Clinical Patterns and Treatment Outcome in Patients with Melancholic, Atypical and Non-Melancholic Depressions

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Abstract

Objective: To assess sociodemographic, clinical and treatment factors as well as depression outcome in a large representative clinical sample of psychiatric depressive outpatients and to determine if melancholic and atypical depression can be differentiated from residual non-melancholic depressive conditions.

Subjects/Materials and Method: A prospective, naturalistic, multicentre, nationwide epidemiological study of 1455 depressive outpatients was undertaken. Severity of depressive symptoms was assessed by the Hamilton Depression Rating Scale (HDRS) and the Self Rated Inventory of Depressive Symptomatology (IDS-SR30). IDS-SR30 defines melancholic and atypical depression according to DSM-IV criteria. Assessments were carried out after 6–8 weeks of antidepressant treatment and after 14–20 weeks of continuation treatment.

Results: Melancholic patients (16.2%) were more severely depressed, had more depressive episodes and shorter episode duration than atypical (24.7%) and non-melancholic patients. Atypical depressive patients showed higher rates of co-morbid anxiety disorders and substance abuse. Melancholic patients showed lower rates of remission.

Conclusion: Our study supports a different clinical pattern and treatment outcome for melancholic and atypical depression subtypes.

Introduction

The broad heterogeneity of clinical depression has long encouraged research seeking to identify depressive subtypes that show causal, and even more importantly, treatment specificity [1,2]. As yet inconsistencies in research findings have failed to convincingly demonstrate absolute depressive sub-types, contributing to the default model of differentiating depressive states dimensionally. The historical controversy about the nature, definition and classification of atypical and melancholic subtypes [3–5] in particular has gained strength in preparation of the DSM-5 manual [6,7]. Differing options for future DSM depressive categories include weighting depressive sub-types, as against providing specifiers for major depressive episodes or distinct qualitative affective disorders [1,4,5,8–12]. According to previous studies, melancholic depression affects about 25–30% of depressive populations [13,14] and is clinically characterized by distinct quality of mood, non-reactivity of mood to circumstances, anhedonia, psychomotor disturbance, cognitive impairment and symptoms of vegetative dysfunction such as terminal insomnia, diurnal mood variation with worsening in the morning and weight loss [7,15]. From a biological perspective, hypercortisolism, neuroimaging features and disturbances in sleep architecture have been associated with melancholia [4,10]. Melancholic patients are held to respond better to Electroconvulsive therapy (ECT) and to certain pharmacological approaches such as tricylic antidepressants (TCA) rather than to selective serotonin reuptake inhibitors (SSRIs) [16]. Compared to non-melancholic depression, melancholia rarely responds to placebos, psychotherapies or social interventions [17]. Depressive patients with melancholic features have worse outcomes and reduced probability of remission from major depressive disorder compared to those with non-melancholic depression [18]. Some authors have therefore argued that melancholia is a disease entity on the basis of its psychopathology, biology and differential response to treatment [12] and have proposed new diagnostic criteria [4].

By contrast, atypical depression (initially contrasted with the so-called ‘typical’ endogenous or melancholic depressive condition) is characterized by significant mood reactivity, severe fatigue, anxiety, hypersomnia, increased appetite and a personality style...
of rejection sensitivity. Selective response to monoamine oxidase inhibitors (MAOIs), polysomnographic changes and endocrine features have been interpreted by some authors as also positioning atypical depression as a distinct entity [19] while others have argued for the primacy of a personality style rejection sensitivity and response to salient stressors [20,21]. This condition appears common, with studies indicating rates ranging from 20% to 35% of depressed patients [21,22], while it appears to have an earlier age of onset and a more chronic course of illness than melancholia [23].

While such studies prioritize these depressive subtypes as the most promising categorical candidates in future DSM-5 classificatory model, the available evidence is largely limited to clinical trial studies with narrow inclusion criteria and very stringent treatment conditions. The naturalistic design of the present study provides an opportunity to assess sociodemographic, clinical and treatment factors as well as depression outcome in a large representative clinical sample of psychiatric depressive outpatients, to determine if melancholic and atypical depression can be positioned as distinctive clinical entities.

