FAMILY RELATIONSHIPS AND HEALTH LOCUS OF CONTROL AS COVARIABLES IN THE EVOLUTION OF MAJOR DEPRESSIVE DISORDER

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SUMMARY

Background: *In a two-year study, we compared the efficacy of noradrenergic and serotonergic antidepressants with and without the addition of 100 mg acetylsalicylic acid (ASA) in subjects suffering from major depressive disorder (MDD). In this article we examine the influence of the health locus of control, family relationships and personality traits on the progress of MDD.*

Subjects and methods: *40 people with MDD (MDD group) were randomly assigned to the different treatment groups. They were followed in parallel with a group of 20 'healthy' subjects (HG). At the beginning of the study, sociodemographic data were collected, and patients were asked to complete the Multidimensional Health Locus of Control (MHLC) scale, the NEO Five-Factor Inventory (NEO-FFI), and the Family Adaptation and Cohesion Scale (FACES III). During the study subjects were regularly assessed using the Hamilton Depression Scale (HDS), the Short Form Health Survey (SF-12) and the Clinical Global Impression scale (CGI).*

Results: *Regardless of the type of treatment, physical health is the best predictor of variation at two years in the MDD group; 45% of variance is explained by a linear regression model that includes three variables from the MHLC, FACES III and NEO-FFI scales. Similarly, 40% of CGI and 24% of HDS variance is predicted. These explanatory variables are statistically less powerful in the MDD group than the HG group.*

Conclusion: *While drug treatment is a determinant in changes on the HDS, CGI and SF12 scales, factors such as family relationships, MHLC or personality are important covariates of these changes. The question remains whether we can influence these covariates to improve the response to antidepressants.*

Key words: *depression - MHLC - FACES III - NEO-FFI*

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INTRODUCTION

The efficacy of antidepressant medication remains a major research challenge. Despite new generations of antidepressants that have revolutionized treatment administration compared to older tricyclics, it appears that they have not, ultimately, improved responses or remission rates (Zdanowicz et al. 2008). Amitriptyline and clomipramine thus continue to appear as the most effective treatments in meta-analyses, while new drugs such as agomelatine, escitalopram or vortioxetine are emerging (Parikh et al. 2018; Cipriani et al. 2018). At the same time, randomized studies find that, regardless of the antidepressant, 60–70% of patients respond, whereas in 'real life' this rate is only ±30% (Keller et al. 2000). How can we increase the number of responders? It is possible that there are different MDD profiles that are more or less sensitive to a given treatment (Drysdale et al. 2017)? While another strategy consists in adding an NSAID to the antidepressant, results have proven to be very inconsistent. Finally, with respect to long-term effectiveness, knowledge remains very fragmented. At present, we only know that psychotherapy prevents the risk of relapse (Teasdale et al. 2000).

In the past, noradrenergics have sometimes shown to perform better than serotonergics. Therefore, in this context, in 2012 we launched a two-year study to compare a selective serotonin reuptake inhibitor (escitalopram) with a serotonin and norepinephrine reuptake inhibitor (duloxetine); both with and without 100 mg acetylsalicylic acid (ASA). We published the first results in 2017 (Zdanowicz et al. 2017). These findings showed that when ASA was combined with duloxetine, there was a more rapid improvement in the Hamilton Depression Scale (HDS) score as early as two months (t=-3.114, p=0.01), in the Clinical Global Impression scale (CGI) score at five months (t=-2.119, p 0.05), and a better remission rate (χ^2=6.296, p 0.012) than the escitalopram + placebo subgroup. Our results also showed that the brain-derived neurotrophic factor can be a response indicator. Furthermore, our study investigated other areas that could explain the evolution of MDD, such as the therapeutic alliance, and physical and mental health. While throughout the study physical health was found to be correlated with HDS (r=-0.519**) and CGI (r=-0.536**) scores, the link was only indirect, (Zdanowicz et al. 2018) (r=0.530**).

In this article we look in more detail at the influence of three psychological dimensions: 1) health locus of control; 2) family relationships; and 3) personality.

1) Health locus of control was defined by Walston at the end of the 1970s (Walston et al. 1978) and has not only proved to be a determining factor in the response to antidepressants in randomized studies (Reynaert et al. 1995), but also an indicator of the risk of depression (Zdanowicz et al. 2016).

