribution ($V_{9\text{-}OH\text{-}RISP}$); and 9-OH-risperidone clearance ($CL_{9\text{-}OH\text{-}RISP}$). The analysis estimated fixed effects (parameters describing dose-concentration relationships), and random effects, comprised of inter-individual variability (difference between individual and predicted model parameter values for the sample), and residual variability (system noise, dosage history errors).Model development was carried out using Monolix software (version 2018r; www.lixoft.eu). Parameters were estimated using an iterative approach which provided maximum likelihood estimates and standard errors. Concentrations below the limit of quantification were coded to specify that their true values (and their contribution to the likelihood) could lie anywhere between 0 and 0.1ng/ml. Plasma concentration was converted from ng/mL to mcg/L for use in model building.

The model allowed estimation of the probability of there being more than one subpopulation in relation to risperidone clearance, by including a latent covariate. No assumption was made that latent categories corresponded solely to CYP2D6 genotype, as multiple factors contribute to hepatic metabolism in older people. Residual variability was estimated separately for risperidone and 9-OH-risperidone. Covariates (height, age, gender, smoking, ethnicity, weight) were incorporated in a stepwise manner, through visual inspection of covariate plots

and regression analysis in R for categorical covariates. Models were evaluated using goodness-of-fit criteria, including diagnostic scatter plots, visual predictive checks, degree of shrinkage, change in inter-individual variability, model precision, and approximate likelihood ratio tests. A change in log likelihood estimate was considered significant if =>4 (equivalent to $p<0.05$, one degree of freedom), and accompanied by no change or a decrease in Bayesian Information Criteria.

**Pharmacokinetic biomarkers and clinical outcome**

Model based estimates were used to calculate peak, trough, and average concentrations of risperidone, 9-OH-risperidone and active moiety (their combined concentrations) for each individual, across the dosage interval. Concentration-to-dose ratio for the active moiety was calculated from trough estimates, to allow comparison with recommendations regarding personalised dosing of risperidone. (15) Each pharmacokinetic biomarker was individually considered as an independent variable (regressor) in a binary logistic model which described the probability of EPS. The model accounted for random effects, and adjusted for potential confounders (age, sex, MMSE, height, weight). Best fit models were used to simulate and predict plasma concentrations and probability of EPS.

**Results**

**Sample characteristics**

Of 110 risperidone treated patients, 65 (59.1%) were randomised to risperidone treatment in phase one, 31 (28.2%) in phase two, and 14 (12.7%) in phase three (188 plasma samples, collected 26.9±69.9 hours post dose). After excluding four samples, taken after 180 hours (above six half-lives post dose), data from 108 patients remained (52 (47.3%) men, aged 78.4±6.7 years, weight 68.9±14.7 kg, height 1.6±0.1m, MMSE 14.6 ±6.2); sampled 18.1±26.8 hours post dose, after 92.4±76.8 days treatment with 1.0±0.7 mg/day of risperidone (risperidone plasma concentrations 2.4±3.1ng/mL, 9-OH-risperidone plasma concentrations 10.0±8.4 ng/mL; 20 (10%.8%) risperidone and 2 (1.8%) 9-OH-risperidone samples were below the limit of quantification).

Eight participants with Baseline SAS scores of six or more (indicating EPS *prior* to commencing risperidone), were excluded from the analysis of outcome data. Those with Baseline EPS had greater global cognitive impairment (MMSE 7.8±7.0 versus 15.2±5.8, Mann Whitney U, $p<0.0001$) but there were no differences in other characteristics (Table 1). SAS and Barnes rated treatment emergent EPS occurred in 14 (14%), eight of whom were recorded as having parkinsonism (moderate severity) in the AE log. Other AEs included

sedation in 13 (13%) ('mild' in ten, 'moderate' in two, and 'severe' in one),falls in five (5%), postural hypotension in two (2%) and ECG abnormalities in three (3%) patients (Table 1). Those with EPS were prescribed a higher risperidone dose (1.7±0.9mg versus 0.9±0.5mg; Mann Whitney U, $p$<0.003), had lower MMSE scores (10.2±4.2 versus 16.0±5.6, Mann Whitney U, $p$<0.0001) and a greater proportion (5 (37.5%) versus 6 (7.0%) patients) were treated with concomitant anti-depressant medication (trazodone) (chi-squared $p$=0.007, odds ratio = 7.4, 95% CI 1.9-29.2).

