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DEPRESSION AND PHYSICAL HEALTH, THE THERAPEUTIC ALLIANCE AND ANTIDEPRESSANTS

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SUMMARY

Background: *In a two-year study we compared the efficacy of noradrenergic (duloxetine D) and serotonergic (escitalopram E) antidepressants with and without the addition of 100 mg acetylsalicylic acid (ASA) in subjects suffering from a major depressive episode (MDE). The results showed that the D + ASA (DASA) group improved more rapidly than the E + placebo (EP) subgroup. In particular, Hamilton Depression Scale (HDS) scores improved as early as two months, Clinical Global Impression (CGI) scores improved at five months, and remission rates were better. In the course of this study, we also investigated the role of the therapeutic relationship (alliance) on both the progress of the MDE, and patients' mental and physical health.*

Subjects and methods: *40 people suffering from an MDE were randomly assigned to treatment groups. At the beginning of the study sociodemographic data were collected, and the Helping Alliance Questionnaire (HAQ) was completed. During the study, patients were regularly assessed using the HDS, CGI and the Short Form Health Survey (SF-12).*

Results: *Subgroup comparisons revealed that HAQ scores are not correlated with HAD scores, but a correlation was found with remission rates (r=0.316*). Similarly, at all times, HAQ scores were correlated with physical health ($p<0.05$), which is in turn correlated with HDS and CGI scores.*

Conclusion: *Physical health is linked to the level of depression. While the alliance with the patient is not directly correlated with the intensity of depression, is it correlated with their physical condition and its improvement. For patients, improving their physical health appears to be more important than improving their mental health. These observations must be confirmed.*

Key words: *depression – alliance – therapeutic relationship – antidepressant drugs – physical health*

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INTRODUCTION

The efficacy of antidepressant medication remains a major research challenge. Although new generations of antidepressants have revolutionized treatment compared to older tricyclics, ultimately, they do not seem to have improved response or remission rates (Zdanowicz et al. 2008). The long-term efficacy of antidepressants and the comparative effectiveness of noradrenergic (SNRI) and serotonergic (SSRI) treatments remain poorly-explored. Similarly, in the context of the psychoimmunology hypothesis, the administration of an adjunctive anti-inflammatory drug, such as acetylsalicylic acid (ASA), to increase the effectiveness of an antidepressant has shown inconsistent results.

Therefore, in 2012 we launched a study to compare, over a two-year period the effectiveness of an SSRI (escitalopram: E) with an SNRI (duloxetine: D), each with concomitant administration of either 100 mg ASA or a placebo. The initial results were published in 2017 (Zdanowicz et al. 2017). These showed that for the SNRI + ASA group, Hamilton Depression Scale (HDS) scores improved at two months ($t=-3.114$, $p=0.01$), Clinical Global Impression (CGI) scores had improved at five months ($t=-2.119$, $p=0.05$), and remission rate improved ($\chi^2=6.296$, $p= 0.012$) compared to the SSRI + placebo (EP) subgroup.

The 2012 study also sought to investigate the influence of the therapeutic relationship on depression, and, more generally, on the health of the patient as many previous studies have highlighted:

- The determinant role of the alliance in treatment and, in particular, in patients suffering from a major depressive episode (MDE) (De Bolle et al. 2010, Martin et al. 2000).

And, on the other hand:

- The reciprocal influence of depression on health and vice versa. Physical comorbidities associated with depression are well-established (Coulehan et al. 1990), and studies demonstrating the impact of physical health on depression have found an effect, notably in the elderly (Berkman et al. 1986).

SUBJECTS AND METHODS

Subjects

This randomized, open-label study began on 1 June 2012 with the first 40 inpatients that met the inclusion criteria. Patients were followed up for two years. Inclusion criteria were as follows:

- the patient must meet DSM-IV-R criteria for a MDE;
- it must be the patient's first or second MDE;
- 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 oesophageal 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 for the duration of the study.

Volunteer screening was conducted, and written consent was validated by the local ethics committee (under B03920072846). Patients were then randomly allocated to one of the four experimental groups. In total, 40 patients completed the study. The antidepressant + placebo group (n=20) comprised a duloxetine + placebo (DP) subgroup (n=11), and an escitalopram + 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).

Methods

No further medication was administered to patients in remission (defined as the disappearance of all of diagnostic criteria for a MDE) 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).

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 monthly income (€; <1000, 1000–2000, 2000–3000, 3000–4000, >4000).
- The relationship between the patient and his/her therapist, and the relationship between the therapist and the patient, based on the revised Helping Alliance Questionnaire (HAQ) (Luborsky et al. 1996).

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 by the therapist following each visit. The level of physical health (physical functioning, daily life functioning, physical pain, and general health), and mental functioning (vitality, social functioning, daily mental life functioning, and mental health) was assessed using the Short Form Healthy Survey (SF12) (Ware et al. 1996) and recorded at 0, 6, 12, 18, and 24 months.

A 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. 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 the mean ± standard deviation.

RESULTS

Patient demographics

The study group comprised seven men and 33 women, with a mean age of 40.33±14.37 years. Monthly income was 1800±723 € and household size was 2.7±1.5 people. Comparisons of the ASA and placebo groups only found a significant difference in age (ASA group, 46.4 years; placebo group, 34.25 years; t=2.98, p=0.05). No correlation was found between age and HDS scores, except at month one (p=0.026, r=-0.352). No significant difference was observed between the duloxetine and escitalopram groups, and the two groups were statistically similar in terms of income (t=0.086, p=0.932).

Depression, remission and therapeutic relationship

The mean HDS score was 23.83±3.2. No correlation was found between HAQ and HDS scores and recidivism. The only significant correlation was found between the level of remission and therapists' HAQ scores (p=0.01, r=0.404**) – but not patients' HAQ scores.

