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Therapeutic D2/3 receptor occupancies and response with low amisulpride blood concentrations in very late-onset schizophrenia-like psychosis (VLOSLP)

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Running Head: Amisulpride PK, D2/3 occupancy and response in VLOSLP

Keywords: [^{18}F]fallypride, D2/3 occupancy, amisulpride, VLOSLP, antipsychotic,

Key points:

- The study aimed to investigate amisulpride dose- concentration (Caverage), D2/3 receptor occupancy and outcome in VLOSLP and compare this with Alzheimer's disease (AD)

- Clinically relevant responses were observed at 50-100mg/day, Caverage 41-129ng/ml), with mild EPS emerging at 96ng/ml (In AD, severe EPS emerged at 60ng/ml)
- Caudate occupancy was 44-59% in 3 patients imaged at Caverage 41-70ng/ml) (In AD, caudate occupancy 58-74% the same Caverage range)
- Further investigation of age and diagnosis-specific threshold sensitivities for EPS is warranted and therapeutic drug monitoring studies are a potentially feasible future approach

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Abstract

Objective: Antipsychotic drug sensitivity in very late-onset schizophrenia-like psychosis (VLOSLP) is well documented, but poorly understood. This study aimed to investigate blood drug concentration, D2/3 receptor occupancy, and outcome in VLOSLP during open amisulpride prescribing, and compare this with Alzheimer's disease (AD).

Methods: Blood drug concentration, symptoms (suspiciousness, unusual thought content, hallucinations) and extrapyramidal side-effects (EPS), were serially assessed during dose titration. [^{18}F]fallypride imaging was used to estimate D2/3 receptor occupancy. Average steady state drug concentration (Caverage) was estimated by incorporating pharmacokinetic (PK) data into an existing population PK model (25 AD participants, 20 healthy older people).

Results: Eight patients (original target 20) were recruited (6 women; 76 ± 6 years), 6 of whom complied with treatment: blood samples were obtained from 5; and paired imaging data from 3 participants. Mean+-SD reduction in symptoms was 74 ± 12% (Caverage 92.5+-39.4ng/ml). Mild EPS (Simpson Angus Scale, SAS, score of 4), which did not lead to treatment withdrawal, emerged at Caverage 96ng/ml (in AD, severe EPS, SAS score of 15, emerged at 60ng/ml). In 3 participants, imaged at an optimal dose of 50mg/day (Caverage 41-70ng/ml), caudate occupancy was 44-59% (compared to 58-74% in AD).

Conclusions: Despite small sample size, our findings are highly relevant and suggest that, similar to AD, 50mg/day amisulpride is associated with clinically relevant responses and occupancies >40% in VLOSLP. Although the two groups overlap in terms of minimum clinically effective dose, the AD group were more susceptible to emergent EPS. It is unclear, due to small sample size, whether these differences are accounted for by a steeper concentration-occupancy curve in AD. Therapeutic drug monitoring studies of amisulpride offer a potentially feasible approach to future investigation of age and disease-specific threshold sensitivities for EPS. Alongside this, research should focus on understanding and addressing barriers to service engagement in VLOSLP

Introduction

Older people with very late- (>60 years) onset schizophrenia-like psychosis (VLOSLP) (Howard et al., 2000), are amongst the most challenging mental health patient groups to engage and treat (Sin Fai Lam et al., 2016). Typically presenting with systematised persecutory beliefs, they generally lack insight into their illness or the potential benefits of treatment (Howard et al., 1994) and are unwilling to engage with older adult mental health teams (Sin Fai Lam et al., 2016). In those who initially accept antipsychotic drug treatment, heightened susceptibility to extrapyramidal side effects (Howard et al., 2000; Uchida et al., 2008) only increases the likelihood of non-compliance and subsequent disengagement from treatment and follow-up (Reeves et al., 2002; Hudson et al., 2004).

