Psychiatria Danubina, 2019; Vol. 31, Suppl. 3, pp 411-415 *Conference paper*

THE THERAPEUTIC ALLIANCE - ITS IMPACT ON ANTIDEPRESSANT THERAPIES IN MAJOR DEPRESSIVE CONDITIONS AND ON THE OVERALL HEALTH

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SUMMARY

Background: *Based on our 2012 study and a review of the literature on the therapeutic alliance we asked ourselves different questions: does the alliance exert a real influence on the evolution of depressive affects, the rate of remission and the physical and global health?*

Subjects and methods: *In a two-year study, forty people with major depressive disorder are randomly assigned to groups that receive a SSRI (escitalopram) or a SNRI (duloxetine), each group receive concomitant ASA (100 mg) or a placebo. Sociodemographic data are recorded and patients under went regular assessments with the Hamilton depression scale (HDS) and Clinical Global Impression (CGI) scale, the Helping Alliance Questionnaire (HAQ) and the Short Form Health Survey (SF-12).*

Results: *There is no significant difference in efficacy between the two antidepressants or between antidepressant treatment with and without ASA. However, subgroup comparisons reveal that the duloxetine + ASA (DASA) subgroup showed a more rapid improvement in HDS score as early as 2 months (t=-3.114, p=0.01), in CGI score at 5 months (t=-2.119, p 0.05) than the escitalopram + placebo (EP) subgroup. Regardless of the treatment arm, the remission rate at 2 years is 50%. Among patients in remission a majority, 65%, have a high level of alliance in opposition to nonresponders who have found mostly a low level of alliance (χ^2 = 6.296, p 0.012). HAQ scores are not correlated with HAD scores, but a correlation is found with remission rates (r=0.316*). At all times, HAQ scores are correlated with physical health.*

Conclusion: *Our findings suggest that a noradrenergic agent combined with ASA is more effective in treating depression than a serotonergic agent alone. A good alliance improves effectiveness of anti-depressant treatment of 1.85 and leads to an improvement of the physical health rather than directly on the depressive feelings.*

Key words: *depression - antidepressant drugs - alliance - physical health*

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INTRODUCTION

Starting the treatment of depressive patients remains a therapeutic challenge. From 2012 to 2014, we carried out a comparative study to compare the efficacy of a SNRI (duloxetine) and a SSRI (escitalopram) and their combination with either a placebo or 100 mg of acetylsalicylic acid (ASA). The initial results published in 2017 (Zdanowicz et al. 2017) show that the association of SNRI and ASA improves the HDS score (Hamilton Depression Scale) at 2 months (t=-3.114, p=0.01) the CGI (Clinical Global Impression) at 5 months (t=-2.119, p=0.05) and the remission rate (χ^2=6.296, p=0.012) compared to the SSRI + placebo group. This suggests that a noradrenergic agent combined with an acetylsalicylic acid is more efficient than a serotoninergic agent alone. Based on the same study, we wondering the influence of the therapeutic alliance on health indicators such as the HDS, the perception of the therapeutic alliance by the patient and the clinician on the basis of the "Helping Alliance Questionnaire" (HAQ) and the patient's overall health (SF12 i.e. "The 12-item Short Form Health Survey"). Since the emergence of the concept of therapeutic alliance, it has been used increasingly in medical literature. Its definition has been widely altered and reshaped over the years. The most common involves the existence of an affective link bonding the therapist and the patient along with an agreement on the objectives and the resources which are necessary for a correct implementation of the treatment. In 1979, Downing & Rickels suggested that some quite different factors from pharmacological properties, such as the therapeutic alliance, can affect the response both to a placebo and drugs. In 1996, Krupnick et al. studied the effect of the therapeutic alliance on psychotherapies and pharmacological treatments on the basis of a multicentre study carried out within the framework of the "National Institute of Mental Health (NIMH) treatment of depression collaborative research program (TDCRP)". The patients (n=225) had been split into 4 groups: psychotherapy, cognitive and behavioural therapy, undergoing a pharmacological treatment (imipramine) and placebo. The study demonstrates a significant relationship between the quality of the alliance and the response, and variability in responses to treatments, whatever their modality (odd ratio to 3). Thus, this interest in the alliance revealed that it turns out to be the best pronostic and predictive, known factor of therapeutic responses to many treatments, yet vastly underestimated in pharmacologic studies. It contributes therefore directly to the success of the management of patients with depression (De Bolle et al. 2010). Finally, it has been demonstrated over the years that a relationship exists between organic and psychiatric diseases, although it is often underestimated (Mantelet 2003, Cottencin 2009). The physical symptoms of depression are often

