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PSYCHIATRY AND PRECLINICAL PSYCHIATRIC STUDIES - ORIGINAL ARTICLE

Patient characteristics driving clinical utility in psychiatric pharmacogenetics: a reanalysis from the AB-GEN multicentric trial

J. M. Menchón[1,2,3] · J. Espadaler[4] · M. Tuson[4] · J. Saiz-Ruiz[1,5] · J. Bobes[1,6,7] · E. Vieta[1,8,9] · E. Álvarez[1,10,11] · V. Pérez[1,12]

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Abstract
Clinical utility of commercial multi-gene pharmacogenetic tests in depression is starting to be studied with some promising results on efficacy and tolerability. Among the next steps is the definition of the patient profile that is most likely to benefit from testing. Here we present a reanalysis of data from the AB-GEN randomized clinical trial showing that clinical utility of pharmacogenetic testing can be markedly influenced by patient characteristics such as age, baseline severity and duration of current depressive episode.
Trial registration ClinicalTrials.gov NCT02529462.

Keywords Depression · Pharmacogenetics · Precision medicine · Antidepressant response · Randomized clinical trial · Baseline severity

Background

Antidepressant medications are the mainstay of treatment for moderate-to-severe major depressive disorder (MDD). However, their average efficacy is low (Rush et al. 2006), and low treatment adherence (Sheehan et al. 2008) further limits real-world effectiveness. Selection of antidepressants in the treatment of MDD is largely based upon trial and error, as first-line drugs display similar efficacy in undifferentiated populations (Cipriani et al. 2009).

Common genetic variation has been estimated to explain up to 42% of variance in antidepressant response (Tansey et al. 2013) and several association studies have shown links between genetic variants and MDD pharmacotherapy outcomes, although genome-wide studies suggest no single polymorphisms of large effect (Singh et al. 2014). These studies have prompted the development of many commercial pharmacogenetic (PGx) tests in psychiatry (Bousman and Hopwood 2016), although proper assessment of clinical utility with prospective randomized trials is being undertaken

✉ V. Pérez
vperezsola@parcdesalutmar.cat

1 Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Madrid, Spain

2 Departament de Psiquiatria, Hospital Universitari de Bellvitge, Institut d'Investigació Biomèdica de Bellvitge (IDIBELL), Barcelona, Spain

3 Departament de Ciències Clíniques, Facultat de Medicina, Universitat de Barcelona, Barcelona, Spain

4 AB-Biotics SA, Barcelona, Spain

5 Departamento de Psiquiatría, Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), Hospital Universitario Ramón y Cajal, Universidad de Alcalá, Madrid, Spain

6 Área de Psiquiatría, Facultad de Medicina, Universidad de Oviedo, Oviedo, Spain

7 Instituto Universitario de Neurociencias del Principado de Asturias (INEUROPA), Oviedo, Spain

8 Institut Clínic de Neurociències, Hospital Clínic de Barcelona, Universitat de Barcelona, Barcelona, Spain

9 Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain

10 Servei de Psiquiatria, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

11 Institut d'Investigació Biomèdica Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain

12 Institut de Neuropsiquiatria i Addiccions (INAD), Hospital del Mar, Universitat Autònoma de Barcelona, Barcelona, Spain

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only in a few of them (Bradley et al. 2018; Perez et al. 2017; Altar et al. 2015; Singh 2015).

Meta-analyses indicate that patient characteristics such as baseline severity and age (Fournier et al. 2010; Tham et al. 2016) strongly influence the efficacy of antidepressants, and patients with more than one failed medication trial or a long-lasting depressive episode are routinely excluded from antidepressant trials (Wisniewski et al. 2009). Yet, to date, little attention has been paid to the study of such patient characteristics on the clinical utility of pharmacogenetic testing.

Neuropharmagen (AB-Biotics SA, Barcelona, Spain) is a commercial PGx-based tool whose clinical utility in MDD was recently studied in a naturalistic, multicentric, randomized, blinded clinical trial (Perez et al. 2017). The trial (AB-GEN) was designed with broad inclusion and reduced exclusion criteria, to obtain a representative sample of treatment-seeking depressed patients in clinical settings. Thus, the inclusive nature of the clinical trial has allowed us to study the impact on pharmacogenetic testing clinical utility of several patient characteristics known to influence patient outcomes in MDD such as age, baseline severity and time from diagnosis, in a post hoc manner.