The mechanisms underlying antipsychotic drug sensitivity in VLOSLP are poorly understood, as research in older people with schizophrenia rarely distinguishes between patients on the basis of age of illness onset (Jeste and Maglione, 2013; Uchida et al., 2008), and the focus of research is increasingly directed towards those with dementia, who are at greatest risk of antipsychotic related morbidity and mortality (Jennum et al., 2015; Jeste et al., 2008; Maust et al., 2015; Howard et al., 2016). Age-related changes in pharmacokinetics (PK), which reduce drug clearance, contribute to side effects by increasing blood drug concentration for a given dose (Feng et al., 2008; Uchida et al., 2009b). However this effect is not consistent across all antipsychotics (Bigos et al., 2008) and fails to account for the heightened sensitivity of people with dementia and VLOSLP to EPS (Howard et al., 2000) compared to people with an earlier onset of schizophrenia.

Since the therapeutic window of striatal dopamine D2/3 receptor occupancy was first described for antipsychotic drugs (Farde et al., 1992; Kapur et al., 1995), positron emission tomography (PET) has been used to guide safe and effective prescribing in young people (Uchida et al., 2011; Sparshatt et al., 2009; Lako et al., 2013). In contrast, there is a relative paucity of imaging data in older clinical populations. Occupancy studies carried out in older patients with schizophrenia prescribed risperidone and/or olanzapine, have consistently reported EPS at lower than anticipated threshold occupancies (Uchida et al., 2009a; Graff-

Guerrero et al., 2015; Uchida et al., 2014). These data suggest that age-related pharmacodynamic changes, which increase functional outcomes for a given D2/3 receptor occupancy, contribute to antipsychotic drug sensitivity.

We have recently used an adapted [^{18}F]fallypride imaging protocol (Clark-Papasavas et al., 2014; Dunn et al., 2013) to investigate the relationship between dose, blood drug concentration and central D2/3 receptor occupancy in older patients with Alzheimer's disease (AD) and VLOSLP who were prescribed amisulpride off label to treat psychosis symptoms, as part of an open treatment study. Amisulpride dose-concentration (Reeves et al., 2016), and concentration-occupancy profiles across a 25-75mg/day dose range have been previously described in the AD group (Reeves et al., 2017). Low amisulpride blood concentrations (9-109ng/ml), which in all but one individual were below the recommended optimal therapeutic range (100-319 ng/ml) (Hiemke et al., 2011; Sparshatt et al., 2009) for the treatment of positive symptoms in schizophrenia, were associated with high D2/3 receptor occupancies (43-84% in the caudate), symptomatic improvement and emergent EPS (Reeves et al., 2017).

Our findings suggest that increased occupancy for a given blood drug concentration plays a key role in antipsychotic drug sensitivity in older people with AD, and implicate the blood brain barrier, which controls central drug access. However, the relative importance of the contribution of age and AD-specific changes to increased D2/3 receptor occupancy is unclear. The current study involves the analysis of data from VLOSLP participants in the study, and aims to explore amisulpride dose-concentration-occupancy relationships and compare this with the situation in AD.

Methods

Sample

Patients with VLOSLP were recruited from the South London and Maudsley NHS Foundation Trust immediately prior to commencing amisulpride treatment. Participants were included on the basis of meeting diagnostic criteria for VLOSLP (Howard et al., 2000), and having no

previous history of psychotic illness (prior to 60 years), traumatic brain injury, epilepsy, significant cardiorespiratory disease, needle phobia, any contraindication to amisulpride, or features suggestive of dementia. Patients were excluded if antipsychotic medication had been prescribed in the past 2 weeks (6 weeks if prescribed depot medication), or if unable to give informed consent. The study was approved by Berkshire Research Ethics Committee (REC reference 11/SC/0486).

Additional data sources

In order to estimate average steady state concentration of amisulpride across the 24 hour dosage interval, PK data from patients with VLOSLP were combined with PK data from:

(i) AD participants from the open study, which included 41 blood samples taken from 25 participants during steady state amisulpride treatment with 25-75mg/day (8 (32%) men; 82 +-6.6 years) (Reeves et al., 2016).