**Pharmacokinetic model**

The base model included a latent covariate with two categories (the model failed to converge using a covariate with three categories). Parameters were estimated with good precision, apart from $V_{9\text{-OH-RISP}}$ (relative standard error 60.1%). Residual variability was 0.1 mcg/L (56.2%) for risperidone and 0.7 mcg/L (28.2%) for 9-OH-risperidone. Covariate testing identified a significant contribution of log transformed age (tAge) to the variability in risperidone clearance (β =-0.3, $p$=9.13e-04). Inclusion of an age effect on $CL_{RISP}$ increased the precision of the model (Supplementary Table 1) and reduced the estimated probability of being in latent category 1 from 32% to 22%. Stepwise testing of other covariates on clearance parameters did not improve the precision or model fit. Model based predictions, based on the mean age (78.4 years) of the sample, suggested that for patients assigned to latent category one, risperidone clearance was 8.7L/hr ($t_{1/2}$ 22 hours), compared to 34.2L/hr ($t_{1/2}$ 5 hours) for those in latent category two. Patients in latent category one were thus considered to represent 'functionally poor' metabolisers (PM). Predictions based on the observed contribution of age to risperidone clearance estimated that, for those aged 88 years, risperidone clearance would be reduced by 22% ($t_{1/2}$ 28.8 hours in PM and 6.5 hours in functionally normal metabolisers (NM). Based on $V_{9\text{-OH-RISP}}$ and $CL_{9\text{-}OH\text{-}RISP}$, $t_{1/2}$ 9-OH-risperidone was 27 hours. Visual predictive checks, (VPCs) shown as percentile plots, superimposed on observed data, are shown in Supplementary Fig 1.

**Pharmacokinetic biomarkers and functional metaboliser status**

Of the 100 participants included in the analysis of clinical outcome, 18 were categorised as PM. There were no differences in clinical or demographic or clinical variables in PM and NM. Cholinesterase inhibitors were prescribed in a higher proportion of PM (four (77.8%) versus 37 (45.1%), chi squared $p$=0.01, odds ratio 1.27, 95% confidence interval (CI) 1.04-1.53), and a higher proportion of PM were women (14 (77.8%) versus 39 (47.6%), chi squared $p$= 0.02, odds ratio 1.24, 95% CI 1.04-1.49). PM were prescribed a lower dose of

risperidone (0.7±0.4 mg/day versus 1.1±0.7mg/day, Mann Whitney U, $p$=0.007), and had higher concentrations across all pharmacokinetic biomarkers (Supplementary Table 2). Trough active moiety concentration-to-dose ratio was markedly increased in PM (20.2±7.2 versus 7.6±4.9 ng/mL per mg/day, Mann Whitney U, $p$<0.0001), shown in Fig 1. There were no differences in the proportion of participants with emergent EPS in PM and NM.

**Pharmacokinetic biomarkers and clinical outcome**

Associations between individual pharmacokinetic biomarkers and EPS are detailed in Table 2. Pharmacokinetic biomarkers showed a significant association with EPS, achieving greatest significance in relation to trough concentrations of 9-OH-risperidone (Adjusted odds ratio 15.79; 95% CI 4.66-53.51 and the active moiety (Adjusted odds ratio 16.61; 95% CI 5.98-46.0). MMSE also contributed significantly to the best fit regression models (Table 2). Model-based simulations (Fig 2) suggest that for NM aged 75 years with an MMSE of 15, 1mg/day risperidone would be associated with minimal risk of EPS. For those aged 75 years with an MMSE of 5, a dose reduction to 0.5mg/day would be required. For those aged 85 years, the dose would need to be reduced by 50% to achieve equivalent plasma concentrations, and PM would require very low alternate daily dosing (0.25-0.5mg/48 hours in those aged 75 years, and 0.125-0.25mg/48 hours in those aged 85 years).

