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ORIGINAL ARTICLE

Plasma prolactin levels are associated with the severity of illness in drug-naive first-episode psychosis female patients

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Abstract

Patients with schizophrenia frequently present hyperprolactinemia as a consequence of antipsychotic treatment. However, an increase in circulating prolactin levels has also been shown in patients without previous treatment. Our objective was to compare prolactin levels between antipsychotic-naive first-episode psychosis (AN-FEP) patients and healthy controls (HC). As part of an FEP program (*Programa Asistencial Fases Iniciales de Psicosis* [PAFIP]), 270 AN-FEP patients and 153 HC were eligible for this study. Serum prolactin levels were measured by an automated immunochemiluminescent assay. Subjects' sex and having an AN-FEP diagnosis both had an effect on prolactin levels, with higher levels in women than in men, and in AN-FEP patients than in HC. Moreover, plasma prolactin levels showed a negative correlation with the SAPS scores in AN-FEP female patients. AN-FEP patients have increased levels of prolactin, which might be stress-induced. This, together with the association of higher prolactin with a lower severity of the disease, suggests that prolactin might play a neuroprotective role, especially in women.

Keywords First-episode psychosis · Prolactin · Schizophrenia · Women

Introduction

Prolactin is a polypeptide hormone mainly synthetized by specialized cells of the anterior pituitary gland, the lactotrophs (Marano and Ben-Jonathan 2014). Besides its role in lactogenesis, prolactin regulates several physiological processes, including the immune response, reproductive behavior, osmoregulation, and angiogenesis (Cabrera-Reyes et al. 2017). In addition, prolactin is involved in the regulation of nervous system-related processes, such as stress and trauma responses, energy balance, food intake, anxiety, neurogenesis, and pain (Patil et al. 2014). Prolactin is under the inhibitory control of dopamine, released from the tuberoinfundibular dopaminergic neurons (Grattan 2015). Prolactin secretion is stimulated by several factors, including estradiol, opioid peptides, oxytocin, thyrotropin-releasing hormone (Grattan 2015), psychosocial stress (Lennartsson and Jonsdottir 2011), or inflammation (Jimena et al. 1998).

The relationship between prolactin and psychiatric disorders, such as bipolar disorder, major depression, or schizophrenia, has been the focus of studies for more than three decades (Cookson et al. 1982; Maeda et al. 1975; Nicholas et al. 1998). It is widely accepted that patients treated for schizophrenia have elevated prolactin levels in plasma, secondary to the blockade of dopamine receptors by antipsychotic drugs (Grigg et al. 2017; Nordstrom and Farde 1998; Winning 2002). However, the relationship between hyperprolactinemia and schizophrenia might be more complex, and not merely a consequence of treatment with antipsychotics. Studies assessing circulating prolactin levels in antipsychotic-naive first-episode psychosis (AN-FEP) patients are scarce, and have reported contradictory results.

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Thus, whereas some initial studies reported lower or normal serum prolactin levels in AN-FEP patients (Chatterjee 1988) or drug-free chronic schizophrenia patients (Kleinman et al. 1982; Kuruvilla et al. 1986), recent work has found higher prolactin levels or higher hyperprolactinemia rates in AN-FEP patients, compared with controls (Aston et al. 2010; Garcia-Rizo et al. 2012; Petrikis et al. 2016; Riecher-Rossler et al. 2013). Shrivastava et al. only found higher levels in AN-FEP patients than controls in male subjects (Shrivastava et al. 2012), and Albayrak et al. studied men only, again finding higher levels in patients than in controls (Albayrak et al. 2014). However, other studies have found higher average prolactin levels in female than in male patients after correction for the normal biological variation between sexes (Ittig et al. 2017). It has been suggested that hyperprolactinemia in AN-FEP patients could be stress-induced (Riecher-Rossler et al. 2013), although recent longitudinal studies in first-episode psychosis patients have failed to correlate perceived stress or life stressors with prolactin levels (Lally et al. 2017).

Little is known about the association between prolactin levels and psychopathological characteristics in schizophrenia. Whereas a positive correlation between prolactin levels and negative symptom scores has been found (Akhondzadeh et al. 2006; Jose et al. 2015), other studies did not find such an association (Kuruvilla et al. 1993; Otani et al. 1996). Regarding AN-FEP patients, previous studies assessing the association between prolactin levels and the severity of psychopathology have obtained non-significant results (Ittig et al. 2017; Petrikis et al. 2016).

