

SELECTIVE SEROTONERGIC (SSRI) VERSUS NORADRENERGIC (SNRI) REUPTAKE INHIBITORS WITH AND WITHOUT ACETYLSALICYLIC ACID IN MAJOR DEPRESSIVE DISORDER

Nicolas Zdanowicz, Christine Reynaert, Denis Jacques, Brice Lepiece & Thomas Dubois

Université Catholique de Louvain, Psychosomatics Unit, Mont-Godinne University Hospital, Yvoir, Belgium

SUMMARY

Background: Antidepressant medication efficacy remains a major research challenge. Here, we explored four questions: whether noradrenergic antidepressants are more effective than serotonergic antidepressants; whether the addition of 100 mg acetylsalicylic acid (ASA) changes antidepressant efficacy; whether the long-term efficacy differs depending on the antidepressant and the addition of ASA; and whether serum levels of brain-derived neurotrophic factor (BDNF) are clinically informative.

Subjects and methods: In a two-year study, forty people with major depressive disorder were randomly assigned to groups that received an SSRI (escitalopram) or an SNRI (duloxetine), each group received concomitant ASA (100 mg) or a placebo. Sociodemographic data were recorded and patients underwent regular assessments with the Hamilton depression scale (HDS) and clinical global impression (CGI) scale. Serum levels of BDNF were measured four times per year.

Results: There was no significant difference in efficacy between the two antidepressants or between antidepressant treatment with and without ASA. However, subgroup comparisons revealed 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 ($t=-2.119$, $p=0.05$), and a better remission rate ($\chi^2=6.296$, $p=0.012$) than the escitalopram + placebo (EP) subgroup. Serum BDNF before treatment was also higher in the DASA subgroup than in the EP subgroup ($t=3.713$; $p=0.002$).

Conclusion: This suggests two hypotheses: either a noradrenergic agent combined with ASA is more effective in treating depression than a serotonergic agent alone, or the level of serum BDNF before treatment is a precursor marker of the response to antidepressants. Further research is needed to test these hypotheses.

Key words: depression - efficacy - antidepressant drugs - BDNF - acetylsalicylic acid

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BACKGROUND

The efficacy of antidepressant medication remains a major research challenge. Despite new generations of antidepressants that have revolutionized treatment compared to older tricyclics, they do not seem to have ultimately improved responses or remission rates (Zdanowicz et al 2006). The long-term efficacy of antidepressants and the comparative effectiveness of noradrenergic and serotonergic treatments remain poorly explored. Similarly, in the context of the psychoimmunology hypothesis, the strategy of administering an adjunctive anti-inflammatory drug to increase the effectiveness of an antidepressant has shown inconsistent results. The role and effects of aspirin (acetylsalicylic acid; ASA) in the treatment of depression were the subject of an extensive review by Baune (2016), which indicated that the effectiveness of this approach, if any, depends on the antidepressant, and that ASA may even weaken the action of SSRIs. In psychoimmunology, the clinical usefulness of measuring brain-derived neurotrophic factor (BDNF) levels remains a matter of debate (Bares et al 2016, Hashimoto et al 2016, Chan et al 2016). BDNF is a neurotrophin related to neuronal survival, synaptic signaling, and synaptic consolidation. The neurotrophin hypothesis of depression postulates that it results from stress-induced decreases in BDNF expression. This suggests that BDNF can serve as a marker

predicting the response to treatment. Unfortunately, results from clinical studies have been inconsistent, with some showing no increase in BDNF production during antidepressant treatment (consistent with the neurotrophin hypothesis), and others showing a decrease.

To investigate our four questions, we conducted a two-year study comparing an SSRI (escitalopram) with an SNRI (duloxetine), each with concomitant administration of either 100 mg of acetylsalicylic acid (ASA) or a placebo.

SUBJECTS AND METHODS

Subjects

We carried out a randomized, open-label study from June 1st 2012 on the first 40 inpatients meeting 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 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.

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. 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).

Procedure

Volunteer screening was conducted, and written consent was validated by the local ethics committee (under the Belgium B03920072846 agreement. Patients were then randomized into one of the four study groups. Assessments were carried out at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 12, 18 and 24 months. No more medication was administered to patients in remission (disappearance of all of diagnostic criteria for the major depressive episode) at six months, but follow-up continued until the end of the study. For patients who left the study, the last score obtained was recorded for the remaining assessments.

At time 0, the following assessments were carried out:

- 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).

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. Serum BDNF was measured using an enzyme-linked immunosorbent assay at 0, 3, 6, and 12 months.

Parametric statistical analysis was carried out using SPSS 22, taking Type 1 and 2 errors into account. No post hoc tests were 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 $p < 0.05$. Data are presented as the mean \pm standard deviation.

Table 1. Response, remission and relapse

	n	Responders	% Responders	Remission	% Remission	Relapse
Total	40	21	52.5	20	50	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	1

RESULTS

Patient demographics

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

Depression severity

The mean HDS score was 23.83 ± 3.2 . Scores were comparable between the duloxetine and escitalopram groups ($t = 0.126$, $p = 0.901$), and the mean score in the ASA group was not statistically different from that of the placebo group ($t = 0.14$, $p = 0.814$).

Response and remission

Of the 40 patients, 21 responded within three months of treatment (50% reduction in HDS score) and 20 were in remission at six months. One patient had relapsed at two years. Table 1 shows that the largest difference was between remission rates in the DASA and EP subgroups ($\chi^2 = 6.296$, $p = 0.012$).

Change in CGI

CGI scores are presented in Figure 1. As with the remission rate, the greatest difference in CGI was between the DASA and EP subgroups. This difference was statistically significant at 5 months ($t = -2.119$, $p = 0.05$).

