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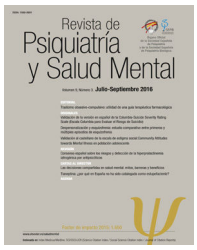

SCIENTIFIC LETTER

# Amerindians may need clozapine dosing similar to that of Asians

## Los amerindios pueden necesitar las mismas bajas dosis de clozapina que los asiáticos

*Dear Editor:*

Clozapine is mainly metabolized by the cytochrome 1A2 (CYP1A2). CYP1A2 activity ranges from lowest in female non-smokers to highest in male smokers (estrogens are inhibitors and smoking is an inducer). To reach a therapeutic response requires 350 ng/ml of serum clozapine concentration. The concentration-to-dose (C/D) ratio[1] represents the linear relationship between clozapine dose and concentration.[1] A very high C/D ratio indicates a poor metabolizer (PM) phenotype[1,2] which can be explained by a potent inhibitor such as fluvoxamine, systemic inflammation and possibly obesity.[1,2] After excluding non-adherence, a very low clozapine C/D ratio indicates an ultrarapid metabolizer (UM) phenotype, possibly explained by powerful inducers such as carbamazepine.[2] Valproate is usually a mild inducer or inhibitor.[1,2]

Having less CYP1A2 activity than Caucasians, Asians need lower clozapine doses according to: (1) a meta-analysis,[3] (2) a study of 5 Asian samples,[2] and (3) a review of Asian dosing.[4] Asians typically had clozapine C/D ratios from 1.2 to 2.4; Asian female non-smokers need 150 mg/day and male smokers 300 mg/day to reach 350 ng/ml.[4]

The Amerindians (the indigenous people from the Americas) are of East Asian origin.[4] This reanalysis of a sample[5] from Mexico City with trough steady-state levels identified 52 Mexican average metabolizers after excluding potential clozapine PMs and UMs. We explored the clozapine dosages needed to reach 350 ng/ml after stratification by sex and smoking (Table 1) and compared them with those from the 5 Asian samples.[2]

In 19 female non-smokers from Mexico City, the recommended average clozapine dosage was 185 mg/day which is: (1) within the range of 145–189 mg/day in similar Asians, and (2) not far from the weighted mean of 166 mg/day in 233 Asian female non-smokers.

In 18 male non-smokers from Mexico City, the recommended average clozapine dosage was 199 mg/day which is: (1) within the range of 194–205 mg/day in similar Asians, and (2) not far from the weighted mean of 210 mg/day in 209 Asian male non-smokers.

In 5 female smokers from Mexico City, the recommended average clozapine dosage was 330 mg/day, but this group was too small for the authors to comment. In 10 male smokers from Mexico City, the recommended average clozapine dosage was 288 mg/day which is: (1) within the range of 259–294 in similar Asians, and (2) not far from the weighted mean of 270 mg/day in 127 Asian male smokers.

The sample of Mexico City fits within the Asian samples, suggesting similar clozapine clearance and need for the same low clozapine doses as Asians, but this data is limited by the lack of control for inflammation and obesity. Many American countries have populations of Amerindian origin; thus, future clozapine studies need to explore dosing after better control of variables and careful consideration of ancestry. Until then, psychiatrists working in the Americas may need to use clozapine doses ranging from 150 to 300 mg/day for average-metabolizer patients with predominant Amerindian ancestry. These clozapine doses are lower than those required for average-metabolizer patients of Caucasian and/or African ancestry.[1]

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**Table 1** Comparing mean clozapine C/D ratios after stratification by sex and smoking status in 5 Asian samples ($N = 508$) and in a study in Mexico City ($N = 52$[a]).