Methods

Study design and patient data

The AB-GEN study was a randomized, 12-week long, multicentric clinical trial, comparing antidepressant therapy as usual (TAU) to pharmacogenetic test-guided antidepressant therapy selection (PGx-guided), in adult patients with major depressive disorder (MDD). The primary endpoint [response based on the Patient Global Impression of Improvement, PGI-I, scale (Guy 1976)] was obtained in double-blinded manner in phone calls, while secondary variables such as 17-item Hamilton Depression Rating Scale, HDRS-17 (Hamilton 1960), were assessed in a single-blinded manner. Additional details on the AB-GEN study design and the Neuropharmagen PGx test were described elsewhere (Perez et al. 2017).

Statistical analyses

Post hoc analyses were conducted on the AB-GEN study population to assess the clinical utility of PGx-guided therapy at study endpoint (week 12) on PGI-I response (i.e. score of ≤ 2), HDRS score change, and HDRS response (i.e. change $\geq 50\%$). The effect of patient age was assessed by comparing the response rates in aged (≥ 60 years) vs. non-aged patients, and the cutoff was raised to 65 years old for a sensitivity analysis. Cutoffs were chosen based on previous meta-analyses (Tham et al. 2016). The effect of time from diagnosis was assessed by comparing diagnoses up to 1 years old to older than 1 year, and up to 5 years old to older than 5 years, these two cutoffs corresponding to the median and mean time from diagnosis in the AB-GEN population (Perez et al. 2017). Finally, depression severity was graded as mild (HDRS ≤ 17), moderate (HDRS 18-24) and severe (HDRS ≥ 25), and the effect of depression severity was evaluated by comparing response rate in mild vs. moderate + severe depression, and in mild + moderate vs. depression.

Binary and continuous variables were compared by means of Chi-square test and Student *T* test for independent samples, respectively. A two-sided significance threshold of $p = 0.05$ was applied. Statistical analyses were performed using SAS version 9.3 software (SAS Institute Inc., Cary, NC, USA).

Results

The study population was described elsewhere (Perez et al. 2017). Table 1 shows that subpopulations used in this reanalysis were reasonably balanced regarding demographic and clinical characteristics. Also, the number of individuals was evenly distributed between the PGx-guided and TAU study arms in these subpopulations, except for the severe depression (HDRS ≥ 25) subpopulation, where more individuals had been allocated to PGx-guided treatment than to TAU (37 vs 23, $p = 0.0313$).

PGx testing significantly improved response rates in non-aged subjects (below 60 years old) compared to TAU, both according to PGI-I and HDRS (Table 2). Conversely, clinical utility on aged subjects was null. Identical findings were obtained when setting the cutoff at below < 65 years old ($n = 271$, data not shown). PGx testing also consistently improved response rates in subjects with moderate-to-severe depression regardless of the scale, while no effect was observed for those with mild depression. In severe depression, a trend towards a benefit was observed with HDRS response rate but not with other measures. As to time from diagnosis, a significant improvement was observed for PGI-I response rate and HDRS change in those with diagnoses up to 1 year old, but not on HDRS response. Similar findings were obtained when increasing the cutoff to 5 years, with the effect on HDRS response becoming significant. Conversely, the effect was null in those with older diagnoses.

Discussion

Reanalysis of data from the AB-GEN study shows that age, baseline severity and time from diagnosis, which are known to influence antidepressant efficacy, also affected the

Table 1 Baseline demographic and clinical data of the subpopulations analyzed in this study