(ii) A richly sampled phase I study carried out in healthy older people, each sampled 14 times over 72 hours following a single oral 50mg amisulpride dose (10 (50%) men; age = 68.7 ± 4.1 years) (Hamon-Vilcot et al., 1998). Venous blood samples (n=280) were obtained from 20 healthy older participants. Amisulpride (racemate) concentrations were determined using a validated HPLC (high performance liquid chromatography) method (detection limit 0.5 ng/ml).

Baseline and Follow up Assessments

Clinical assessments were carried out at baseline and every 14 ± 7 days during dose titration, and included i) Psychotic symptoms were rated using the summed total score of 3 items from the Brief Psychiatric Rating Scale (BPRS) which are most relevant for very late-onset SLP: unusual thought content, suspiciousness, and hallucinations (Overall, 1988). Each item is scored on a 7 point scale, where 1 indicates ‘symptom not present’ and 7 ‘extremely severe’ (ii) EPS were indexed as present or absence by scores of 3 or more on the clinician-rated

Simpson-Angus Scale (SAS) (3-5=mild; 6 or more =severe) (Simpson and Angus, 1970) and/or 2 or more on the Barnes Akathisia scale (Barnes, 1989).

Amisulpride dose titration and blood sampling

Patients commenced amisulpride treatment at 50mg/day and were followed up every 14+-7 days, until an optimum dose was achieved (defined as >25% reduction in BPRS summed 3 item total scores). Compliance with medication (pill counts, discussion with a carer), concomitant medication and clinical outcome (symptom ratings, side effects) were recorded at each visit. Amisulpride venous blood concentration was measured prior to each dose increase, with the timing of blood samples coinciding with follow-up assessments and/or imaging. Blood samples were analysed in a secure, CPA accredited laboratory (Clinical Toxicology Unit, Kings College Hospital). Amisulpride (racemate) blood concentrations were determined using validated LC-MS/MS (liquid chromatography with tandem mass spectrometry) method, with a detection limit of 9ng/ml. Prolactin concentration was measured using chemiluminescence immune assay (Siemens Advia Centaur XP assay), with a detection limit of 6.4 mIU/L (0.29 ng/ml).

PET Procedure

Participants were scanned on a GE (GE Healthcare, Hatfield, UK) VCT Discovery PET-CT camera (FWHM 5mm), at St Thomas' Hospital PET Centre, using an interrupted [^{18}F]fallypride imaging protocol adapted specifically for use in older patients (Clark-Papasavas et al., 2014; Dunn et al., 2013) . [^{18}F]fallypride was administered via a single bolus intravenous injection of 250MBq. Each scan consisted of three 20-minute dynamic scans (3D mode, each preceded by low dose CT for attenuation correction) at baseline (0-20, 70-90, 220-240 minutes) and post-treatment (0-20, 40-60, 130-150 minutes); shorter post-treatment scan duration reflecting the fact that amisulpride occupancy of D2/3 receptors reduces the time required for [^{18}F]fallypride to achieve a transient equilibrium (Kegeles et al., 2008; Vernaleken et al., 2011). [^{18}F]fallypride binding potential BP_{ND} (Innis et al., 2007) was quantified using a simplified

reference tissue model with cerebellar reference region (Lammertsma and Hume, 1996). Preprocessing was performed using statistical parametric mapping version 8 (www.fil.ion.ucl.ac.uk/spm) and all other analyses using Matlab (www.mathworks.com). Non-attenuation corrected, 3 dimensional iteratively reconstructed PET scans (GE 'VuePoint') were used for frame-by-frame realignment. Transformations were applied to attenuation corrected, filtered back projected PET images which were used for quantification, and attenuation corrected-VuePoint PET images used for warping atlases. The cerebellum was defined using the Automated Anatomical Labeling atlas (Tzourio-Mazoyer et al., 2002) and regions of interest (caudate, putamen, thalamus) were defined using the Tziortzi atlas (Tziortzi et al., 2011). Atlases were warped to subject space via a [^{18}F]fallypride template in standard space (Dunn et al., 2013). Percentage reduction in BP_{ND} between pre ($BP_{PRE)}$ and post (BP_{POST}) treatment scans was used to estimate occupancy, as follows: $[(BP_{PRE}-BP_{POST})/BP_{PRE}]*100$.