Methods

Study design and population

The main objectives and details of the RESIST study have been described previously [24]. Briefly, the RESIST is a large prospective naturalistic multicentre study conducted in regional outpatient Spanish settings. Four hundred psychiatrists proportionally distributed by regions within Spain’s 17 regional communities were selected to participate, and each asked to recruit five outpatients. Inclusion in the study required participants to sign a written informed consent, to be over 18 years of age, to meet Major Depression diagnoses according to DSM-IV criteria, and to have had 6–8 weeks of antidepressant drug treatment. Recruitment took place under naturalistic clinical conditions in outpatient settings. Data were collected during two routine visits after obtaining written consent, and with the first assessment occurring after at least six weeks of antidepressant therapy.

A total of 374 (86%) psychiatrists accepted the invitation to contribute, and 1870 patients were initially recruited. Of those, 140 patients were excluded from the current analyses as they were in remission at first assessment, 275 were excluded due to: change of treatment (n = 171, 9.1%), patients not having a second assessment (n = 68, 3.6%) incomplete or missing data (n = 36, 1.9%), leaving 1595 patients in the provisional sample. Data collection took place from February to June 2009 after receiving the approval of the Teknon Medical Center ethical committee (Barcelona, Spain). Thus, our analyses were undertaken on a sample of 1455 patients.

Measures

Sociodemographic and clinical characteristics. Data collected at the first visit included sociodemographic characteristics (age, gender, current occupation, marital status, education, living status and environment), history and clinical features of the depressive disorder (age at onset, first or recurrent episode, number of previous episodes, length of current episode), DSM-IV-TR comorbid psychiatric diagnoses and comorbid medical diseases.

Severity and improvement assessment. The severity of depressive symptoms was assessed by the Hamilton Depression Rating Scale (HDRS) and the Self Rated Inventory of Depressive Symptomatology (IDS-SR30). The HDRS21 includes 21 items, each rated on a 0–2 or 0–4 scale by the clinician, with a range for the total score from 0 (without depressive symptoms) to 66 (severe depressive symptoms). The IDS-SR30 assesses 30 symptoms obtaining a total score with a range from 0 (without depressive symptoms) to 84 (severe depressive symptoms). At each assessment the HDRS21 and IDS-SR30 measures were administered. The IDS-SR30 to assess all core criterion diagnostic depressive symptoms as well as DSM-IV atypical and melancholic symptom features [25,26].

Definition of melancholic and atypical depression

For the purpose of this study, melancholic and atypical depression were defined using algorithms from selected items of IDS-SR30 developed by the STAR*D research group [13,22], and with such definitions corresponding to DSM-IV criteria. According to those specific definitions for assigned melancholic depression, patients were required to score 2 or 3 on the IDS-SR30 anhedonia and non-reactive mood items and score positively on at least 3 of the following criteria: distinct quality of mood, diurnal mood variation with worsening symptoms in the morning, psychomotor retardation, psychomotor agitation, appetite or weight decrease, early morning awakening and self-outlook. For assigned atypical depression, patients were required to score 0, 1 or 2 for mood reactivity and affirm at least two of the following items: 2 or 3 for leaden paralysis, 2 or 3 for weight gain or increased appetite, 2 or 3 for hypersomnia, and 3 for interpersonal sensitivity.

Antidepressant treatment characteristics

Treatment modality was determined by the clinician’s individual decision. Any drug type, dose, regimen of antidepressant or concomitant medication was allowable and entirely at the discretion of the psychiatrist. Change of treatment for any reason resulted in exclusion from the study. Description of antidepressant treatment was collected at the second visit. For the present analysis antidepressant types were divided into three categories: Selective Serotonin Reuptake Inhibitors (SSRIs), Selective Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs) and Tricyclic Antidepressants (TCAs). Antidepressant regimes were classified as monotherapy (using only one antidepressant during the study period) and combination therapy (using more than one antidepressant during the study period). Concomitant medication was categorized as additional use of antipsychotic, mood stabilizer and anxiolytic/hypnotic (benzodiazepine) medication.

Definition of treatment outcomes

HDRS21 remission was defined as having a HDRS21 score ≤7, and IDS-SR30 remission was defined as having an IDS-SR30 score ≤14 after 16–20 weeks of antidepressant treatment.

Statistical analyses

T-tests compared differences between groups for quantitative variables. Chi-square tests and unadjusted odds ratios (ORs) were calculated to explore differences between patient groups for qualitative variables. In order to assess the relative strength of each variable, we ran separate binary logistic regression analyses. Each of these regressions was re-run controlling for age, gender and severity of depression as they were significantly different. These analyses examined for group differences and to quantify the magnitude of effects, being reported as adjusted ORs with 95% C.I. These control factors (age, gender and severity) were chosen to enhance our comparison procedures and to ensure that group differences were not likely due to differences on the demographic and clinical factors. Statistical analyses were conducted using SPSS.
for Windows Version 19.0. A probability level of 0.05 was considered statistically significant.