For completeness, the same analysis was carried out in relation to sedation, but there were no significant associations, although the patient rated as having 'severe' sedation had active moiety concentrations of 43.39 ng/ml (the highest in the sample), and also had treatment emergent EPS. The number of participants with other emergent side effects was too small to investigate through the use of logistic regression.

## Discussion

**Pharmacokinetic and pharmacodynamic contributions to EPS**

The consensus, based on meta-analyses of placebo controlled trials of risperidone in people with psychosis in AD, is that 1 mg/day risperidone may optimally balance efficacy and adverse effects. (3, 7, 18) However, meta-analyses can only inform the 'average' dose requirements, but are less able to identify subgroups who are most susceptible to side-effects. In this analysis we have investigated the pharmacokinetic (dose-concentrations) and pharmacodynamic (concentration-outcome) contribution to EPS, to guide safer prescribing.

We estimated that 22% of patients were 'functionally poor' metabolisers, and observed an independent effect of age on risperidone clearance. Pharmacokinetic biomarkers were robust

predictors of EPS, with higher trough concentrations of 9-OH-risperidone and active moiety providing the best fit for the data. Lower MMSE, a marker of more severe global cognitive impairment, was an independent predictor of EPS. Model based simulations suggest that, for NM aged 75 years with an MMSE of 15 (moderate AD severity), 1mg/day would be associated with minimal risk of EPS, but a dose reduction to 0.5mg/day would be required for those with an MMSE of 5. For those aged 85 years, a 50% dose reduction would be required and, for PM, alternate day dosing would be required to avoid excessive exposure.

Drug metabolism is a major contributor to pharmacokinetic variability and, in older adults, the relative importance of genotype is difficult to disentangle from physiological and clinical factors. (15) In the absence of information on *CYP2D6* genotype, the extent of any genetic contribution to functional metaboliser status is unclear, although estimates of risperidone clearance in PM and NM were broadly consistent with estimates for *CYP2D6*-predicted 'intermediate' and 'extensive' metabolisers, (10) with a single patient having a risperidone: 9-OH-risperidone ratio greater than one (suggestive of a genetically poor metaboliser) (15).

Age was independently associated with risperidone clearance and, when incorporated into the model, led to the reassignment of six patients who were initially categorised as PM. Although previous research has not shown an effect of age specifically on risperidone clearance, (10) a 30% decrease in hepatic metabolism in those aged over 70 years has been observed for other CYP2D6 substrates (19) and it is thus likely that our findings are explained by the older age of CATIE-AD participants. The long $t_{1/2}$ (27 hours) of 9-OH-risperidone in the sample as a whole is consistent with age-related impairment in renal clearance in CATIE-AD participants, which resulted in high trough concentrations of 9--OH-risperidone. This is important as the association between trough active moiety concentrations and EPS was largely explained by 9-OH-risperidone.

(12)The absence of an association between pharmacokinetic biomarkers and sedation warrants further consideration, as it may reflect the fact that distinct pharmacological mechanisms underpin sedation and EPS. However methodological limitations need to be taken into account, as sedation was not measured using a standardized scale, but was identified solely from the AE log. This is important as only eight participants were rated as having EPS in the AE log, compared to the 14 identified using SAS and Barnes scores. Prior exposure to antipsychotic drug before randomization also needs to be considered, as this may have reduced our ability to detect a relationship between sedation and pharmacokinetic

biomarkers. This was not the case for EPS, as patients who scored above the threshold cut off on SAS or Barnes at baseline were excluded from further analysis.