Change in HDS

HDS scores are presented in Figure 2. Once again, the greatest difference was between the DASA and EP groups. These differences were statistically significant at the following time points (months): 2 ($t = -3.114$, $p = 0.01$), 3 ($t = -2.648$, $p = 0.021$), 6 ($t = -2.623$, $p = 0.019$), 12 ($t = -2.429$, $p = 0.025$), 18 ($t = -2.429$, $p = 0.028$) and 24 ($t = -2.414$, $p = 0.029$).

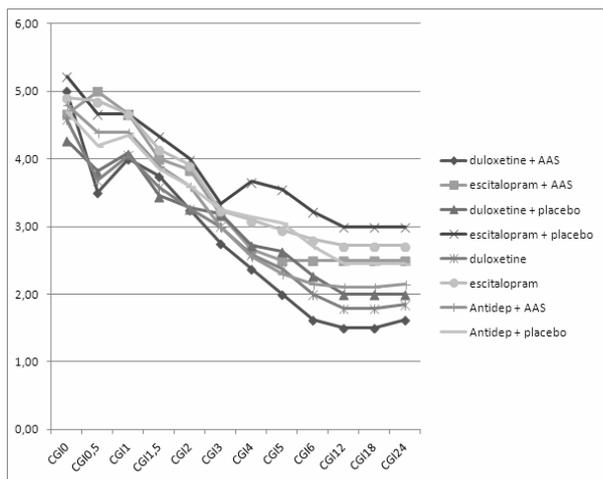


Figure 1. Evolution CGI

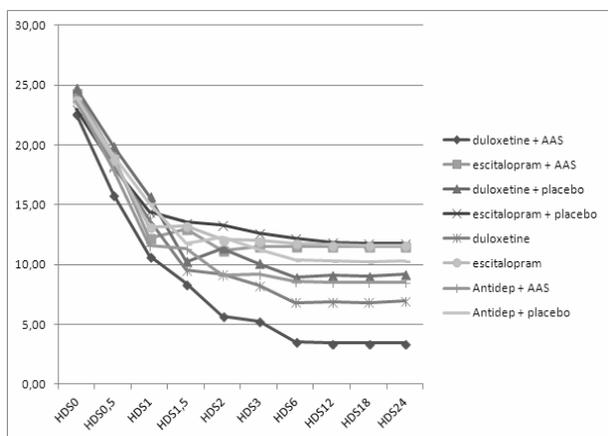


Figure 2. Evolution HDS

BDNF

A decrease in serum BDNF concentration was observed in all patient groups during the study (Figure 3). The largest difference between groups was at time 0, between the DASA and EP subgroups ($t=3.713$; $p=0.002$).

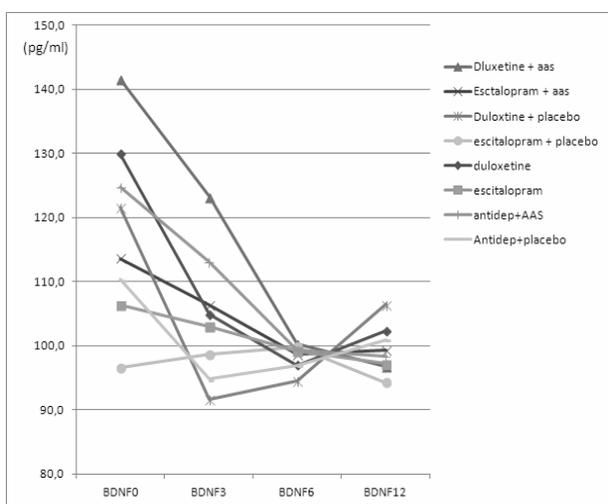


Figure 3. Evolution of serum levels of BDNF

DISCUSSION

The first point to note is the small sample size, which greatly limits the generalizability of our conclusions. Despite this, we were surprised by the lack of difference between the antidepressant + placebo and antidepressant + ASA groups, and more so by the differences between the DASA and EP subgroups. There was no difference in short- or long-term effect between the SNRI and SSRI, or between the presence and absence of ASA with an antidepressant. However, when ASA was added to the SNRI, the cumulative effect of these two substances improved efficacy from the second month and continued to the end of the observation period. These results are in agreement with those presented by other authors (see Background), although it seems to be less related to a lack of efficacy of the SSRI + ASA combination and more to a greater efficacy of the SNRI + ASA combination. At least that is what we believed until we examined the results of the BDNF assay. In partial agreement with the literature, the elevated BDNF level seemed to be a marker of response to antidepressants, and its concentration decreased with treatment time. However, BDNF levels in our study were highest in the DASA subgroup and lowest in the EP subgroup before treatment began. We therefore propose an alternative hypothesis: the SNRI + ASA combination is not more effective, but this subgroup of patients in our study happened to have the best physiological response due to greater spontaneous BDNF production. Examining this hypothesis requires a new study in which patient group allocation is based on the level of serum BDNF prior to treatment.

CONCLUSION

Our study raises two possible hypotheses: either the combination of a noradrenergic agent and ASA is more effective than a serotonergic drug alone, or the level of serum BDNF prior to treatment is a precursor marker of the response to antidepressants. Further research is needed to test these hypotheses.

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Conflict of interest: None to declare.

Contribution of individual authors:

All authors make substantial contributions to conception and design, and/or acquisition of data, and/or analysis and interpretation of data.

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Correspondence:

Nicolas Zdanowicz, MD, PhD
Université Catholique de Louvain, Psychosomatics Unit,
Mont-Godinne University Hospital
5530 Yvoir, Belgium
E-mail: Nicolas.zdanowicz@uclouvain.be