Thus, in the present study, we set out to compare the plasma prolactin levels of a large cohort of AN-FEP patients with those of healthy controls. In addition, we aimed to assess potential differences within sex and age groups. Finally, we were interested in studying associations between the severity of psychopathology and the levels of prolactin at diagnosis.

Materials and methods

Study setting and participants

Data for this study were obtained from a large clinical intervention program of FEP (Programa Asistencial Fases Iniciales de Psicosis [PAFIP]) (Crespo-Facorro et al. 2007) conducted at the University Hospital Marques de Valdecilla, Santander, Spain. Patients were referred to the program when presenting an FEP and were admitted according to the following inclusion criteria: (1) aged 15–60 years; (2) met the DSM-IV criteria (according to the Structured Clinical Interview for DSM-IV, SCID-I) 6 months after inclusion for a principal diagnosis of schizophrenia, schizophreniform disorder, schizoaffective disorder, brief reactive psychosis, or psychosis non-otherwise specified; (3) habitually living in the catchment area; (4) no prior treatment with antipsychotic medication; and (5) current psychotic symptoms of at least moderate severity, as assessed by one of the five items of the Scale for the Assessment of Positive Symptoms (SAPS). This program fulfilled the standards for research ethics and was approved by the local institutional review board (NCT02534363 and NCT0235832). Written informed consent was obtained from all subjects after complete description of the study. As patients included in PAFIP program could have been treated with antipsychotic for less than 6 weeks, for the specific aim of this study, only those patients that had not received any antipsychotic treatment prior to the day of prolactin assessment were selected. At study intake, two patients were taking selective serotonin reuptake inhibitors. Patients with levels of prolactin above 100 ng/mL were excluded, as such high prolactin levels might be related to other somatic disorders or to unreported antipsychotic exposure.

Clinical evaluation

Clinical variables were measured at intake in the PAFIP program. Depressive symptoms were assessed by the Calgary Depression Scale for Schizophrenia (CDSS) (Addington et al. 1993). Positive and negative symptoms were evaluated by means of the SAPS (N. Andreasen 1984) and Scale for the Assessment of Negative symptoms (SANS) (N. C. Andreasen 1989), respectively. The SANS and SAPS scores were used in generating dimensions of positive, disorganized, and negative symptoms (Grube et al. 1998).

Sample extraction and prolactin measurement

Blood samples were extracted after night fasting (10 to 12 h) between 8 am and 10 am. Prolactin levels were assessed by immunochemiluminescent automated assay in an Advia Centaur Chemistry System from Siemens (SIEMENS Health Care Diagnostics, Newark, Del) using the reagents supplied by the manufacturer. The sensitivity of the assay was 0.3 ng/mL. The reference range for the laboratory was 2.8 to 29.2 ng/mL for women and 2.1 to 17.7 ng/mL for men. The average intra- and inter-assay coefficients of variation were 2.7 and 3.6%, respectively.

Statistical methods

A general linear model was used to assess the effect of sex and diagnostic group on the levels of prolactin. Thus, log-transformed prolactin values were introduced as the dependent variable, and sex and diagnostic groups as independent variables. Age and body mass index (BMI) were entered as covariates. X^2 test was used to compare categorical variables. Bivariate correlations were established with the Pearson correlation coefficient. Linear regression, entering log-transformed prolactin values as the dependent variable and different clinical

variables of interest as independent variables, was used to assess their association. BMI and age were used as covariates. Bonferroni's method was use to correct for multiple correlations.

We also conducted an exploratory analysis stratified by sex and age ranges (15–25, 25–35, 35–45, and > 45 years) in order to assess whether sex differences differ by age range. We decided to include these analyses because estrogen levels drop after menopause in women, and estrogens antagonize the inhibitory action of dopamine on PRL secretion (Gudelsky et al. 1981). These analyses would allow to compare prolactin levels between premenopausal (age ranges < 45) vs. peri/postmenopausal women (age ranges > 45). Differences between prolactin levels in age subgroups were analyzed with Student's *t* test or the Mann-Whitney *U* test, as appropriate. The whole analysis was performed with SPSS v.24 (SPSS Inc., Chicago, IL, USA).