Statistical analysis

Demographic and clinical data were described using SPSS (version 22.0). Values are shown as mean ± SD. The original recruitment target was 20 patients, to allow direct comparison with AD patients and to control for age. Blood drug concentration is highly dependent on the timing of blood sampling and, to control for this, average steady state drug concentration across the dosage interval (Caverage) was estimated by incorporating PK data into a previously described, oral 2 compartment population PK model for amisulpride, developed from 25 AD and 20 healthy older participants (Reeves et al., 2016) (see additional data sources). The model described 5 parameters (i) an absorption constant (ka), (ii) a central compartment (V1), (iii) a peripheral compartment (V2), (iv) an inter-compartmental distribution constant (Q), (v) an elimination constant (CL), which includes renal and systemic clearance. Initial parameter estimates were based on previously described values (Reeves et al., 2016), and incorporated covariate effects (age and a scaling factor based on standard 70kg body weight) on CL.

The population approach uses nonlinear mixed effects (NLME) modelling to examine dose-concentration relationships, identify sources of variability and make predictions for a typical

person in the population of interest (Ette et al., 2004; Duffull et al., 2011). NLME modelling, implemented using Monolix software (version 4.33; www.lixoft.eu), simultaneously estimates fixed effects (value for the average subject in the sample), and random effects (inter-individual variability, IIV) variance for parameters describing dose-concentration relationships and residual errors variance (unexplained variability, reflecting system noise, dosage history errors and/or model misspecifications). IIV 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).

As described previously (Reeves et al., 2016), residual error was modelled separately for healthy older people and participants in the clinical study, to account for inter-study differences; and was 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 concentration of the ith subject and corresponding model-predicted concentration; and ε_{ij} was assumed to be normally distributed (mean of 0, variance $\sigma^{2.}$). The model was evaluated using goodness-of-fit criteria, including diagnostic scatter plots, visual predictive checks, degree of shrinkage model precision, and likelihood ratio. Individual parameter estimates from the model included Caverage.

Results

VLOSLP sample characteristics

Eight patients (6 women; age 76 ± 6 years) were recruited, 2 of whom were withdrawn due to lack of compliance with study procedures. Demographic and clinical data are presented in Table 1. In the 6 patients who complied with treatment, baseline BPRS 3 item total score was 18.3 +- 2.2 (6.5 +- 0.6 unusual thought content; 6.8 +- 0.4 suspiciousness; 5.0 +- 2.0 hallucinations). Following treatment with 50-100mg/day amisulpride, there was a 74 ± 12 % reduction in BPRS 3 item total scores (76 ± 15%, unusual thought content; 68% ± 20%, suspiciousness; and 69% ± 34%, hallucinations), with complete resolution of symptoms (BPRS score of 3) in 2 participants (Table 1). Mild EPS which did not lead to treatment

discontinuation (SAS scores 3, and 4), emerged in 2 participants; and 1 patient developed hyponatraemia secondary to syndrome of inappropriate antidiuretic hormone secretion, (SIADH), which led to withdrawal from the study.

Pharmacokinetic, prolactin, imaging and clinical outcome data

Mean +-SD amisulpride blood concentration (n=5) was 69.5+-34.9 ng/ml; and corresponding PRL concentration (5.6+-1.5 pre-treatment), was 95+-41ng/ml (15+-3 hours post dose) after 21-191 days of treatment *(PRL 88+-72ng/ml in AD)*. When PK data were incorporated into the existing PK model (Table 2), parameters estimates were consistent with those previously described (Reeves et al., 2016), and estimated Caverage was 92.5+-39.4 ng/ml (range 41.5-129ng/ml). Mild EPS, (SAS score of 4), emerged at a lower threshold Caverage of 96ng/ml (75mg/day), and one participant developed akathisia (Barnes score of 3) at 129ng/ml. *In previously described AD participants, severe EPS (SAS scores of 11, 15 and 16) emerged at Caverage of 60, 61 and 62 ng/ml in 3 participants* (Reeves et al., 2017). Figure 1 shows Caverage, plotted against SAS scores for a) AD and b) VLOSLP groups, separated on the basis of mild (scores of 3-5) and severe (scores of 6 or above) EPS.