	Study arm	Age (years)	Gender (% female)	Baseline HDRS	Antidepressant failures	Time from diagnosis (years)
Less than 60 years old	PGx ($n=111$)	46.1 ± 8.8	59.5	19.5 ± 6.0	3.1 ± 2.4	4.2 ± 7.1
	TAU ($n=122$)	45.3 ± 9.6	62.3	18.9 ± 5.9	3.0 ± 1.9	4.0 ± 6.5
	p value	0.525	0.658	0.479	0.806	0.818
60 years and older	PGx ($n=44$)	65.9 ± 5.7	75.0	19.5 ± 6.0	2.9 ± 1.9	6.5 ± 8.8
	TAU ($n=39$)	67.6 ± 6.8	66.7	19.3 ± 5.3	3.2 ± 2.1	8.4 ± 10.6
	p value	0.222	0.403	0.879	0.638	0.368
Baseline HDRS < 18	PGx ($n=61$)	50.5 ± 12.1	55.7	13.6 ± 2.7	3.3 ± 2.4	6.0 ± 8.6
	TAU ($n=61$)	50.1 ± 15.2	67.2	13.1 ± 2.7	2.9 ± 2.4	6.2 ± 8.5
	p value	0.880	0.193	0.403	0.392	0.877
Baseline HDRS ≥ 18	PGx ($n=91$)	51.9 ± 11.5	68.1	23.4 ± 3.9	2.9 ± 2.1	4.0 ± 6.7
	TAU ($n=96$)	51.5 ± 11.6	61.5	22.7 ± 3.6	3.1 ± 1.7	4.0 ± 7.0
	p value	0.813	0.340	0.199	0.340	0.973
Baseline HDRS ≥ 25	PGx ($n=37$)	53.0 ± 10.3	67.6	27.3 ± 2.8	3.1 ± 2.6	4.0 ± 7.1
	TAU ($n=23$)	50.0 ± 9.2	56.5	27.9 ± 2.8	3.0 ± 1.3	2.6 ± 3.8
	p value	0.253	0.388	0.394	0.751	0.371
Up to 1 year from diagnosis	PGx ($n=79$)	50.0 ± 12.6	59.5	19.7 ± 6.1	2.3 ± 1.2	0.3 ± 0.3
	TAU ($n=73$)	47.2 ± 12.9	64.4	19.1 ± 5.4	2.9 ± 1.7	0.3 ± 0.3
	p value	0.177	0.535	0.504	0.057*	0.605
Up to 5 years from diagnosis	PGx ($n=113$)	50.9 ± 12.3	60.2	19.8 ± 6.1	2.6 ± 1.5	1.0 ± 1.2
	TAU ($n=111$)	48.4 ± 12.0	64.9	19.6 ± 5.6	2.8 ± 1.7	1.1 ± 1.3
	p value	0.112	0.469	0.861	0.314	0.570
More than 5 years from diagnosis	PGx ($n=42$)	53.9 ± 11.3	73.8	18.7 ± 5.5	4.1 ± 3.2	15.3 ± 7.9
	TAU ($n=50$)	56.0 ± 14.1	60.0	17.6 ± 5.8	3.5 ± 2.3	13.9 ± 9.0
	p value	0.431	0.163	0.350	0.305	0.453

Values indicate means and SD, unless otherwise indicated

*$p < 0.10$ for the comparison between PGx and TAU

clinical utility of PGx testing. To our knowledge, this is the first study to assess the impact of age on the clinical utility of PGx testing. Meta-analyses indicate that the benefit of most antidepressants over placebo in elderly subjects is limited at best (Tedeschini et al. 2011; Tham et al. 2016). Our results indicate that PGx testing was mostly beneficial in non-elderly subjects, this effect being robust to exact age cutoff (60 or 65 years old). Conversely, addition of PGx testing is unlikely to produce further clinical benefit in elderly subjects. More studies are needed to clarify whether this is due to a mechanistic failure of antidepressants in the brains of the elderly, or to current pharmacogenetic information not being applicable to the elderly (because being mostly derived from non-elderly subjects).

Baseline severity also influenced the clinical utility of PGx testing. In this regard, our study replicates the findings from Bradley et al. (Bradley et al. 2018) using the same severity cutoffs: PGx testing resulted in a significant improvement in moderate-to-severe depression (baseline HDRS ≥ 18), but not in patients with mild depression. A preliminary analysis in the original publication of the AB-GEN study considered the effect of baseline severity on HDRS response only, which was assessed in a single-blind manner (Perez et al. 2017). Here we have extended this analysis, showing that the effect is consistent both on PGI-I response (double-blinded assessment) and HDRS score change. On the other hand, the study from Bradley et al. also found a more significant effect in the subsample containing severely depressed patients only (baseline HDRS ≥ 25), but no significant effects could be observed in our study for the equivalent subsample. Noteworthy, the number of severely depressed patients was markedly lower in our study, and their distribution between the PGx and TAU groups was significantly uneven, thus limiting the statistical power of this later analysis.