Health and the therapeutic relationship

The physical and mental health of patients is clearly poorer than healthy controls (physical health (PH) 36.74/51.14, t=6.353, p<0.000; mental health (MH) 35.10/51.51, t=5.846, p<0.000). The composition of the 'healthy' patient group is described in earlier work (Zdanowicz et al. 2011). Even if, at the end of the study, patients described themselves as being better, both in terms of their physical (36.74 → 39.09, t=-2.032, p=0.049) and mental health (35.10 → 40.81, t=-2.476, p=0.018) differences with the control group at 24 months remain significant (PH 39.09/52.39, t=4.659, p<0.000; MH 40.81/52.70, t=3.965, p<0.000).

Table 1. Correlation between SF12 and HAQ

	HAQ patient	HAQ therapist
PH0	-0.035	0.309*
PH6	-0.281	0.442**
PH12	0.197	0.489**
PH18	0.189	0.476**
PH24	0.220	0.530**
MH0	-0.154	0.319*
MH6	0.237	0.066
MH12	0.225	0.127
MH18	0.222	0.109
MH24	0.215	0.111

* Correlation is significant at the 0.05 level (bilateral);
** Correlation is significant at the 0.01 level (bilateral)

Table 2. Correlations between SF12, HDS and CGI

	HDS0	HDS6	HDS12	HDS18	HDS24	CGI0	CGI6	CGI12	CGI18	CGI24
PH0	*-0.442**	-0.357*	-0.338	-0.341	-0.337	-0.144	-0.297	-0.350*	-0.350*	-0.351*
PH6	-0.255	*-0.478***	-0.472**	-0.482**	-0.488**	0.032	*-0.482***	-0.476**	-0.476**	-0.468**
PH12	-0.397*	-0.502**	*-0.501***	-0.507**	-0.501**	0.017	-0.463**	*-0.524***	-0.524**	-0.510**
PH18	-0.421*	-0.499**	-0.508**	*-0.508***	-0.500**	0.001	-0.467**	-0.524**	*-0.524***	-0.509**
PH24	-0.380*	-0.519**	-0.522**	-0.527**	*-0.519***	0.014	-0.479**	-0.534**	-0.534**	*-0.536***
MH0	0.150	0.053	0.043	0.047	0.046	0.138	-0.103	-0.037	-0.037	-0.057
MH6	-0.170	*-0.388**	-0.364*	-0.360*	-0.359*	0.223	*-0.479***	-0.472**	-0.472**	-0.495**
MH12	-0.133	-0.385*	*-0.422**	-0.419*	-0.407*	0.280	-0.507**	*-0.530***	-0.530**	-0.549**
MH18	-0.174	-0.416*	-0.446**	*-0.443***	-0.433*	0.297	-0.534**	-0.554**	*-0.554***	-0.566**
MH24	-0.171	-0.425*	-0.451**	-0.450**	*-0.440**	0.302	-0.537**	-0.570**	-0.570**	*-0.583***

* Correlation is significant at the 0.05 level (bilateral); ** Correlation is significant at the 0.01 level (bilateral);
*** Correlation is significant at the 0.001 level (bilateral)

Table 1 shows that the alliance, as perceived by the therapist, is an important factor in improving the patient's physical condition.

Health and depression

Table 2 shows that there is a significant correlation between patients' physical and mental health, on the one hand and, on the other hand, the intensity of depression and clinician's assessment of its severity. However, what is surprising in this table is the virtual absence of a correlation at time 0 - the link between 'health' and 'depression' dimensions only appears in the sixth month. We see two possible interpretations. First, it should be noted that the SF12 is completed by the patient, while the psychiatrist completes the HDS and the CGI. The first possibility is that it is a univocal mechanism that is dependent on the therapist: he/she has to have seen the patient several times before his/her evaluation becomes consistent with his/her patient's perceptions. The second possibility is that a dynamic process operates between the therapist and the patient, who come to an 'agreement' on the evaluation of the situation.

DISCUSSION

The first point to note is the study's small sample size, which greatly limits the generalizability of our conclusions. Despite this, several points deserve further discussion. First, unlike earlier work, we did not find a direct link between the alliance and the intensity of depression. The only direct link was found with the remission rate. On the other hand, the relationship described by the clinician is clearly linked to the patient's perception of their health and its improvement. What is very surprising, however, is that an effect is seen regarding patients' physical, rather than their mental health. Physical health is clearly associated with the intensity of depression and, if both improve, it does not return to the ad integrum level when compared to the control group.

It appears that psychiatrists believe that they are acting on the patient's depression and that the HDS scores are proof. On the other hand, it appears that patients are more preoccupied by their physical health, and any improvement in the intensity of their depression is secondary to this physical improvement. Finally, therapists believe that they can achieve complete remission, while for the patients, even after two years, there is still no return to normal.

How can we interpret these differences? In the elderly, it is commonly understood that depression can occur as a result of chronic pain due to progressive, age-related loss of autonomy. Therefore, we tend to think of depression in the elderly as an evolution that begins with deteriorating physical health, which transitions into depression. Conversely, in adults we understand that a depressive state can subsequently be expressed by somatic complaints. But perhaps we are wrong. It may be that even adults feel physically impaired before they say that they are depressed.

CONCLUSION

Physical health is linked to the level of depression. While the relationship with the patient is not found to be directly correlated with the intensity of depression, it is correlated with physical health and its improvement. For patients, it appears that improving their physical health is more important than improving their mental health. These observations must be confirmed.

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Contribution of individual authors:

All authors made a substantial contribution to the design of the study, and/or data acquisition, and/or the data analysis and its interpretation.

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