Results

Prolactin levels in patients and controls

The present study included 270 AN-FEP patients and 153 healthy controls (HC). The distribution of diagnosis at the 6-month follow-up was schizophrenia ($n = 126$), schizophreniform disorder ($n = 84$), brief psychotic disorder ($n = 35$), unspecified psychotic disorder ($n = 19$), schizoaffective disorder ($n = 5$), and delusional disorder ($n = 1$). Prolactin levels did not differ among diagnostic groups ($p = 0.906$). There was no significant age difference between AN-FEP patients and HC (mean age AN-FEP 29.7 ± 7.5 vs. 31.3 ± 10.4 years; $p = 0.443$). However, the groups' sex proportions did differ, with 50.7% of men among AN-FEP patients and 60.8% among HC ($p = 0.046$). Adjusted by age and BMI, diagnostic group ($p = 0.001$) and sex ($p < 0.001$) showed a significant effect on prolactin levels, with higher levels in women than in men, and in AN-FEP patients than in HC. There was no significant interaction between both variables ($p = 0.437$). Regarding the rate of hyperprolactinemia, this was higher in AN-FEP patients than in HC for both men (27.7% vs. 5.4%; $p < 0.001$) and women (27.8% vs. 10%; $p = 0.008$) (Table 1).

Prolactin levels in age subgroups

Age stratification showed that female AN-FEP patients had higher prolactin levels than HC in the 15–25-year-old (mean prolactin 26.1 ± 21.1 vs. 16.3 ± 6.7 ng/mL; $p = 0.03$) and 35–45 ranges (mean prolactin 22.3 ± 18.0 vs. 9.0 ± 2.5 ng/mL; $p = 0.007$), with a trend toward significance in the 25–35 group (mean prolactin 26.4 ± 20.0 vs. 18.6 ± 14.0 ng/mL; $p = 0.075$). In the latter age range, there were no statistically significant differences in the levels of prolactin (mean prolactin 16.5 ± 10.8 vs. 13.2 ± 8.4 ng/mL; $p = 0.452$). The same analysis among men showed that although AN-FEP patients had higher prolactin levels than HC, these differences were not statistically significant, only showing a trend toward significance in the 15–25 range (mean prolactin 15.1 ± 10.4 vs. 10.4 ± 4.1 ng/mL; $p = 0.058$) (Fig. 1).

Prolactin and severity of psychopathology

To assess whether plasma levels of prolactin were associated with the severity of psychopathology, bivariate correlations were undertaken between prolactin levels in patients with the main psychopathological scales. Given the prolactin differences between men and women, this analysis was done by splitting the sample. Whereas prolactin in male AN-FEP patients did not correlate with any of the scales, prolactin levels in female AN-FEP patients negatively correlated with the SAPS ($r = -0.252$; $p = 0.003$), the positive dimension ($r = -0.154$; $p = 0.039$), and the disorganized dimension ($r = -0.215$; $p = 0.019$), adjusting for age and BMI (Table 2) (Fig. 2). After correcting for multiple comparisons, only correlation with the SAPS remained significant ($p = 0.021$).

Discussion

In the present study, prolactin levels have been evaluated in a large cohort of AN-FEP patients ($n = 270$) and compared with those of HC ($n = 153$). This is, to the best of our knowledge, the largest cohort of AN-FEP patients in which prolactin plasma levels have been assessed. Our main findings are, first, that plasma prolactin levels are higher in AN-FEP patients than in HC, these differences being observed in different age subgroups within women; and second, that prolactin levels in AN-FEP female patients negatively correlate with the severity of the disease in terms of positive symptoms.

Previous studies assessing prolactin in AN-FEP patients have reported rates of hyperprolactinemia ranging from 10.7 (Lally et al. 2017) to 35 (Ittig et al. 2017), 39 (Riecher-Rossler et al. 2013), and 46.2% (Aston et al. 2010). In addition, higher prolactin levels in AN-FEP patients compared with HC have been reported (Garcia-Rizo et al. 2012; Petrikis et al. 2016), and our results are in line with this. On the contrary, Shrivastava et al. only found higher levels in AN-FEP patients than controls in men (Shrivastava et al. 2012). However, it must be taken into account that their sample size was rather small ($n = 20$).