2) In the same vein, the links between family dynamics and depression have been the subject of numerous

studies. We know that disagreements within couples (Whisman et al. 1999, 2012) and family conflicts (Campbell & Thomas 1986, Stark et al. 2012, Widmer & Reuben 1991) also directly impact the development, course, and severity of MDD. In earlier work (Zdanowicz et al. 2016) we showed that there was a correlation between intensity of depression and the functioning of the family of origin.

3) Finally, during a prospective, two-year study of a healthy sample, certain personality traits, such as conscientiousness (see below), were found to be predictive of mental health status (Zdanowicz et al. 2012).

SUBJECTS AND METHODS

Subjects

We carried out a randomized, open-label study from June 1st 2012 on the first 40 inpatients meeting inclusion criteria. Patients were followed up for two years. Inclusion criteria for the MDD group were as follows:

The patient must meet DSM-IV-R criteria for a major depressive episode:

- It must be the patient's first or second depressive episode;
- No symptoms of depression during the preceding two years;
- No history of other psychiatric disorders on Axis I of the DSM-IV-R;
- No history of gastritis, or gastric or esophageal ulcers;
- Aged between 18 and 63 years;
- At the beginning of the study the patient must be free of any other medical condition.

Patients taking depressogenic drugs (e.g. beta blockers, morphine derivatives) were excluded, and no formal psychotherapy took place during the study.

Volunteer screening was conducted, and written consent was validated by the local ethics committee (under agreement number B03920072846). Patients were then randomized into one of the four study groups. In total, 40 patients completed the study. The antidepressant + placebo group (n=20) comprised a duloxetine (D) + placebo (DP) subgroup (n=11), and an escitalopram (E) + placebo (EP) subgroup (n=9); the antidepressant + ASA group (n = 20) comprised a duloxetine + ASA (DASA) subgroup (n=8) and an escitalopram + ASA (EASA) subgroup (n=12).

In parallel, we formed a second group of 20 'healthy' subjects. Twenty Caucasians were selected at random from the telephone directory and enlisted following written agreement and signed consent. Subjects who had been diagnosed with any psychiatric disorder on Axis I of the DSM IV or who suffered from any physical pathology (unless it was chronic and stable) were excluded. Results regarding changes in this healthy group have already been published (Zdanowicz et al. 2011, 2012).

Methods

No further medication was administered to patients in the MDD group who were in remission (disappearance of all of diagnostic criteria for a major depressive episode) at six months, but follow-up continued until the end of the study. For patients who left, the last score obtained was recorded for the remaining assessments (the Last Observation Carried Forward method).

The protocol outlined below was applied to all members of both groups:

At time 0, the following assessments were carried out:

- The Mini-International Neuropsychiatric Interview: to exclude any past or present psychiatric pathology.

- Sociodemographic data: age; gender; number of people in the household; and socioeconomic status, evaluated by approximate net income per month (€; <1000, 1000–2000, 2000–3000, 3000–4000, >4000).

- Olson's questionnaire (Family Adaptation and Cohesion Scale FACES III (Olson 1986)): to investigate family dynamics. This model evaluates two dimensions of the functioning of a relational system: cohesion and adaptability. Cohesion is defined as "the emotional ties that every member develops with regard to the others". Adaptability is "the ability of the system to change its power structure, its roles and rules in response to stressful situations".

- Wallston's MHLC scale (Multidimensional Health Locus of Control) (Wallston et al.1978). This model explores how people relate to their own health. While certain individuals think they can act to avoid or fight disease (an internal 'health locus of control'), others attribute the causes of their health to destiny, or the influence of 'others' (members of the family or health professionals). The MHLC distinguishes three sub-scales: Internality (IHLC, Internal Health Locus of Control), Powerful Others (PHLC, Powerful others Health Locus of Control), and Chance (CHLC, Chance Health Locus of Control).

- Personality was measured according to the NEO-FFI typology (Costa 1992). This instrument explores five dimensions of personality: neuroticism, extraversion, openness, agreeableness, and conscientiousness. Neuroticism refers to emotional stability and adaptability. The more present this dimension, the more the subject feels negative affect such as fear, sadness, anger, guilt, disgust, and embarrassment. Extroverts are sociable, although gregariousness is only one facet of extraversion. Extrovert people prefer large groups, are active, energetic, verbose, and optimistic. Open participants are curious about everything that originates in their internal and external universe, and their life is rich in experiences. They typically conceive new ideas, adopt unconventional values, and experience intense positive and negative emotions. Participants who have low scores on the openness dimension tend to be conservative and conventional in their opinions and behaviors. People

who score high on agreeableness are altruistic, likable, helpful, and think they are likely to get help in return. Conversely, people who score low are ego-centric, suspicious of others' intentions, and are more likely to compete than cooperate. Conscientiousness refers to the capacity to manage one's desires. This capacity for self-control supports active planning, organizing, and carrying out tasks. A positive score is associated with academic and professional success. A negative score is correlated with exaggerated and painful requirements, a compulsive need for order and cleanliness, and work overload.