badly investigated and unfortunately wrongly attributed. And yet physical comorbidities related to depression have been rightly defined (Cottencin 2009, Coulehan et al. 1990) and are mostly interpreted as a consequence of the patient's thymic condition. However, studies carried out on animals and human subjects, have shown that emotional conditions, in particular depression and stressful situations, are related to an alteration of neuronal, hormonal and immunological conditions (Schleifer et al. 1984). In this perspective, based on our 2012 study, we questioned ourselves as to the role of the therapeutic alliance on depression, its treatment and remission rate; but also, on the patient's overall health.

SUBJECTS AND METHODS

Subject

A 2-year study is carried out on a group of 40 patients. Inclusion criteria were as follows: presence of a major depressive condition defined by the DSM IV items; 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. Patients taking depressogenic drugs (e.g. beta blockers, morphine derivatives) were excluded, and no formal psychotherapy took place for the duration of the study. In total, 40 patients completed the study and sign a written consent, validated by the ethics committee (Belgium, n° B03920072846). The antidepressant + placebo group (n=20) comprised a duloxetine + placebo (DP) subgroup (n=11) and an escitalopram + placebo (EP) subgroup (n=9); antidepressant + ASA group (n=20) comprised a duloxetine + ASA (DASA) subgroup (n=8) an escitalopram + ASA (EASA) subgroup (n=12).

Methods

During the remission stages, defined by the absence of symptoms of the major depressive condition (DSM IV), medication is discontinued unlike the monitoring that goes on for another 2 years. For patients who left the study, the last score obtained was recorded for the remaining assessments (LOCF). Patients are firstly evaluated by "The Mini International Neuropsychiatric Interview" in order to rule out any previous or present psychiatric disorder. The "Helping Alliance Questionnaire (HAQ)" (Luborsky et al. 1996) evaluates the doctor's relationship of trust in the patient and vice versa. Socio-demographic data are gathered, such as the age, sex, social status (defined according to the patient's monthly salary) and the number of homemakers. At 0, 0.5, 1, 1.5, 2, 3, 6, 12, 18, and 24 months, patients were assessed with the 17-item Hamilton depression scale (HDS). The clinical global impression (CGI) scale was completed at each visit as well as the SF12 ("The 12-item Short Form Health Survey") (Ware & Keller 1996) questioning both the overall physical health (pain, everyday physical functioning, etc …) and the sanity (vitality, the patient's social functioning, everyday mental functioning and well-being). The SF12 is filled in by the patient while the psychiatrist fills in the HDS and the CGI. Parametric statical analysis are carried out using the SPS25 while taking into account the type 1 and 2 errors. No post-hoc test was carried out. Pearson correlation analysis was carried out for possible 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 $p<0.05$. The data is presented as an average ± the standard derivation.

RESULTS

Demographic data

The study is conducted with 7 men and 33 women. The mean age is 40.33+14.37; the average salary is 1,800 + 723€ and the average number of people at home 2.7 + 1.5. Both groups are statistically similar in terms of income ($t=0.086$, $p=0.932$). There is no correlation between the age and the HDS except in the first month ($p=0.026$, $r=-0.352$). Comparisons of the ASA and placebo groups reveals a significant difference in terms of age (ASA group 46.6 years old; placebo group 34.25 years old; $t=2.98$, $p=0.05$) but there is no significant correlation between the age and HDS score. No significant difference is observed between the duloxetine group and the escitalopram group.

Therapeutic alliance and intensity of the depression

The mean HDS score is 23.83+3.2 (Figure 1). No correlation has been shown between the HDS and HAQ scores. There is no difference in average in the HAQ score for the patients with one recurrence or not.