Statistical modelling of the relationship between risperidone active moiety plasma concentrations and $D_{2/3}$ receptor occupancy (20) in adults with schizophrenia, suggests that trough concentrations of 10.5-38.2 ng/mL are associated with 60-78% occupancy in the striatum, and 6.5 ng/mL (95% CI, 3-10 ng/mL) is associated with 50% occupancy. In CATIE-AD participants, EPS emerged from trough active moiety concentrations of 3.4 ng/mL (of which 3.2 ng/mL was 9-OH- risperidone), and concentrations exceeded 10ng/mL (60% occupancy) in eight of 14 patients with EPS. In the absence of occupancy data, it is unclear whether the emergence of EPS at such low concentrations signifies a leftwards shift in the concentration-occupancy curve, similar to that observed during amisulpride treatment. (5) This is possible, as risperidone and 9-OH-risperidone are substrates for P-glycoprotein, (21) a blood brain barrier efflux transporter that is marked reduced older people with AD. (22). However age or disease-specific changes in brain drug distribution, clearance, and competition with endogenous dopamine at receptor sites need to be considered. (5)

Pharmacodynamic changes (reduced $D_{2/3}$ receptor reserve, altered signal transduction) which lead to a greater functional outcome for a given occupancy are also important. We have previously observed EPS at low striatal $D_{2/3}$ receptor occupancies (60% compared to 80% in young people), in risperidone-treated older people with schizophrenia, (23, 24) and amisulpride-treated older people with psychosis in AD. (5) Given the error margin of occupancy predictions, we cannot rule out the possibility that occupancy was under-estimated in a proportion of those with active moiety concentrations less than 10ng/mL. (20)

The observed association between lower MMSE score, a marker of greater neuropathological change, and emergent EPS is consistent with previous clinical observations in risperidone treated patients (15). Furthermore, an association between agitation, antipsychotic use and death in those with more severe dementia has been reported in a recently published cohort study (25). The mechanisms of antipsychotic-induced EPS are not fully understood, but $D_{2/3}$ receptor antagonism of inhibitory dopaminergic inputs to striatal medium spiny neurones and cholinergic interneurones may play a key role. (2) It is unclear whether the risk of EPS in those with lower MMSE scores reflects greater in networks that modulate motor control, or is associated with as yet unidentified factors that potentiate EPS.

**Limitations**

Limitations to the analysis include sparse sampling, which meant it was not possible to estimate within-subject variability in clearance of risperidone or 9-OH-risperidone, or to investigate the contribution of concomitant medications to pharmacokinetic variability. Neither was it possible to investigate the contribution of comorbid medical conditions to variability in pharmacokinetics or emergent side effects. The lack of information on renal function is a major limitation, given the significant association between plasma concentrations of the renally eliminated metabolite and emergent EPS. This needs to be addressed in future studies.

We cannot account for the fact that those with emergent EPS were more likely to have been prescribed concomitant trazodone, given the small sample size and uncertain exposure (dose, continuity of the prescribed drug) of individual participants to trazodone. However, we cannot rule out the possibility of potential drug-drug interactions, including an interaction with P-glycoprotein, for which trazodone is a substrate. Preclinical studies have shown that selective serotonin reuptake inhibitors potentiate antipsychotic-induced EPS and this may be relevant as trazodone acts as a weak reuptake inhibitor (2). The issue of polypharmacy is an important one, as antipsychotic drugs are often initiated alongside other drug treatments, including sedating antidepressants and the downstream effects of central drug-drug interactions are poorly understood. Other limitations relate to the CATIE-AD study design, which may have reduced our ability to detect associations between pharmacokinetic indices and clinical outcome. This includes flexibility in starting dose (low or high), and the option of making adjustments or of discontinuing a phase, based on clinician judgement.

**Dose adjustments needed to avoid treatment emergent EPS**

This analysis represents a step towards safer risperidone prescribing and argues strongly for age- and MMSE- related dose reductions. From a pragmatic perspective, clinicians should ‘start low go slow’ (0.5-1mg/day) in those aged 75 years with moderate stage AD, and ‘start low, stay low’ (maximum 0.5mg/day) in those aged 75 years with severe AD. For those aged 85 years, the dose should be halved, and alternate daily dosing considered if side effects emerge, as it is likely that the person has slower active moiety clearance.