Technical issues meant that it was only possible to carry out 5 pre-treatment scans (mean+-SD binding potential, BP_{PRE}: 16.31 $\pm$ 1.32, caudate; 20.58 $\pm$ 2.0, putamen;1.49 $\pm$ 0.17, thalamus), and of 5 post-treatment scans were attempted, only 3 produced data of sufficient quality due to technical issues (n=1) or tolerability (n=1) (mean+-SD binding potential, BP_{POST}: 7.59 $\pm$ 1.56, caudate; 11.95 $\pm$ 3.94, putamen; 0.72 $\pm$ 0.25, thalamus). Caverage and corresponding caudate occupancy in 3 participants with paired imaging data, imaged at an optimum 50mg/day dose, was 41ng/ml (44%), 63ng/ml (51%) and 70ng/ml (59%). *In AD, caudate occupancy ranged from 58-74% across Caverage 41-70ng/ml*. Caverage, plotted against caudate occupancy is shown for VLOSLP and AD participants in Figure 2.

Discussion

This study aimed to characterise amisulpride dose-PK-occupancy relationships in VLOSLP, using an adapted imaging protocol. Carrying out imaging studies in older people is highly

challenging, particularly when combined with an active drug treatment, and participation requires a degree of insight and a level of engagement rarely achieved in people with VLOSLP (Howard et al., 1994; Sin Fai Lam et al., 2016). As a consequence, recruitment and retention were poor and, in addition, technical issues meant that it was only possible to obtain a complete dataset in 3 participants. Heightened sensitivity to EPS is well documented in VLOSLP (Howard et al., 2000; Uchida et al., 2008; Jeste and Maglione, 2013) and open label trial data suggests that ~100mg/day (range 50-200mg/day) amisulpride is efficacious in VLOSLP (Psarros et al., 2009), compared to older patients with an earlier illness onset, who tolerate doses up to 400mg/day (Riedel et al., 2009). Our findings were consistent with this, as clinically relevant responses were observed in VLOSLP patients at 50-100mg/day, and correspondingly low blood drug concentrations. Small sample size meant that it was not possible to fully characterise the non-linear PK-occupancy curve in VLOSLP. However, our findings suggest that 50mg/day amisulpride is associated with occupancies which achieve the therapeutic window (>40%) required to treat positive symptoms in young adults with schizophrenia (Sparshatt et al., 2009).

Occupancy data during low dose (50-100mg/day) amisulpride treatment is highly variable in young adults, ranging from below 10% (Martinot et al., 1996; Xiberas et al., 2001) to 40% (la Fougere et al., 2005; Meisenzahl et al., 2008) in the striatum. This is partly accounted for by methodological differences (tracer, imaging modality, timing of the scan in relation to dose, scan duration) (Meisenzahl et al., 2008), but also reflects the steeper gradient of the occupancy slope at low blood drug concentrations (Vernaleken et al., 2004). Our findings suggest that, similar to AD, 50mg/day (Caverage (41-70ng/ml) was associated with occupancies at least as high as those observed in young adults (Bressan et al., 2003; Lako et al., 2013; Sparshatt et al., 2009). As discussed previously (Reeves et al, 2017), tracers with higher affinity (low dissociation constant) such as [18F]fallypride require higher concentrations of competing drug to displace them from receptor sites than those of lower affinity, leading to lower apparent occupancy (Seeman, 2011; Seeman, 2014; Seeman and Van Tol, 1995). In vivo, this is particularly problematic if there is insufficient imaging time for the tracer to achieve

equilibrium in the D2/3 rich striatum (Olsson and Farde, 2001; Xiberas et al., 2001; Vernaleken et al., 2011). Although sampling times for the current study were guided by previous post-treatment [18F]fallypride protocols (Kegeles et al., 2008; Kessler et al., 2006), we cannot rule out the possibility that we have under-estimated the true extent of the differences between young adults previously studied and those with AD and VLOSLP.