Results

Sociodemographic variables

Final analyses were undertaken on 1455 subjects. Study criteria assigned 237 (16.2%) as having melancholic depression and 360 (24.7%) as having atypical depression. Sociodemographic characteristics associated with melancholic and atypical depression (after adjusting for severity of depression) are summarized in Table 1. Depressive subtypes did not differ significantly across sociodemographic variables except for gender and age. Melancholic patients were slightly older than non-melancholic and atypical depressive patients. Males were over-represented with a melancholic diagnosis whereas females had higher rates of atypical depression.

Clinical variables

Melancholic patients were more severely depressed than non-melancholic patients after 6-8 weeks of Antidepressant Treatment (ADT) (mean 53.8, SD 9.1 vs 34.1, SD 11.2 on the IDS-SR 30 measure and 26.7, SD 6.1 vs 16.9, SD 6.9 on the HDRS 21 measure) and after 16-20 weeks (mean 19.1, SD 12.8 vs 15.6, SD 10.5-IDS-SR 30, and 8.7, SD 6.4 vs 7.1, SD 5.0, HDRS 21). Further, melancholic patients were more severely depressed than atypical patients after 6-8 weeks of treatment (mean 53.8, SD 9.1 vs 43.2, SD 10.0 in IDS-SR 30 and 26.7, SD 6.1 vs 20.5, SD 7.0 on HDRS 21) but did not differ in severity after 16-20 weeks. Also there were severity differences between atypical and non-atypical subjects after 6-8 weeks (mean 43.2, SD 10.0 vs 35.7, SD 13.4-IDS-SR 30, and 20.5, SD 7.0 vs 17.9, SD 7.7, HDRS 21 and after 16-20 weeks of treatment (mean 18.9, SD 11.9 vs 15.3, SD 10.5-IDS-SR 30, and, 8.41, SD 5.5 vs 7.04–SD 5.2–HDRS 21).

There were no statistical differences in age at depression onset but melancholic patients had more depressive episodes than the other depressed subjects (4.3 vs 3.6 in atypical and 3.6 in non-melancholic) and with shorter episode duration (11.6 weeks vs 14.4 in non-melancholic vs 14.4 in atypical).

Atypical depressive patients had higher rates of comorbid anxiety disorders (43.9% vs 34.2% in melancholic patients; OR = 1.35, CI = 1.06–1.7) and higher rates of co-morbid substance abuse (13.3% vs 8.4% in melancholic patients; OR = 0.52, CI = 0.3–0.79). (Table 2)

Treatment outcome

Measures of remission and their association to melancholic and atypical depression are compared in Table 3. The remission rates (as quantified by the HDRS21 and IDS-SR30) were significantly lower in melancholic patients compared with non-melancholic and atypical patients after adjustment for age, gender and severity at 6-8 weeks. Melancholic subjects showed a lower probability of remission (OR = 0.63, CI = 0.5–0.81–IDS-SR 30 and OR = 0.75, CI = 0.59–0.96–HDRS 21) than atypical subjects.

Treatment-related variables

Treatment-related characteristics of the sample and differences by depressive subtypes are summarized in Table 4. Melancholic subjects received higher rates of SSRI medication than non-melancholic subjects (OR = 1.5, CI = 1.1–2.0) and lower rates of SSRI medication than non-melancholic (OR = 0.4, CI = 0.2–0.6) and atypical patients (OR = 2.0, CI = 1.3–3.2). Melancholic patients also had higher rates of receiving concomitant antipsychotic medication (OR = 2.7, CI = 1.7–4.4).

Discussion

In our sample, 16.2% of the patients exhibited melancholic features and 24.7% atypical features of depression. Our study provides further empirical evidence in support of a different clinical profile and treatment outcome in melancholic and atypical depressive patients in comparison to those with non-melancholic depression, thus arguing for their positioning as qualitatively distinct from other forms of depression. Comparing both groups, melancholic patients were predominantly male, older, had higher depression severity scores, lower remission rates, more previous depressive episodes, while they were treated with SNRI and antipsychotics drugs more frequently. Patients with atypical depression were more likely to be female, younger, to have less severe depression, fewer episodes, longer duration of episodes, and higher comorbidity involving anxiety and substance abuse disorders. Both groups show no differences in other sociodemographic variables or in age of onset of their condition. Our study also supports the validity of melancholic and atypical depression as clinical subtypes differing from each other and from non-melancholic depressive patients.