| Group | Sample | *N* | Age (year) | Dose (mg/day) | C/D ratio | | Dose to reach[b] |
|---|---|---|---|---|---|---|---|
| | | | | | Clozapine | Total | >350 ng/ml (mg/day) |
| ♂ smokers | Beijing 1 | 22 | 46.6 | 271 | 1.34 ± 0.59 | 1.98 ± 0.84 | 261 |
| | Beijing 2 | 49 | 40.6 | 341 | 1.31 ± 0.95 | 1.90 ± 1.22 | 267 |
| | Taipei | 22 | 36.1 | 286 | 1.19 ± 0.54 | 1.82 ± 0.84 | 294 |
| | Seoul | 15 | 37.3 | 378 | 1.35 ± 0.71 | 2.05 ± 1.01 | 259 |
| | Vellore | 19 | 39.0 | 401 | 1.29 ± 1.07 | | 271 |
| Weighted mean | | 127 | | | 1.30 | | 270 |
| | Mexico City | 10 | 38.9 | 275 | 1.29 ± 0.88 | | 280 |
| ♀ smokers | Beijing 1 | 5 | 54.6 | 301 | 1.50 ± 0.58 | 1.90 ± 1.22 | NC |
| | Beijing 2 | 2 | 39.0 | 313 | 1.11 ± 0.46 | 1.50 ± 0.46 | NC |
| | Taipei | 3 | 36.3 | 325 | 1.24 ± 0.48 | 2.03 ± 0.80 | NC |
| | Seoul | 1 | 38 | 450 | 0.88 | 1.59 | NC |
| Weighted mean | | 11 | | | 1.30 | | 270 |
| | Mexico City | 5 | 31.4 | 230 | 1.06 ± 0.24 | | 330 |
| ♂ non-smokers | Beijing 1 | 35 | 37.2 | 230 | 1.71 ± 0.78 | 2.49 ± 1.04 | 205 |
| | Beijing 2 | 65 | 42.8 | 262 | 1.50 ± 0.90 | 2.12 ± 1.12 | 233 |
| | Taipei | 29 | 36.0 | 300 | 1.80 ± 1.07 | 2.65 ± 1.42 | 194 |
| | Seoul | 26 | 31.0 | 347 | 1.70 ± 0.84 | 2.58 ± 1.02 | 206 |
| | Vellore | 54 | 33.8 | 329 | 1.78 ± 1.19 | | 197 |
| Weighted mean | | 209 | | | 1.67 | | 210 |
| | Mexico City | 18 | 35.7 | 294 | 1.76 ± 1.13 | | 199 |
| ♀ non-smokers | Beijing 1 | 64 | 45.1 | 202 | 2.11 ± 0.74 | 2.97 ± 1.00 | 166 |
| | Beijing 2 | 75 | 46.5 | 297 | 2.03 ± 1.64 | 2.87 ± 2.12 | 172 |
| | Taipei | 31 | 39.1 | 254 | 2.38 ± 1.41 | 3.38 ± 2.00 | 147 |
| | Seoul | 25 | 32.4 | 282 | 2.41 ± 1.02 | 3.72 ± 1.52 | 145 |
| | Vellore | 28 | 36.2 | 323 | 1.85 ± 1.16 | | 189 |
| Weighted mean | | 233 | | | 2.12 | | 166 |
| | Mexico City | 19 | 38.2 | 228 | 1.89 ± 1.14 | | 185 |

C/D: concentration-to-dose; NC: not calculated due to the small sample size.

[a] There were some patients with low doses (≤100 mg/day), which is a problem because they were frequently used for an indication other than treatment-resistant schizophrenia and they appear to be associated with non-linear kinetics. After eliminating those patients contaminated with valproate and those with low doses (≤100 mg/day), there were 52 patients left.

[b] Mean dose needed to reach a concentration of 350 ng/ml was calculated by dividing 350 by mean clozapine C/D ratio.