Therapeutic alliance and response to the treatment

Of the 40 patients, 21 responded within 3 months (50% decrease in HDS score), 20 patients were in remission at 6 months and 1 patient had relapsed at 2 years (Table 1). Taking an anti-depressive molecule is thus associated to a remission rate of around 50%. Basing ourselves on the therapist's HAQ results for the 40 patients, with a minimum of 60 and a maximum of 92 we obtain an average of 77.10% on the therapist's HAQ. This one is used as a "clearcut" to transform our quantitative into a qualitative alliance scale, splitting the HAQ data into 2 categories: low and high alliances. Out of those 50% remission rate, 35% are patients taking an antidepressive molecule with a low therapeutic alliance; yet their association with a good alliance increases this rate to 65%. Establishing a good therapeutic relationship would thus increase the efficiency of the antidepressive treatment by 1.85 (Table 2).

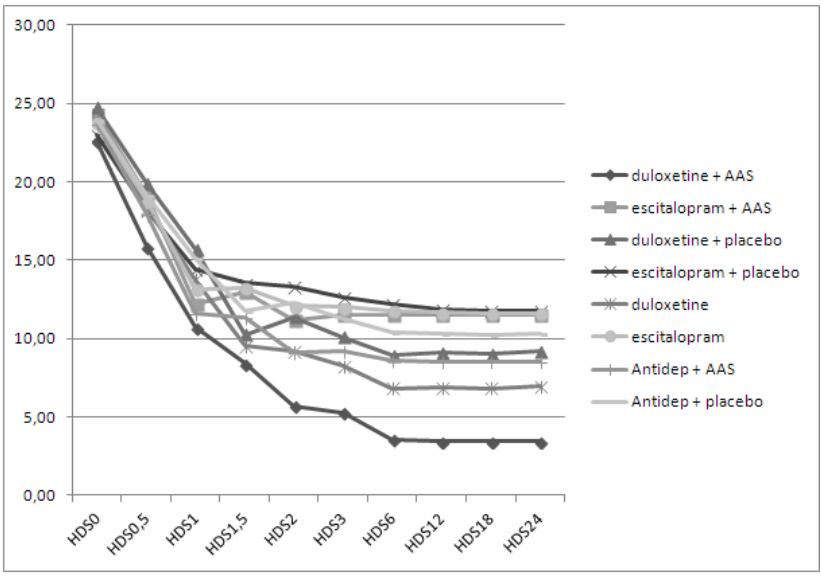

Figure 1. Evolution of the Hamilton Depression Scale (HDS) during the study according to the treatment type

Table 1. Response to treatment, remission and relapse

	n	Responders	%	Remission	%	Relapse
Total	40	21	52.5	20	50.0	1
Duloxetine + AAS	8	4	50.0	8	100	0
Escitalopram + AAS	12	8	66.7	2	16.7	0
Duloxetine + placebo	11	7	63.6	6	54.5	1
Escitalopram + placebo	9	2	22.2	4	44.4	0
Duloxetine	19	11	57.9	14	73.7	1
Escitalopram	21	10	47.6	6	28.6	0
Antidep + AAS	21	10	47.6	6	28.6	0
Antidep + placebo	20	9	45.0	10	50.0	1

Table 2. Correlations between remission and therapeutic alliance

		Remission Rate No remission	Remission	Total
Therapeutic Alliance	Low alliance	14	7	21
	High alliance	6	13	19
Total		20	20	40

Table 3. Correlation between the Short Form Health Survey (SF-12) including physical health (PH) and mental health (MH) and the Helping Alliance Questionnaire (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

** La corrélation est significative au niveau 0.01 (bilatéral);
* La corrélation est significative au niveau 0.05 (bilatéral)

The differences in distribution for the patients in remission or not, crossed with the patients with a good therapeutic alliance or not, have a chi-square of 4.912 (p=0.027) resulting in a significant difference in distribution between the remission rate and the clinician's HAQ.