The finding that men were more likely to be diagnosed as melancholic and women more likely to be diagnosed as having an atypical depression is consistent with published studies [13,21,22,27]. Older age in melancholic patients has also been described in previous works [28,29]. As no sociodemographic variables except gender and age showed differences between the studied groups, results support the hypothesis that psychosocial determinants have a limited role as contributing to these depressive subtypes. As overviewed in the Introduction, biological factors are likely to play a more relevant role in the development of melancholic or atypical clinical syndromes.

In our sample melancholic subjects were more likely to have briefer and more severe current index depressive episodes. In contrast to most [22,30] but not all previous studies [31,32], we found no support for older age at initial onset in melancholic patients or an earlier age of onset and a more chronic course for atypical depression [33]. Melancholia has been associated with severity and with a shorter duration of the index episode in the STAR-D cohort and a slightly lower age at the time of study entry [13]. In fact, a surprising finding of our sample was a significant higher number of previous episodes in melancholic patients compared with non-melancholic and atypical depressive patients. Despite the clinical and co-morbidity differences between first and recurrent affective episodes [24,54], there are no long-term outcome studies on depressive features and recurrence or chronicity.

In our data, atypical depression was associated with several differing clinical characteristics when compared with melancholic patients: less depression severity, fewer episodes, longer duration of episodes and higher comorbidity with anxiety and substance abuse disorders. It has been reported that patients with atypical depression have an earlier age of onset and a more chronic course of illness compared with melancholic ones [34]. In the STAR-D cohort, participants with atypical features were more likely to be younger at depression onset, to have a longer index episode, a positive history of suicide, lower remission rates and anxious features or chronic depression [35].