The exact causes of hyperprolactinemia in AN-FEP patients are unknown. It could be that the hyperprolactinemic state is reflecting a non-specific stress-related state, because prolactin may be increased in stressful situations along with other stress hormones, including cortisol and ACTH (Jaroenporn et al. 2007; Lennartsson and Jonsdottir 2011). Indeed, psychotic episodes are in themselves traumatic experiences (Rodrigues and Anderson 2017), and it is widely

Table 1 Prolactin levels in AN-FEP patients and controls according to sex

	Healthy controls ($n = 153$)		Antipsychotic naive ($n = 270$)			
	Male ($n = 93$)	Female ($n = 60$)	Male ($n = 137$)	Female ($n = 133$)	p^a	p^b
Age (years)	29.1 ± 6.7	30.6 ± 8.7	27.8 ± 8.2	35.1 ± 11.1	0.042	0.009
Body mass index	26.4 ± 4.0	24.0 ± 4.1	23.1 ± 3.9	22.0 ± 3.4	< 0.001	0.001
Hyperprolactinemia (no./%)	5/5.4%	6/10%	38/27.7%	37/27.8%	< 0.001*	0.008*

	ANCOVA analysis		
	AN-FEP diagnosis	Sex	Sex by AN-FEP diagnosis interaction
	p value	*p* value	*p* value
Prolactin	< 0.001*	< 0.001*	0.240*

[a] *p* value for male healthy controls vs. male patients; [b] *p* value for female healthy controls vs. female patients

*Adjusted for age and body mass index

known that prolactin release may be increased as a part of the stress response (Jaroenporn et al. 2007). Interestingly, prolactin levels have also been found to be increased in individuals at clinical high risk (CHR) for developing a psychotic disorder (Aston et al. 2010). A prospective study that included 39 CHR individuals (Labad et al. 2015) reported increased baseline prolactin levels, as well as increased perceived stress and life stress in those individuals who would develop a psychotic disorder over 1 year when compared to both healthy controls and those CHR who did not develop a psychotic disorder. Furthermore, there is some evidence pointing toward a higher magnitude of the stress response in healthy women than in men (Kirschbaum et al. 1993; Lennartsson and Jonsdottir 2011), which could explain why correlations have been found only in female AN-FEP patients. This is further supported by previous studies, which found higher rates of hyperprolactinemia in female AN-FEP patients than in males (Riecher-Rossler et al. 2013), or higher prolactin levels in female than in male patients, even correcting for the normal biological variation between the sexes (Ittig et al. 2017).

An alternative explanation for the elevation of prolactin plasma levels in AN-FEP patients could be that there is a dysregulation of prolactin secretion at different levels of the tuberoinfundibular pathway, due to an imbalance of prolactin-releasing and prolactin-inhibiting factors. Dopamine regulation of prolactin secretion may be explored in the lab with challenge

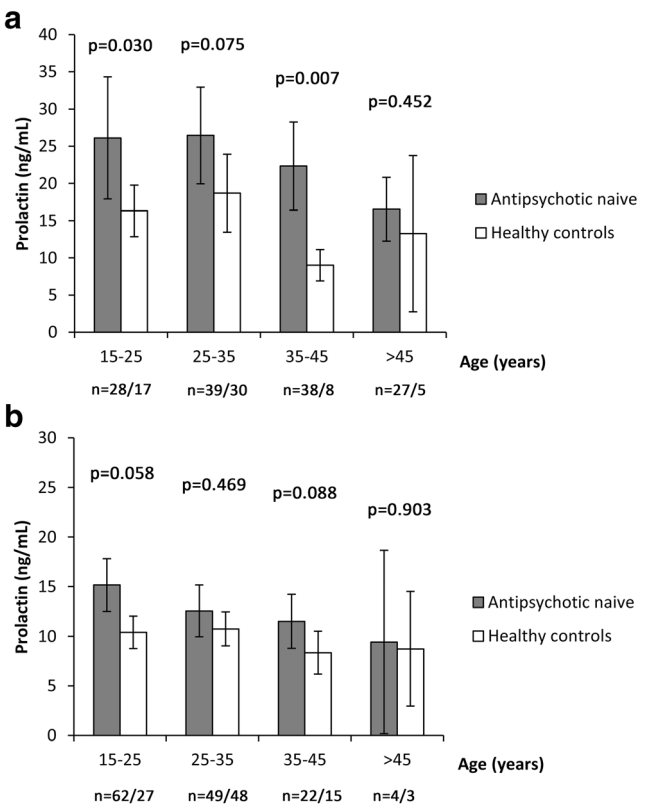

Fig. 1 Prolactin levels in AN-FEP patients in subgroups of age, in female (**a**) and male (**b**) patients