Patients were assessed with the 17-item Hamilton depression scale (HDS) at 0, 0.5, 1, 1.5, 2, 3, 6, 12, 18, and 24 months. The clinical global impression (CGI) scale was completed at each visit. Physical health (physical functioning, physical daily life functioning, physical pain, and general health), and mental health (vitality, social functioning, daily mental life functioning, and mental health) were evaluated with the Short Form Healthy Survey (SF-12) (Ware et al. 1996) were recorded at 0, 6, 12, 18, and 24 months.

Parametric statistical analysis was carried out using SPSS 25, taking Type 1 and 2 errors into account. No post hoc tests were carried out. A Pearson correlation analysis was carried out to identify potential covariates. Where necessary, linear regressions were run. Qualitative variables were compared with the Chi-squared test, and means were compared using Student's t-test. Significance levels were set at $p > 0.95$ and $p < 0.05$. Data are presented as mean ± standard deviation.

RESULTS

Patient demographics

The MDD group contained significantly more women than the HG (33♀/7♂ versus 9♀/12♂ $\chi^2 = 10.091$ p=0.001). The age difference between the two groups was not significant. Subjects in the MDD group had significantly fewer relatives living at home (2.73 versus 4.05; t=3.209; p=0.003). Per-head income was almost double in the MDD group compared to the HG, and around the national average of 1400 euro/ person.

Predictability of HDS in the MDD group

Table 1 shows that the CHLC and I/E ratio of the MHLC are correlated at almost all times with the change in depression intensity measured by the HDS.

Table 1. HDS – MHLC correlations

	CHLC	IE Ratio
HDS 0	0.429**	0.432**
HDS 0.5	0.592**	0.583**
HDS 1	0.638**	0.642**
HDS 1.5	0.437**	0.434**
HDS 2	0.572**	0.563**
HDS 3	0.498**	0.483**
HDS 6	0.535**	0.527**
HDS12	0.543**	0.537**
HDS18	0.533**	0.526**
HDS 24	0.529**	0.521**

*** (Bilateral) correlation is significant at the 0.001 level;
** (Bilateral) correlation is significant at the 0.01 level;
* (Bilateral) correlation is significant at the 0.05 level

There is also a link between HDS and extroversion at one month (r=-0.421*) and with adaptability of the family of origin at one year (r=0.407**).

If we introduce these three explanatory variables into a linear regression (Table 2), 27.7% of the change in HDS at two years can be predicted.

Predictability of the CGI in the MDD group

As with the HDS, the I/E ratio and the CHLC dimension of the MHLC are correlated at virtually all times with change in the CGI (Table 3).

Table 2. Linear Regressions

	Variable	Std Error	F or t	Adjusted R^2 or standardized β
HDS	Total Model	6.714	7.283	0.239***
	IE ratio	0.177	2.658	0.311**
	Externality	0.137	-2.691	-0.330**
	FoAda	0.155	-0.428	-0.052
CGI	Total Model	1.185	6.963	0.408**
	IE ratio	0.046	3.958	0.628**
	FnCo	0.020	2.844	0.479*
	Open	0.062	0.739	0.468
PH24	Total Model	9.386	6.331	0.451**
	FnCo	0.173	-1.302	-0.230
	FoCo	0.206	-1.234	-0.208
	Cons	0.212	-1.114	-0.173
	IHLC	0.542	3.180	0.489**

*** (Bilateral) correlation is significant at the 0.001 level; ** (Bilateral) correlation is significant at the 0.01 level;
* (Bilateral) correlation is significant at the 0.05 level

Table 3. CGI – MHLC correlations

	CHLC	IE Ratio
CGI 0	0.100	0.120
CGI 0.5	0.327*	0.330*
CGI 1	0.517**	0.500**
CGI1.5	0.407**	0.421**
CGI 2	0.522**	0.539**
CGI 3	0.557**	0.593**
CGI 6	0.409**	0.417**
CGI 12	0.385*	0.398*
CGI 18	0.385*	0.398*
CGI 24	0.386*	0.399*

*** (Bilateral) correlation is significant at the 0.001 level;
** (Bilateral) correlation is significant at the 0.01 level;
* (Bilateral) correlation is significant at the 0.05 level

The CGI can also be predicted from the openness of the patient at five months (r=0.330*), six months (r=0.345*) and 24 months (r=0.315*), and from the cohesion of the nuclear family, which is correlated at 12 months (r=0.386*) and 18 months (r=0.386*). If we run a linear regression on these three explanatory variables, 40% of the change in CGI at two years can be predicted (see Table 2).