Personalised prescribing should ideally incorporate knowledge of genetic, environmental and personal variables to determine dosing. This is not currently happening in clinical practice and there has been a lack of empirical data in older people to justify the use of routine therapeutic drug monitoring. A recently proposed personalised prescribing algorithm for risperidone suggests that high trough C/D ratios are indicative of slower active moiety

clearance, due to the combined effect of CYP2D6, 3A4 and renal clearance. (15) Our analysis, which used model-based estimates of trough concentrations, were consistent with this recommendation and suggested that alternate daily dosing may be required in those with higher C/D ratios to avoid emergent EPS. Therapeutic drug screening offers the opportunity to guide dose adjustments with more precision, as the C/D ratio of the active moiety could be derived from a single steady state trough plasma sample, to identify those at higher risk of excessive exposure. It will however be important to replicate these findings in a larger dataset which includes information on renal function, and allows further investigation of the impact of antidepressant use on the observed associations. Alongside this, future studies should evaluate the feasibility and clinical utility of therapeutic drug screening in older people with Alzheimer's disease.

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**Contributors**

SR led the study design, carried out data extraction, carried out data analysis and led on the writing of the paper; JB, HU, RB, BP and RH gave input into the study design and analysis plan; KY, YO and KL extracted data on clinical outcome measures; MO and SR extracted and checked adverse event data JB supervised SR in the analysis of the data, carried out simulations, and led on data presentation; EB and RH gave input into the interpretation and presentation of pharmacokinetic data; all authors contributed to the interpretation of the clinical findings and the writing of the paper, and approved the submitted manuscript.

**Competing interests**

There are no competing interests

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## Figure Legends

**Fig 1. Active moiety concentration to dose ratio**

Estimated concentration to dose (C/D) ratios for the active moiety (ng/mL per mg/day) are shown at trough in those categorised as functionally poor (PM) and functionally normal (NM) metabolisers, aged 75 and 85 years, prescribed 250, 500 and 1000mcg risperidone daily. The red line (7ng/mL per mg/day) represents typical estimates for C/D in a reference group, based on therapeutic drug monitoring studies of risperidone.

**Fig 2. Simulated trough 9-OH-risperidone concentrations and EPS**

Simulated trough 9-OH-risperidone concentrations and the probability of extrapyramidal side effects (EPS) are shown for a population of 100 people in each of the following categories: 75 or 85 years old; with an MMSE score of 5, 10 or 15; prescribed 250, 500 or 100mcg risperidone daily in A) Functionally normal metabolisers (NM) and B) Functionally poor metabolisers (PM).