Therapeutic alliance and overall health

First of all, it should be noted that in a previous study (Zdanowicz et al. 2011) our patients' physical and mental health was worse than the health of the controls in good health (physical health 36.74/51.14, t=6.353, p<0.000; mental health 35.10/51.51, t=5.846, p<0.000). At the end of our study, the patients reporting an improvement in terms of physical health (36.74 → 39.09, t=-2.032 , p=0.049) and mental health (35.10 → 40.81, t=-2.476, p=0.018) still retain a significant difference versus the health of healthy controls (physical health 39.09 / 52.39;

Table 4. Correlations between Hamilton depression scale (HDS), clinical global impression (CGI) scale and the Short Form Health Survey (SF-12)

	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***

*** La corrélation est significative au niveau 0.001 (bilatéral); ** La corrélation est significative au niveau 0.01 (bilatéral); * La corrélation est significative au niveau 0.05 (bilatéral)

t=4.659; p<0.000; mental health 40.81 / 52.70; t=3.965; p<0.000). By looking into the influence of therapeutic alliance on the patient's physical health and mental sanity (Table 3), we notice a significant correlation between the improvement of the patient's physical health and the clinician therapeutic alliance throughout the study. We can't objectivize a significant relationship between both the patient's and the clinician's HAQ's, on the one hand, and the improvement of the patient's sanity, on the other hand. Besides, there is a correlation between the patient's physical health and sanity on the one hand, and the intensity of his depression and his clinical improvement on the other hand (Table 4) significant from the sixth month of the treatment.

DISCUSSION

It must first be pointed out that because of the limited size of our sample, we cannot allow ourselves to generalize our conclusions. However here are our observations.

After two years of study, we objectivize a 50% remission rate with patients suffering from a major depressive condition. By analysing the influence of the therapeutic alliance on this remission rate, 35% are taking an antidepressive molecule alone, the remaining 65% result from the taking of an antidepressant combined with a good therapeutic alliance. The alliance seems to multiply by 1.85 the efficiency of the antidepressant. Based on the HAQ, the SF12 and the HDS, no correlation is found between the HDS score and the HAQ. A significant relationship is showed between the remission rate and the HAQ. From the point of view of overall health, the clinicians' therapeutic alliance seems directly correlated, at every stage of the study, to the perception of the patient's physical health and improvement. No correlation of the same kind is made to the patient's sanity. The alliance thus affects the physical health more than the subject's psychological health, which turns out to be fairly surprising. Finally, a significant correlation between the patient's physical health and the HDS score is objectivized. Starting from these different assumptions, our hypothesis would be that the therapeutic alliance, through its influence on the patient's physical health perception, would make it possible, indirectly, to obtain a significant increase of the remission rate. As a result, the gain in remission would be, indirectly, related to the improvement of the patient's physical health, in particular thanks to the tie that binds the clinician's HAQ to the HDS (Zdanowicz et al. 2018). Symptoms and ties binding psychiatric disorders and organic diseases (Mantelet 2003, Cottencin 2009, Coulehan et al. 1990) as well as the impact of the physical health on the depression of elderly people (Berkman et al. 1986) may reinforce our hypothesis that perhaps, just like the geriatric patients in whom depression seems to be secondary to the presence of chronic pain inducing a progressive deterioration of the autonomy, the adult patient firstly experiences a certain physical malfunction prior to a decreased autonomy, leading to the expression of a depressive table. The thymic condition of elderly people could be a reaction to the deterioration of their physical health, the opposite of what is generally claimed in adult subjects. On this base, we could understand the close link that unites depression and physical health. Knowing that therapists' evaluations of therapeutic alliance are predicting therapeutic progress, the alliance could be directly related to the evolution of the symptoms, and, as a result, the effect of the treatment of the depression, although there may be an unavoidable inter-subject variability between the patients.

CONCLUSION

Our results suggest that the therapeutic alliance perceived by the clinician plays a much bigger part than could have been thought at the beginning. In addition to being a predictive and prognostic factor in the response to many forms of treatment, it influences the patient's perception on his physical health in a indirect way, increasing remission rate significantly by multiplying

the efficiency of the antidepressant by 1.85. In conclusion, the management by the psychiatrist would require a psychological aspect as well as a physical aspect. The quality of that relationship will thus be the decisive factor in the pronostic of the patient's depression. Our results reinforce the assumptions made by Krupnick et al. in 1996 on the role of therapeutic alliance in results of psychotherapy and pharmacotherapy. However, because of the limited size of our sample, it is difficult to extrapolate our results. It would be interesting to continue investigating the impact of this therapeutic alliance on our daily practice.

Acknowledgements: *None.*

Conflict of interest: *None to declare.*

Contribution of individual authors:

Aurore Sourdeau & Nicolas Zdanowicz each made substantial contributions to the design of the study, and/or data acquisition, and/or the data analysis and its interpretation.

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