Regarding anxiety and comorbid substance abuse disorder, while our findings are consistent with previous studies [20,36,37], it should be noted that some symptoms that are part of the definition of atypical depression used for this study (i.e. leaden paralysis and interpersonal rejection) are associated with anxiety itself and may have confounded results related to anxiety.
| Variable          | Melancholic (n = 237) | Non Melancholic (n = 1218) | Atypical (n = 360) | Non Atypical (n = 1095) | Melancholic vs Non Melancholic | Atypical vs non Atypical | Melancholic vs Atypical |
|-------------------|-----------------------|-----------------------------|--------------------|-------------------------|-------------------------------|--------------------------|------------------------|
|                   | n Mean (SD) or %      | n Mean (SD) or %            | n Mean (SD) or %   | n Mean (SD) or %        | t, p or OR (95% CI)           | t, p or OR (95% CI)      | t, p or OR (95% CI)    |
| Age-yr            | 237 48.7 (12.3)       | 1218 47.5 (13.1)            | 360 47.2 (12.4)    | 1095 47.8 (13.2)        | t = -1.32, p = 0.018          | t = 0.78, p = 0.430      | t = 1.44, p = 0.15     |
| Gender Male       | 96 19.1               | 406 80.9                    | 107 21.3           | 395 78.7                |                               |                          |                        |
|                   | Female                | 141 14.8                    | 812 85.2           | 253 26.5                | OR = 1.5 (1.07 – 2.1)*        | OR = 0.63 (0.47 – 0.85)** | OR = 0.53 (0.36 – 0.79)** |
| Employment        | Employed             | 99 14.7                     | 569 85.3           | 165 24.5                |                               |                          |                        |
|                   | Unemployed            | 35 18.4                     | 154 81.6           | 46 25.1                 | OR = 0.72 (0.46 – 1.13)       | OR = 0.9 (0.6 – 1.35)     | OR = 1.21 (0.72 – 2.03) |
|                   | Housework             | 61 17.1                     | 305 82.9           | 91 25.3                 | OR = 1.08 (0.62 – 1.87)       | OR = 0.9 (0.55 – 1.48)   | OR = 0.93 (0.48 – 1.81) |
|                   | Retired               | 42 20.2                     | 190 79.8           | 58 25                   | OR = 1.07 (0.66 – 1.75)       | OR = 0.8 (0.52 – 1.23)   | OR = 0.83 (0.46 – 1.46) |
| Marital status    | Never married         | 34 11.9                     | 252 88.1           | 67 23.4                 |                               |                          |                        |
|                   | Married               | 152 17.2                    | 734 82.8           | 225 25.4                | OR = 0.72 (0.42 – 1.26)       | OR = 1.02 (0.65 – 1.62)   | OR = 1.32 (0.7 – 2.49)  |
|                   | Widowed               | 20 19.6                     | 82 80.4            | 20 19.6                 | OR = 0.86 (0.52 – 1.42)       | OR = 1.27 (0.82 – 1.97)   | OR = 1.25 (0.68 – 2.29) |
|                   | Divorced              | 31 17.1                     | 150 82.9           | 48 26.5                 | OR = 1.09 (0.55 – 2.19)       | OR = 0.71 (0.37 – 1.34)   | OR = 0.63 (0.26 – 1.48) |
| Education         | Incomplete primary    | 46 17                       | 225 83             | 67 24.7                 |                               |                          |                        |
|                   | Complete primary      | 81 16.7                     | 405 83.3           | 119 24.5                | OR = 0.84 (0.47 – 1.49)       | OR = 0.78 (0.48 – 1.26)   | OR = 0.98 (0.51 – 1.87) |
|                   | Secondary             | 77 16.5                     | 391 83.5           | 107 22.9                | OR = 0.89 (0.55 – 1.5)        | OR = 0.78 (0.53 – 1.16)   | OR = 0.91 (0.52 – 1.57) |
|                   | University            | 33 14.3                     | 197 85.7           | 67 29.1                 | OR = 1.06 (0.67 – 1.67)       | OR = 0.72 (0.50 – 1.04)   | OR = 0.74 (0.44 – 1.26) |
| Lives             | Alone                 | 39 15.1                     | 220 83.4           | 70 27                   |                               |                          |                        |
|                   | Accompanied           | 198 16.6                    | 998 81.9           | 290 24.2                | OR = 0.84 (0.52 – 1.36)       | OR = 1.36 (0.91 – 2.06)   | OR = 1.58 (0.89 – 2.8)  |
| Environment       | Rural                 | 68 17                       | 332 83             | 89 22.3                 | OR = 1.01 (0.72 – 1.4)        | OR = 0.85 (0.63 – 1.14)   | OR = 0.89 (0.59 – 1.33) |
|                   | Urban                 | 169 16                      | 886 84             | 271 25.7                |                               |                          |                        |

*Adjusted for IDS-SR30 depression severity *p<0.05**p<0.01
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Table 2. Clinical characteristics associated to melancholic and atypical depression.