| **Table 1. Demographic and Clinical Characteristics of Risperidone-Treated CATIE-AD Participants** | | |
|---|---|---|
| **Characteristic** | **No Baseline EPS (n=100)** | **Baseline EPS (n=8)** |
| Age, Mean (SD), years | 78.1(6.6) | 80.5 (7.4) |
| Men, Number (%) | 53 (53) | 4 (50) |
| Weight, Mean (SD), kg | 69.1 (15.2) | 66.3 (7.4) |
| Height, Mean (SD), m | 1.6 (0.1) | 1.6 (0.1) |
| MMSE, Mean (SD) | 15.2 (5.8) | 7.8 (7.0) *** |
| Ethnicity, White American, Number (%) | 80 (80%) | 8 (100%) |
| Married, Number (%) | 65 (65) | 5 (63) |
| Living in own/family home, Number (%) | 89 (89) | 7 (87.5) |
| Smoking status (current smoker), Number (%) | 5 (5%) | 0 |
| Prescribed medication (continuous), Number (%) | | |
| Cholinesterase Inhibitor | 51 (51) | 4 (50%) |
| Antidepressant | 11 (11%) | 1 (13) |
| Hypnotics, anxiolytics | 15 (15) | 0 |
| Number (%) randomised to risperidone<br>Phase 1; Phase 2; Phase 3 | <br>60 (60); 28 (28); 12 (12) | <br>4 (50); 2 (25); 2 (25) |
| **Data included in pharmacokinetic model** | | |
| Risperidone dose, Mean (SD) mg/day | 1.0 (0.7) | 1.3 (1.0) |
| Number of plasma samples | 172 | 12 |
| Time of plasma sampling, Mean (SD) hours since last dose | 17.0 (25.9) | 22.4 (30.4) |
| Number of days treatment, Mean (SD) | 91.5 (77.3) | 73.4 (74.9) |
| Risperidone plasma concentrations, Mean (SD), ng/mL | 2.2 (3.1) | 0.5 (0.9) |
| 9-OH-risperidone plasma concentrations, Mean (SD), ng/mL | 9.3 (8.1) | 10.2 (10.6) |
| **PK model categorised as a poor metaboliser* | *18 (18)* | *0* |
| **Clinical Outcome (n=100, only those without baseline EPS were included)** | | |
| Treatment emergent EPS, Number (%) | 14 (14.0) | |
| Sedation, Number (%) | 13 (13.0) | - |
| Falls, Number (%) | 5 (5.0) | - |
| Postural hypotension, Number (%) | 2 (2.0) | - |
| ECG abnormalities, Number (%) | 3 (3.0) | - |

Abbreviations: ECG, Electrocardiogram; EPS, extrapyramidal side effects; MMSE, Mini-Mental State Examination; SD, standard deviation.

*** $p<0.0001$ (all other findings ns)

| Table 2. Pharmacokinetic Biomarkers and Emergent EPS (n=100) | | | |
|---|---|---|---|
| **Regressor #** | **Wald test p value** | **BIC** | **Adjusted OR (95% CI)** |
| **Peak plasma concentrations, ng/mL** | | | |
| Risperidone<br>MMSE | 0.04<br>ns | 73.0 | 11.02 (2.35-115.58)<br>0.03 (0.003-1.67) |
| 9OH-Risperidone<br>MMSE | <0.0001<br><0.0001 | 65.9 | 13.87 (4.26-45.15)<br>0.006 (0.0006-0.06) |
| Active Moiety<br>MMSE | ns<br>ns | 66.6 | 4.71 (0.68-32.79)<br>0.03 (0.0003-2.69) |
| **Trough plasma concentrations, ng/mL** | | | |
| Risperidone<br>MMSE | ns<br>ns | 74.8 | 1.77 (0.65-4.81)<br>0.78 (0.31-1.46) |
| 9OH-Risperidone<br>MMSE | <0.0001<br><0.0001 | 60.6 | 15.79 (4.66-53.51)<br>0.007 (0.0008-0.066) |
| Active Moiety<br>MMSE | <0.0001<br><0.0001 | 61.7 | 16.61 (5.98-46.0)<br>0.007 (0.0008-0.056) |
| **Average plasma concentrations, ng/mL** | | | |
| Risperidone<br>MMSE | ns<br>0.03 | 73.3 | 7.54 (0.60-95.54)<br>0.25 (0.07-0.90) |
| 9OH-Risperidone<br>MMSE | <0.0001<br><0.0001 | 60.6 | 13.87 (3.66-52.4)<br>0.007 (0.0006-0.09) |
| Active Moiety<br>MMSE | <0.0001<br><0.0001 | 61.9 | 9.67 (3.03-30.88)<br>0.01 (0.0009-0.11) |

Binary logistic regression models accounted for random effects,and adjusted for potential confounders including gender and log transformed age, MMSE, height, weight, and gender. A backward method was used, which removed variables that did not contribute to the model (significance threshold $p<0.05$). For each best fit model, the $\beta$ regressor effect coefficient (standard error) value was used to calculate a Wald statistic, its $p$ value, based on the chi squared statistic, and adjusted odds ratio (95% confidence interval). Regression models were not significant for sedation and are not shown in the Table.