Previous imaging studies have estimated occupancy in (risperidone and/or olanzapine) treated older patients with schizophrenia, by comparing D2/3 receptor availability with a healthy older control group, and described a therapeutic window of occupancy (50-60%) compared to young adults (Graff-Guerrero et al., 2015; Uchida et al., 2014); findings that are not explained by differences in D2/3 receptor availability between 'antipsychotic free' patients and healthy older people (Nakajima et al., 2015). Importantly, the above studies observed no difference in concentration-occupancy relationships between young and older adults.

It is possible that our finding of higher than anticipated occupancy in both AD and VLOSLP compared to young adults may reflect the unique properties of amisulpride (lower lipophilicity, poor blood brain barrier (BBB) penetration relative to other antipsychotics) (Natesan et al., 2008), which make the drug a more sensitive tool with which to explore BBB integrity in older people. It will thus be important to use comparable methodology (drug, tracer, sampling times, method of analysis) in future studies. Other central mechanisms also need to be considered, as we cannot rule out the possibility that age and/or disease-specific changes in distribution and clearance of amisulpride *within* the central nervous system (Uchida et al., 2009b), and/or reduced competition due to lower endogenous dopamine levels (Volkow et al., 1994) in those of extreme age contributed to higher occupancies.

Our findings suggest there is some overlap between AD and VLOSLP in terms of minimally clinically effective dose, but there are also clear differences in sensitivity to side effects, as severe EPS emerged in AD at very low threshold drug concentrations (60ng/ml). Differences between the two groups were not accounted for by variability in the timing of blood samples, as the PK model allowed estimation of average concentration across the dosage interval for each individual, accounting for the impact of age and body weight. It is tempting to speculate

that the exquisite sensitivity in AD is explained by higher occupancy for a given for a given amisulpride blood concentration, due to greater disruption in BBB integrity ((Zeevi et al., 2010). However, it is equally possible that the observed differences simply reflect the inherent variability in concentration-occupancy relationships, or that other confounding factors, such as age, gender, or concomitant medication explain the heightened susceptibility of older people with AD to side effects.

Non-adherence is another potential source of error when attempting to estimate dose-PK-response relationships. Although compliance was facilitated and closely monitored, tablet counts and self-report are not wholly reliable, (Blaschke et al., 2012) and may have contributed to inter-individual variability in parameter estimates, and residual error. The issue of diagnosis is important when psychosis is present in the context of a dementia, and careful screening was thus carried out to exclude patients with suspected Lewy Body Dementia, included dopamine transporter imaging where appropriate (McKeith et al., 1996). While we cannot completely rule out the possibility that Lewy body pathology may have contributed to the observed drug sensitivity in AD group, EPS are sufficiently explained by higher than anticipated occupancies which only exceeded the 60% threshold in the AD group.

Conclusion

Despite the limitations of the clinical dataset, this study indicates that target concentrations to treat psychosis in AD and VLOSLP overlap, and are lower than the currently recommended target range (100-320ng/ml), due to higher than anticipated central D2/3 receptor occupancies. Our preliminary findings also argue strongly for further investigation of disease-specific differences in antipsychotic drug sensitivity, as the target therapeutic range for amisulpride is broader in VLOSLP, possibly due to differences in the PK-occupancy slope. However, these findings are preliminary and should be interpreted cautiously, given the limited sample size. In young adults, it has been shown that amisulpride blood drug concentration is a more sensitive predictor of EPS than D2/3 receptor occupancy (Sparshatt et al., 2009).

Given the challenges faced when attempting occupancy studies in older people, large scale amisulpride therapeutic drug monitoring studies offer a feasible, cost effective alternative approach, and one which will directly inform age- and disease-specific dose adjustments. Alongside this, research needs to be directed towards improving service engagement in people with VLOSLP.

Conflicts of Interest

The authors report no competing interests

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Figure 1. Model estimated Caverage and extrapyramidal side effects

Estimated average steady state amisulpride blood concentrations (Caverage) across a 25-100mg dose titration range are plotted against corresponding Simpson Angus Scale scores, and separated on the basis of absent (white circle), mild (black and white circle) and severe (black circle) extrapyramidal side effects (EPS) in VLOSLP (left) AD (right).