| Variable                      | Melancholic (n = 237) | Non Melancholic (n = 1218) | Atypical (n = 360) | Non Atypical (n = 1095) | Melancholic vs Non Melancholic | Atypical vs non Atypical | Melancholic vs Atypical |
|-------------------------------|-----------------------|-----------------------------|--------------------|-------------------------|-------------------------------|--------------------------|-------------------------|
|                               | n Mean (SD) or %      | n Mean (SD) or %            | n Mean (SD) or %   | n Mean (SD) or %        | t, p or OR (95% CI)          | t, p or OR (95% CI)      | t, p or OR (95% CI)     |
| Age at onset of first MDE-years | 237 39.9 (13.6)       | 1218 40.5 (13.4)            | 360 40.2 (12.9)    | 1095 40.5 (13.7)        | t = 0.67, p = 0.49           | t = 0.45, p = 0.64       | t = -0.23, p = 0.81    |
| Episode                       | First episode         | 118 49.8                    | 654 53.7           | 182 50.6                 |                              |                          |                         |
|                               | Recurrent episode     | 119 50.2                    | 564 46.3           | 178 49.4                 | OR = 0.96 (0.71–1.29)        | OR = 0.95 (0.74–1.23)     | OR = 1.01 (0.72–1.42) |
| Number of previous episodes   | 119 4.35 (3.4)        | 564 3.67 (2.8)              | 178 3.61 (2.8)     | 505 4.61 (2.9)           | t = 2.3, p = 0.02            | t = 0.94, p = 0.34       | t = -2.01, p = 0.04    |
| Length of current episode     | 237 11.6 (7.1)        | 1218 14.4 (9.6)             | 360 14.4 (9.7)     | 1095 13.8 (9.1)          | t = 5.02, p < 0.000          | t = -1.14, p = 0.25      | t = -3.76, p < 0.000   |
| Severity ADT treatment HDRS21 after 6–8 weeks of ADT treatment | 237 26.7 (6.1)        | 1218 16.9 (6.9)             | 360 20.5 (7.0)     | 1095 17.9 (7.7)          | t = -20.2, p < 0.000         | t = 5.55, p < 0.000      | t = 11.08, p < 0.000   |
|                               | HDRS21 after 16–20     | 237 8.7 (6.4)               | 1218 7.12 (5.0)    | 360 8.41 (5.5)           | t = -4.18, p < 0.000         | t = -4.24, p < 0.000      | t = 0.58, p = 0.55     |
| weeks of ADT treatment        | IDS-SR30 after 6–8     | 237 53.8 (9.1)              | 1218 34.1 (11.2)   | 360 43.27 (10.0)         | t = -25.2, p < 0.000         | t = -10.1, p < 0.000      | t = 12.9, p < 0.000    |
| weeks of ADT treatment        | IDS-SR30 after 16–20   | 237 19.1 (12.8)             | 1218 15.6 (10.5)   | 360 18.96 (11.9)         | t = -4.57, p < 0.000         | t = -5.5, p < 0.000       | t = 0.56, p = 0.57     |
| Comorbid Anxiety disorder     | Yes                   | 81 34.2                     | 477 39.2           | 158 43.9                 |                              |                          |                         |
|                               | No                    | 156 65.8                    | 741 60.8           | 202 56.1                 | OR = 1.25 (0.93–1.7)         | OR = 1.35 (1.06–1.7)*     | OR = 0.68 (0.48–0.96)* |
| Comorbid Substance abuse disorder | Yes                  | 20 8.4                      | 117 9.6            | 48 13.3                  |                              |                          |                         |
|                               | No                    | 217 91.6                    | 1101 90.4          | 312 86.7                 | OR = 1.25 (0.74–2.1)         | OR = 0.52 (0.3–0.79)**    | OR = 0.62 (0.35–1.09)* |
| Comorbid Medical disease      | Yes                   | 115 48.5                    | 536 44             | 168 46.7                 |                              |                          |                         |
|                               | No                    | 122 51.5                    | 682 56             | 192 53.3                 | OR = 0.99 (0.73–1.3)         | OR = 0.94 (0.72–1.23)     | OR = 1.07 (0.46–1.49)  |

*Adjusted for gender, age and IDS-SR30 severity of depression  **p < 0.05  **p < 0.01

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### Table 3. Remission associated to depressive subtypes.

| Variable                      | Melancholic (n = 237) | Non Melancholic (n = 1218) | Atypical (n = 360) | Non Atypical (n = 1095) | Melancholic vs Non Melancholic | Atypical vs non Atypical | Melancholic vs Atypical |
|-------------------------------|-----------------------|----------------------------|--------------------|-------------------------|-------------------------------|--------------------------|------------------------|
|                               | n                     | Mean (SD) or %              | n                  | Mean (SD) or %          | Mean (SD) or % OR (95% CI)    | Mean (SD) or % OR (95% CI) | Mean (SD) or % OR (95% CI) |
| IDS-SR30 remission            | Yes                   | 91                         | 38.4               | 638                     | 52.4                          | 150                      | 41.7                   | 579                      | 52.9                          | 0.56 (0.42–0.75)**          | 0.63 (0.5–0.81)**          | 1.14 (0.8–1.6)**          |
|                               | No                    | 146                        | 61.6               | 580                     | 47.6                          | 210                      | 58.3                   | 516                      | 47.1                          | 0.65 (0.49–0.86)**          | 0.75 (0.59–0.96)*           | 1.15 (0.83–1.6)**          |
| HDRS21 remission              | Yes                   | 118                        | 49.5               | 733                     | 60.2                          | 192                      | 53.3                   | 659                      | 60.2                          | 1.24 (0.93–1.6)             | 1.29 (0.94–1.8)             | 1.81 (1.29–2.5)             |
|                               | No                    | 119                        | 50.2               | 485                     | 39.8                          | 168                      | 46.7                   | 436                      | 39.8                          | 1.14 (0.88–1.5)             | 1.24 (0.92–1.7)             | 1.72 (1.21–2.4)             |

*Adjusted for gender, age and IDS-SR30 severity of depression

*p<0.05
**p<0.01

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### Table 4. Treatment related characteristics associated to depressive subtypes.