# Supplementary Material

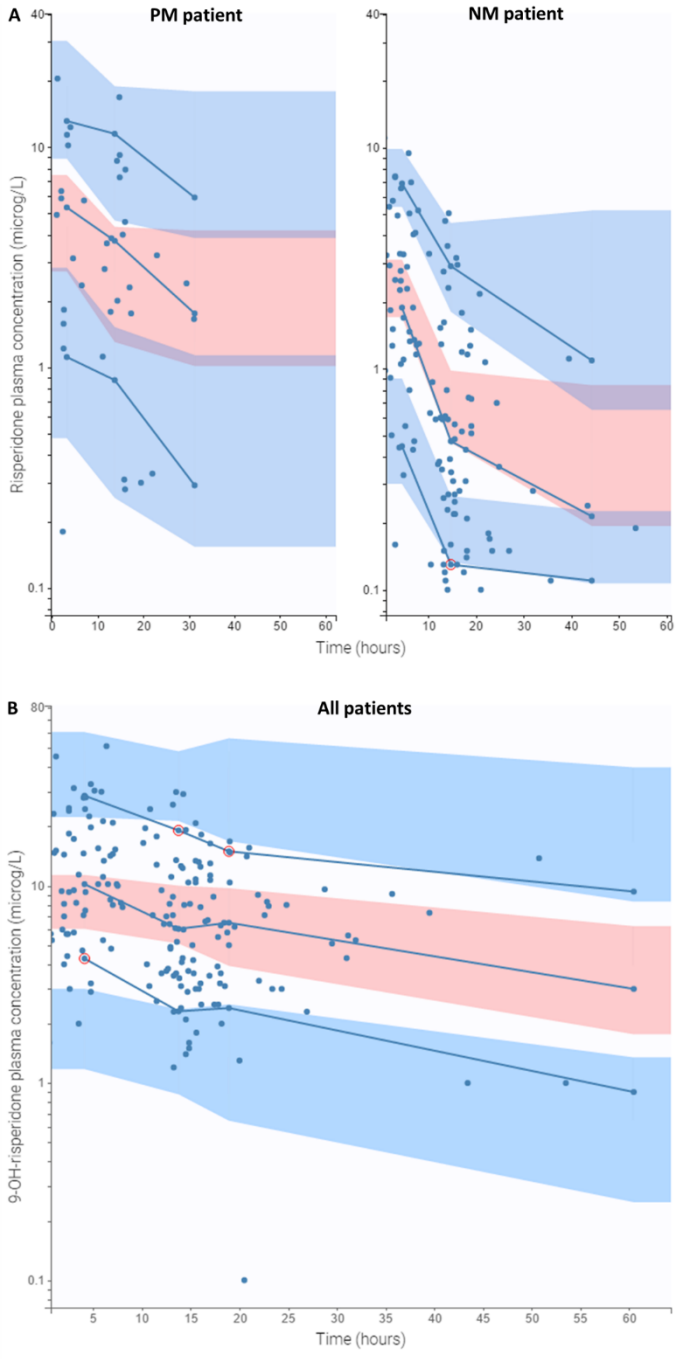
| **Supplementary Table 1. Pharmacokinetic Model for Risperidone and 9-hydroxy-risperidone (n=108)** | | | | |
|---|---|---|---|---|
| Parameters | Base Model | | Final Model | |
| Fixed Effects | Parameter estimates | RSE (%) | Parameter estimates | RSE (%) |
| Ka (/hr) (fixed) | 2 | - | 2 | - |
| $V_{RISP}$ (L) | 281 | 16 | 272 | 16.4 |
| $CL_{RISP}$ (L/hr) | 11.1 | 26.3 | 8.87 | 24.8 |
| *β Latent category (2) CLp* | 1.3 *** | 20.2 | 1.4 *** | 15.8 |
| *β tAge CLp* | - | - | -3.1 *** | 30.2 |
| $V_{9\text{-}OH\text{-}RISP}$ (L) | 1703 | 60.1 | 2030 | 49.2 |
| $CL_{9\text{-}OH\text{-}RISP}$ (L/hr) | 53.2 | 13.6 | 52 | 13.5 |
| Interindividual variability, | | | | |
| ω_ $V_{RISP}$ % | 42.5 | 32.7 | 45.2 | 39.2 |
| ω_ $CL_{RISP}$ % | 53.8 | 23.5 | 46.8 | 20.9 |
| ω_ $V_{9\text{-}OH\text{-}RISP}$ % | 133 | 40.2 | 97.0 | 47.5 |
| ω_ $CL_{9\text{-}OH\text{-}RISP}$ % | 55.4 | 16.4 | 55.6 | 17.6 |
| Residual unexplained variability | | | | |
| σ Risperidone mcg /L (%) | 0.1 (56.2) | 36.6 (15.3) | 0.1(55.6) | 21.1 (11.6) |
| σ 9-OH-risperidone mcg/L (%) | 0.7 (28.2) | 35.4 (16.3) | 0.7 (28.7) | 39.0 (15.0) |
| Probability of being in latent category, % | 31.6 | 35.4 | 21.7 | 40.2 |
| -2 x Log likelihood/ Bayesian Information Criteria | 1700/1766 | | 1688/1759 | |