Figure 2. Caverage, D2/3 receptor occupancy and extrapyramidal side effects

Caverage is plotted against corresponding D2/3 receptor occupancy in the caudate, for 3 VLOSLP participants, none of whom experienced extrapyramidal side effects (EPS) (shown as a dot with outer circle); superimposed on data from AD participants, separated on the basis of presence (black circle) or absence (white circle) of any EPS (SAS>3)

Table 1. Demographic and clinical characteristics of patients with very late-onset schizophrenia-like psychosis (VLOSLP) (n=8)								
Age (years)	68	77	71	73	89	76	76	76
Gender	Female	Female	Female	Male	Female	Female	Female	Male
Place of birth	Nigeria	Cyprus	Pakistan	Ireland	UK	Greece	Sri Lanka	Nigeria
Living status	Alone	Alone	With family	Alone	Residential Care	With husband	With family	Alone
Weight (kg)	58	72	62	90	55	70	42	92
Baseline BPRS score	13	21	19	17	18	15	20	19
Radioactivity (MBq); Specific Activity (GBq/µmol); mass (µg)	250; 100; 0.7	250; 19.1; 1.7	243; 45.9; 0.8	248; 113;0.8	247; 135;0.7	NA	NA	NA
Pre-treatment prolactin (ng/ml)		3.5	5.5	8.1	5.9	5.1	-	-
Pre-treatment BPND	14.58	17.15	17.94	15.56 *	16.30	NA	NA	NA
Maximum dose (mg/day)	nc-	75 [a]	50	100	50	100 [a]	100[b]	nc
Caverage		96	41.5	102.1	69.6	172.0	114.5	
Optimum dose (mg/day)	-	50	50	100	50	75	-	-
Post-treatment BPRS score	-	3	4	5	7	6	3	-
Estimated Caverage (ng/ml)	-	63	41.5	102.1	70	129.3	-	
Post-treatment prolactin (ng/nl)	-	50.0	82.7	92.8	163.5	89.1	-	-
Simpson Angus Score	-	2	0	1	1	3	-	-
Radioactivity (MBq); Specific Activity (GBq/µmol); mass (µg)		248; 24.0; 1.8	250; 156; 0.6	-	250;179; 0.5			
Post-treatment BPND	-	8.39	9.95		6.73	≠	-	-

Post-treatment occupancy (%)	-	51.1	44.5	-	58.7	-	-	-

BPRS –brief psychiatric rating scale score reflects summed total of 3 items (unusual thought content, suspiciousness, hallucinations)
NA -not imaged due to technical diffiuclties
≠ - unable to tolerate imaging
[a] Mild extrapyramidal side effects (EPS) (SAS score 4)
[b] Withdrawal from study due to hyponatraemia
nc – non-compliant, withdrawn from study
*Had been previously treated with olanzapine (discontinued ~

Table 2. Population Pharmacokinetic (PK) Model for Amisulpride in Older People (n=51)		
Parameter	**Estimate (RSE%)**	**IIV% (RSE%)**
ka (/hr)	0.83 (18)	47 (23)
Cl (L/hr) [a, b]	51.5 (7)	38 (14)
V1 (L)	440 (16)	42 (25)
Q (L/hr)	111 (16)	64 (19)
V2 (L)	741 (12)	46 (17)
RUV%	**Estimate (RSE%)**	
Healthy older people (n=20)	13 (6)	na
AD and VLOSLP (n=31)	47 (20)	na

Parameters: ka, absorption rate constant; V1, volume of distribution of central compartment; V2, volume of distribution of peripheral compartment; Q, inter-compartmental clearance; CL, renal and systemic clearance

[a] allometric scaling (power 0.75) fixed for weight on CL; weight centred at 70kg
[b] power effect of -3.11 estimated for age on CL (p=2.3 e-008); age centred at 77 years.

Other abbreviations: AD, Alzheimer's disease; VLOSLP, very late-onset schizophrenia-like psychosis; IIV, inter-individual variability; RUV, residual unexplained variability; RSE, relative standard error; na, not applicable