Table 2 Correlation analysis between prolactin levels and the main scales of severity in AN-FEP patients, according to sex

	Prolactin	
	Male ($n = 133$)	Female ($n = 132$)
Calgary	0.113 ($p = 0.248$)	− 0.086 ($p = 0.167$)
BPRS	0.066 ($p = 0.189$)	− 0.160 ($p = 0.059$)
SAPS	0.053 ($p = 0.231$)	− 0.252 ($p = 0.003$)*
SANS	− 0.009 ($p = 0.860$)	0.026 ($p = 0.525$)
Positive dimension	− 0.025 ($p = 0.966$)	− 0.154 (0.039)
Disorganized dimension	0.084 ($p = 0.144$)	− 0.215 ($p = 0.019$)
Negative dimension	− 0.026 (0.953)	0.002 (0.386)

*Significant after Bonferroni correction (0.021)

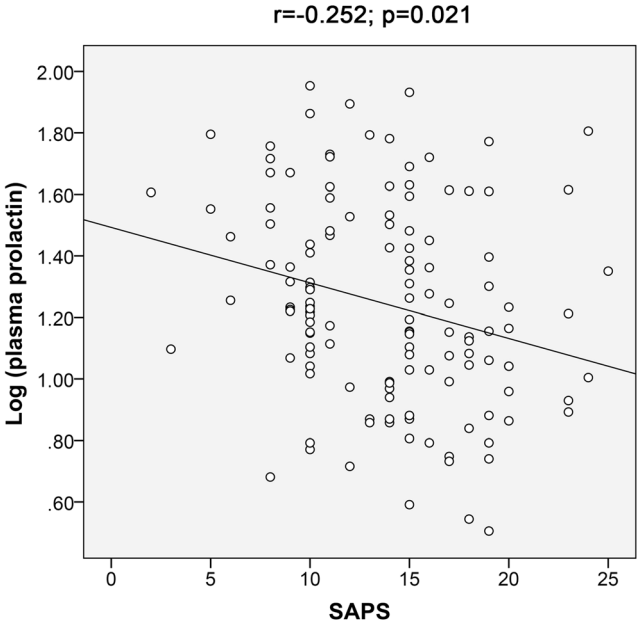

Fig. 2 Graphics for correlation analysis between plasma prolactin and SAPS and negative dimension

studies, administering dopamine agonists (e.g., apomorphine) or dopamine antagonists (e.g., haloperidol). Challenge studies of the tuberoinfundibular pathway that has compared HC and untreated patients with schizophrenia have shown an altered prolactin response with dopamine antagonists (haloperidol) (Keks et al. 1992), but not with dopamine agonists (apomorphine) (Duval et al. 2003; Meltzer et al. 2001). Prolactin-releasing factors may also be explored with TRH administration. Previous studies in untreated patients with schizophrenia have shown an altered response with low doses of TRH, suggesting a "hypersensitive" prolactin-stimulating system (Spoov et al. 2010). Thus, hyperprolactinemia in AN-FEP patients may be explained either by an altered regulation of prolactin secretion or as a stress-related state secondary to the outbreak of psychosis.

According to our results, differences in prolactin levels in women were significant for the 15–25 and the 35–45 age ranges, trending toward significance in the 25–35 range. No differences were found for the over-45 group. Interestingly, this could be due to the fact that postmenopausal women show less reactivity to stress in terms of cortisol release (Villada et al. 2017), and thus differences in stress-induced prolactin might be lessened with age. It has been shown that changes in the sex hormones influence the stress response, particularly the hypothalamic-pituitary-adrenal axis, which is attenuated (Lindheim et al. 1992; Traustadottir et al. 2005). Nevertheless, this issue should be further addressed in larger samples of postmenopausal AN-FEP patients. An alternative explanation for the different results in prolactin levels between premenopausal and peri/postmenopausal women could be the known differences in estrogen levels by reproductive age. As younger premenopausal women have higher estrogen levels compared to those women over 45, it is plausible that this could explain these differences. As already mentioned, estrogens have an antidopaminergic effect which stimulates prolactin secretion (Gudelsky et al. 1981). Thus, it is plausible that this effect could contribute to finding differences between AN-FEP and HC when estrogen levels are higher (ages < 45) but not when they are lower (ages > 45).