Abbreviations*: Ka* -first-order absorption rate constant (fixed at 2); $V_{RISP}$ - Volume of distribution for risperidone; $CL_{RISP}$ - clearance of risperidone; $V_{9\text{-}OH\text{-}RISP}$ - Volume of distribution for 9-OH-risperidone; $CL_{9\text{-}OH\text{-}RISP}$ clearance of 9-OH-risperidone; *β*-beta coefficient*;* *ω* - coefficient of variation of inter-individual variability (expressed as a percentage); *σ* - coefficient of variation of residual unexplained variability (expressed as a percentage); *tAge* – age log transformed and centred around the mean; *RSE* relative standard error; *ne* not estimated

*** $p<0.0001$

**Supplementary Fig 1. Visual predictive checks**

Visual predictive checks (VPC): 95% prediction intervals around the 10th (lower blue shaded area), 50th (pink shaded area) and 90th (upper blue shaded area) percentiles are shown for the final model overlaid to observed data for risperidone in A) Functionally poor metabolisers and B) Functionally normal metabolisers. Each blue circle represents a single plasma sample. Blue lines represent the empirical predictions for each percentile and outliers are circled in red.



| **Supplementary Table 2: Pharmacokinetic Biomarkers and Functional Metaboliser Status** | | | |
|---|---|---|---|
| **Biomarker** | **Functionally Poor, PM(n=18)** | **Functionally Normal, NM (n=82)** | **Mann Whitney U, p value** |
| **Mean (SD) Peak plasma concentrations, ng/mL** | | | |
| Risperidone | 5.4 (3.2) | 3.6 (2.4) | 0.005 |
| 9-OH-Risperidone | 12.7 (7.6) | 9.5 (8.2) | 0.03 |
| Active Moiety | 17.6 (9.1) | 12.4 (9.9) | 0.007 |
| **Mean (SD) Trough plasma concentrations, ng/mL** | | | |
| Risperidone | 3.9 (2.3) | 1.5 (1.4) | <0.0001 |
| 9-OH-Risperidone | 12.5 (7.5) | 9.2 (8.1) | 0.02 |
| Active Moiety | 16.3 (8.7) | 10.7 (9.3) | 0.003 |
| **Mean (SD) Average plasma concentrations, ng/mL** | | | |
| Risperidone | 2.6 (1.6) | 0.5 (0.8) | <0.0001 |
| 9-OH-Risperidone | 12.1 (7.4) | 8.6 (7.8) | 0.01 |
| Active Moiety | 14.6 (8.0) | 9.0 (8.4) | 0.002 |
| **Mean (SD) trough active moiety concentration: dose (C/D) ratio, ng/mL per mg/day** | 20.2 (7.2) | 7.6 (4.9) | <0.0001 |