Utility of PGx was also dependent on time from diagnosis. It is reasonable to expect that, until PGx testing becomes part of clinical routine, patients with long-term depression are among those likely to attempt a PGx-guided treatment to improve their condition. Our results suggest that PGx testing

Table 2 Efficacy outcomes at study endpoint (12 weeks) in the subpopulations analysed in this study

Factor	Subpopulation	Variable	PGx	TAU	*p* value
Patient age	Less than 60 years old	PGI-I responders	46 (46.0%)	32 (29.6%)	**0.015**
		HDRS responders	47 (45.2%)	30 (28.6%)	**0.013**
		HDRS change	−8.0 ± 7.8	−5.6 ± 7.2	**0.020**
	60 years and older	PGI-I responders	19 (52.8%)	20 (55.6%)	0.813
		HDRS responders	13 (35.1%)	19 (55.9%)	0.079
		HDRS change	−8.0 ± 7.5	−9.1 ± 6.4	0.522
Baseline severity	Mild (HDRS < 18)	PGI-I responders	25 (46.3%)	23 (41.8%)	0.638
		HDRS responders	20 (34.5%)	26 (45.6%)	0.223
		HDRS change	−4.5 ± 5.4	−4.8 ± 5.7	0.742
	Moderate + severe (HDRS ≥ 18)	PGI-I responders	40 (48.8%)	29 (32.6%)	**0.031**
		HDRS responders	40 (48.2%)	23 (28.0%)	**0.008**
		HDRS change	−10.5 ± 8.2	−7.6 ± 7.8	**0.020**
	Severe (HDRS ≥ 25)	PGI-I responders	16 (43.2%)	10 (40.0%)	0.800
		HDRS responders	18 (51.4%)	6 (28.6%)	0.094
		HDRS change	−13.0 ± 8.8	−10.2 ± 8.0	0.250
Time from diagnosis of MDD	Up to 1 year	PGI-I responders	38 (54.3%)	24 (36.9%)	**0.043**
		HDRS responders	38 (52.1%)	25 (39.7%)	0.149
		HDRS change	−9.5 ± 8.7	−6.6 ± 7.3	**0.035**
	Up to 5 years	PGI-I responders	47 (48.5%)	31 (32.0%)	**0.019**
		HDRS responders	50 (49.0%)	32 (34.0%)	**0.034**
		HDRS change	−8.8 ± 8.0	−6.2 ± 7.7	**0.022**
	More than 5 years	PGI-I responders	18 (46.2%)	21 (44.7%)	0.891
		HDRS responders	10 (25.6%)	17 (37.8%)	0.207
		HDRS change	−6.0 ± 6.6	−7.0 ± 5.8	0.518

Values for PGI-I and HDRS responders indicate number and percentage, values for HDRS change indicate mean and standard deviation. *p* values in bold are statistically significant

could benefit patients with long-lasting depression. However, there appears to be a limit, as patients with diagnoses older than 5 years seemed to fare worse under PGx than TAU according to the HDRS scale, although the difference was not statistically significant. We can hypothesize that most of PGx information is derived from patients with more recent diagnoses, and might not be fully applicable to patients with diagnoses older than 5 years. We previously reported that the number of antidepressant failures influenced the clinical utility of PGx testing (Perez et al. 2017), and patients with a long-lasting episode are more likely to have experienced several medication failures. However, both patient characteristics display a significant but markedly weak correlation ($r = 0.18$) in our study population. Thus, additional factors to medication failures might play a role to reduce the clinical utility of PGx in patients with diagnoses older than 5 years.

The main limitation of this study is its post hoc nature. Therefore, additional prospective trials are needed to confirm the role of patient characteristics on the clinical utility of pharmacogenetic testing. As psychiatric pharmacogenetic tools seem to be entering the age of due clinical utility validation, identification of patient characteristics driving clinical utility is paramount to identify the patient profile that is most likely to benefit from pharmacogenetic testing. After all, the personalized medicine paradigm should not exclusively apply to which drugs and doses are best for each patient, but also to which tests should each patient undergo to maximize treatment outcome.

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Compliance with ethical standards

Conflict of interest JE and MT are full-time employees of AB-Biotics SA, the company that developed the Neuropharmagen test used in this study. VP, JM and EV have served as consultants for AB-Biotics SA.

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