In female AN-FEP patients, a negative correlation was found between prolactin levels and the SAPS scale suggesting that increasing levels of prolactin would be associated with milder positive symptoms in women. Based in previous knowledge in the field, our results seem to be somewhat counter intuitive since we should expect a positive correlation between prolactin levels and disease severity. Previous studies assessing the association between prolactin levels and the severity of psychopathology in AN-FEP patients have obtained non-significant results (Ittig et al. 2017; Petrikis et al. 2016). However, a prospective study found that AN-FEP patients with higher levels of serum prolactin at baseline had a better outcome at 5 years (Shrivastava et al. 2012). In addition, early relapse following neuroleptic withdrawal was associated with low serum prolactin levels (Kirkpatrick et al. 1992). Elevated prolactin concentrations in patients with schizophrenia are undoubtedly associated with short- and long-term adverse effects, such as gynecomastia, inappropriate lactation, amenorrhea, sexual dysfunction in men, and an increased risk of breast cancer (Baggaley 2008; De Hert et al. 2016; Haddad and Wieck 2004). However, several lines of evidence in animals suggest that prolactin may have protective effects on the brain under stress conditions (see Torner 2016 for a review). In a model of chronic mild stress, the most resilient animals presented higher plasma levels of prolactin and higher prolactin receptor mRNA in the choroid plexus than the more vulnerable ones (Faron-Gorecka et al. 2013). Moreover, prolactin was shown to prevent chronic stress-induced hippocampal neurogenesis reduction (Torner et al. 2009) and to protect the hippocampus during pregnancy and lactation against the high concentrations of glucocorticoids (Morales 2011). Thus, although speculative, increased prolactin in AN-FEP patients could reflect a physiological response to protect the hippocampus or brain structures, against stress-induced damage.

Several limitations should be noted for the present study. First, we are fully aware that prolactin secretion may be regulated by many factors other than age and BMI, the only two factors that were controlled in this study. For instance, differences in diet, sleep parameters, or thyroid status could modify or nullify our findings. Unfortunately, data regarding these variables are not available. There was no control for menstrual cycle-dependent variations in female patients or controls. As prolactin secretion depends in part on the phase of the menstrual cycle, this could be an important source of variability. However, we consider that with such a large cohort of female AN-FEP patients and HC, this may have been counterbalanced across

groups, eliminating any potential effect on prolactin levels. Second, after splitting the female AN-FEP patients' sample into subgroups of age, the size of the older groups was rather small, which might have contributed to the lack of differences in this subgroup. Finally, the cross-sectional study design must be taken into account. Nevertheless, the main strength of this study is the large sample size, the largest, to the best of our knowledge, in which prolactin has been studied in this population.

Conclusions

In summary, our results indicate that plasma prolactin levels are increased in AN-FEP patients compared with HC. This, together with the negative correlation of prolactin levels in female patients with the severity of positive symptoms, suggests that prolactin might be a neuroprotector factor in women suffering an FEP.

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Compliance with ethical standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent was obtained from all individual participants included in the study.

Conflict of interest M.D-A. held a Rio Hortega Research Grant from Instituto de Salud Carlos III. J.L. has received honoraria for lectures or advisory boards from Janssen, Otsuka, and Lundbeck. B. C.-F. received in the last 3 years research funding from Lundbeck that was deposited into research accounts at the CIBERSAM. B. C.-F. has received in the last 3 years honoraria for his participation as a speaker at educational events from Otsuka, Lundbeck, and Johnson & Johnson and has been a consultant and/or advisor to or has received honoraria from Alkermes, Lundbeck, Otsuka, Casen Recordati, and Teva. D. T.-G. declares that she has no conflict of interest. R. A.-A. declares that she has no conflict of interest. V. O.-G. declares that he has no conflict of interest.

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