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# Predictive value of prolactin in first episode psychosis at ten years follow-up

## Valor predictivo de prolactina en los primeros episodios de psicosis durante el seguimiento a diez años

*Dear Editor,*

Although it is widely known that prolactin levels increase in schizophrenia patients treated with antipsychotic drugs,[1] the exact role of this hormone during the course of the disease is not fully understood. Recent studies in this field are consistent with an increase in prolactin levels and even a higher prevalence of hyperprolactinemia among drug-naïve subjects with a first episode psychosis (FEP).[2,3] Although some studies suggest that prolactin levels might predict the risk of developing a psychotic disorder in UHR individuals,[4] other studies have not found such association.[5] Some studies have shown a negative correlation between prolactin levels and disease severity[6,7] as well as with cognitive deficits.[8] Our group has previously shown a negative correlation between prolactin levels and positive symptoms' severity in women with FEP.[3] This, together with evidence in animal models of stress,[9] suggests that prolactin might have a neuroprotective role during FEP. We, therefore, hypothesize that an increase in prolactin in patients with FEP may have a neuroprotective role. A prospective study of the response to treatment in a cohort of FEP patients has been undertaken.

Data for this study were obtained from a large clinical intervention program of FEP (*Programa Asistencial Fases Iniciales de Psicosis* [PAFIP]), conducted at the University Hospital Marques de Valdecilla (Santander, Spain), whose detailed methodology is described elsewhere.[10] All subjects provided written informed consent prior to their inclusion in the study, which was approved by the local ethics committee. This study was conducted as part of a clinical trial ''Longitudinal Long-term Study (10 years) of the Sample of First Episode of Non-affective Psychosis: PAFIP (10PAFIP)'' (ClinicalTrials.gov Identifier: NCT02200588). Selected cases included those with available data regarding basal and prolactin at 10 year and clinical data at 10 years. This allowed for calculating the remission, the response, the duration of active psychotic symptoms after commencing treatment (DAT), the duration of active psychotic symptoms (DAP), and the chlorpromazine accumulated equivalent dose (CAED) at 10 years. Remission was defined as a score in the *Scale for the Assessment of Positive Symptoms* (SAPS) and in the *Scale for the Assessment of Negative Symptoms* (SANS) $\leq 2$ and the absence of relapses in the preceding 6 months to the evaluation.[11] Response was considered when the *Brief psychiatric rating scale* (BPRS) was reduced at least 40% from baseline and the *Clinical Global Impression* (CGI) was $\leq 4$. The DAT was calculated as the time of active psychosis after antipsychotic treatment onset and during subsequent relapses, if present, whereas the DAP was calculated adding the Duration of Untreated Psychosis (DUP) to the DAT. The CAED was estimated according to Gardner et al. (2010).[12] Given that patients included in PAFIP program could have been treated with antipsychotic for less than six weeks, only those patients that had not received any antipsychotic treatment prior to the day of prolactin assessment were selected. Patients with levels of prolactin above 100 ng/mL were excluded, as such a high prolactin levels might be related to other somatic disorders or to unreported antipsychotic exposure.

Fort the comparison of prolactin levels before treatment with the levels at 10 years, the Wilcoxon test was used. In order to determine whether there was any association between prolactin basal levels and the DAT or DAP the Spearman correlation test was used. And in order to assess whether the levels of prolactin before the onset of treatment were predictors of the remission or the response, logistic regression models were used with the later as the dependent variables and basal prolactin as the independent variable. The CAED, sex and age were used as co-variables.

Sixty-five patients fulfilled the inclusion criteria. Prolactin levels significantly decreased at the end of the follow-up period, with a median and interquartile range at the beginning of 14.3 (7.6–24.6) ng/mL and at the end of 8.8 (5.4–14.7) ng/mL ($p = 0.001$) (Table 1). There were no significant correlation between basal prolactin levels and the DAT ($p = 0.715$) or the DAP ($p = 0.332$). The logistic regression model showed a significant association between basal prolactin and remission ($p = 0.047$) when the CAED was introduced as a co-variable (being this also significant [$p = 0.003$]), which did not survive when introducing age and sex as well ($p = 0.244$). There were not significant associations with response ($p = 0.257$) at 10 years follow-up.

According to our results there is no evidence to support any association between the levels of prolactin before the