Predictability of the SF12 in the MDD group

While mental health at two years can be predicted based on the cohesion of the ideal couple (r(6 months)= -5.23**; r(12 months)=-0.421**; r(18 months)=-0.412*; r(24 months)=-0.410*), we are mainly interested in the predictability of physical health (PH) – for two reasons. On the one hand, we know that there is a correlation with HDS and CGI scores (see introduction) and, on the other hand, our earlier work looked at the change in PH over two years in the healthy group (Zdanowicz et al. 2011). If we compare HG and MDD groups at time 0, the PH of MDD subjects is, unsurprisingly, poorer than the HG (PH: 36.74/51.14, t=6.353, p 0.000). What is interesting, however, is that after two years of remission, although members of the MDD group describe themselves as improved (36.74→39.09, t=-2.032, p=0.049), their PH scores remain lower than those of the healthy group (39.09→52.39, t=4.659, p 0.000) (Table 4).

Comparison of explanatory variables between HG and MDD groups

A comparison of means for the two groups suggests that IHLC levels (Δ=3.91; IC=1.624; t=3.419; p 0.000), cohesion in the family of origin (Δ=6.78; IC=2.889; t=3.419; p=0.005), cohesion in the nuclear family (Δ=7.1; CI=1.654; t=2.651; p<0.012), adaptability in the family of origin (Δ=4.54; IC=1.526; t=3.238; p<0.002), and extroversion (Δ=6.75; IC=3.747; t=4.504; p 0.000) are lower in patients with MDD.

Table 4. Physical Health (PH) correlations

	foCo	fnCo	Consc	IHLC
PH0	-0.367*	-0.330	-0.197	0.182
PH6	-0.381*	-0.565**	-00.197	0.502**
PH12	-0.399*	-0.601**	-0.322*	0.329*
PH18	-0.380*	-0.602**	-0.327*	0.250
PH24	-0.390*	-0.520**	-0.362*	0.296

*** (Bilateral) correlation is significant at the 0.001 level;
** (Bilateral) correlation is significant at the 0.01 level;
* (Bilateral) correlation is significant at the 0.05 level
foCo: cohesion of the family of origin; fnCo: cohesion of the nuclear family; Cons: conscientiousness;
IHLC: Internal Health Locus of Control

DISCUSSION

The first point to note is the small sample size, which greatly limits the generalizability of our conclusions. Nevertheless, three points seem important to highlight.

First, we are impressed by the percentage of variance explained in linear regressions. Two groups of variables can be distinguished: on the one hand, HDS scores (20%) and, on the other hand, CGI and PH scores (40%). The HDS is a more specific scale than the CGI (which is inherently more global), and the SF12, especially if only the physical health dimension is considered. It seems to us that the more specific the scale is, the more we should be able to explain a significant part of the variance and, conversely, the less specific the scale is, the more the explanatory effect becomes diluted. It appears that MDD is much more of a global and physical 'disease' than the simple mood dimension (investigated via the HDS) would suggest.

Second, among the explanatory factors, we believe that the 'personality' dimension should not be retained because correlations with traits vary according to the variable studied (HDS, CGI or PH). On the other hand, the Internality dimension of the MHLC is constant, whether measured directly in the IHLC or indirectly in the Internality/ Externality ratio. Similarly, the family, whether nuclear or of origin and especially the cohesion dimension – which is a measure of emotional distance – is also constant.

Third, while we already knew from previous studies, that low Internality or weakly cohesive families are additional risks factors for MDD, we see here that these factors are also dynamic prognostic factors. These factors could therefore not only be used to predict the response of patients, but could also become part of the therapeutic arsenal. Increased cohesiveness and internality could be additional therapeutic weapons.

CONCLUSION

While drug treatment is determinant in changes in HDS, CGI and SF12 scores, factors such as family relationships, MHLC or personality are important covariates. The question that remains is whether we can influence these covariates to improve the antidepressant response.

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