| Variable                      | Melancholic (n = 237) | Non Melancholic (n = 1218) | Atypical (n = 360) | Non Atypical (n = 1095) | Melancholic vs Non Melancholic | Atypical vs non Atypical | Melancholic vs Atypical |
|-------------------------------|-----------------------|----------------------------|--------------------|-------------------------|-------------------------------|--------------------------|------------------------|
|                               | n                     | Mean (SD) or %              | n                  | Mean (SD) or %          | Mean (SD) or % OR (95% CI)    | Mean (SD) or % OR (95% CI) | Mean (SD) or % OR (95% CI) |
| Antidepressant regimen        | Monotherapy           | 174                        | 73.4               | 939                     | 77.1                          | 267                      | 74.2                   | 846                      | 77.3                          | 0.84 (0.6–1.1)              | 0.84 (0.6–1.1)             | 1 (0.7–1.5)               |
|                               | Combination           | 63                         | 26.6               | 279                     | 22.9                          | 93                       | 25.8                   | 249                      | 22.7                          | –                             | –                         | –                       |
| Antidepressant type           | SSRI                  | 31                         | 13.1               | 328                     | 26.9                          | 85                       | 23.7                   | 274                      | 25                            | 0.4 (0.2–0.6)**            | 0.9 (0.7–1.2)             | 2 (1.3–3.2)**            |
|                               | SNRI                  | 167                        | 70.5               | 744                     | 61.1                          | 227                      | 63.1                   | 684                      | 62.5                          | 1.5 (1.1–2)**              | 1 (0.8–1.3)               | 0.7 (0.5–1)              |
|                               | TCA                   | 23                         | 9.7                | 95                      | 7.8                           | 33                       | 9.2                    | 85                       | 7.8                           | 1.2 (0.7–2)                | 1.1 (0.7–1.8)             | 0.9 (0.5–1.6)            |
| Concomitant medication        | Antipsychotics        | 28                         | 11.8               | 56                      | 4.6                           | 22                       | 6.1                    | 62                       | 5.7                           | 2.7 (1.7–4.4)**            | 1 (0.6–1.7)               | 0.4 (0.2–0.8)**          |
|                               | Mood stabilizers      | 7                          | 3                  | 29                      | 2.4                           | 10                       | 2.8                    | 26                       | 2.4                           | 1.2 (0.5–2.8)              | 1 (0.5–2.4)               | 0.9 (0.5–1.7)            |
|                               | Benzodiazepines       | 127                        | 53.6               | 649                     | 53.3                          | 198                      | 55                     | 578                      | 52.8                          | 1 (0.7–1.3)                | 1 (0.8–1.3)               | 1 (0.7–1.4)              |

*Adjusted for gender, age and IDS-SR30 severity of depression

*p<0.05
**p<0.01

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comorbid disorders. Links between atypical depression and comorbid anxiety deserve further investigation.

An important finding related to treatment outcome was the lower remission rate among individuals with melancholic and atypical depression. The naturalistic design of the study gives a special significance to this result as the majority of previous evidence comes from clinical trials comparing few antidepressant options and restricted inclusion criteria. The available data on melancholic depression favors tricyclic than narrow-action antidepressants [7,38,39]. A meta-analysis of 38 double-blind studies concluded that the reversible MAOI moclobemide have higher response rates in depressed patients with melancholic features [40]. While SSRIs have shown efficacy compared to placebo in some studies [41], they appear less effective compared with the SNRI venlafaxine [42]. However, the majority of those studies considered response but not remission as a primary endpoint. When remission is considered and compared, remission rates in melancholic depression with TCA were significantly better than with SSRIs [16]. In the STAR*D cohort, melancholic depression (23.5% of 2,875 depressive patients included) was associated with a significant reduced rate of remission with citalopram, an SSRI. According to the authors of this STAR*D report, this result could be attributed to the overlap between melancholic symptoms and core depressive symptoms rated by the assessment instruments [17]. In atypical depression, the treatment data are quite controversial. MAOIs were reported as superior to TCA's in one study [43]. However, fluoxetine was superior to nortriptyline in another study [44], while response and remission rates were similar between sertraline, fluoxetine and moclobemide in depressed patients with atypical features [45,46].

Our study was not a comparative study of pre-selected antidepressants drugs, and it was intriguing that in such a ‘real world’ clinical setting we found that melancholic patients were treated more frequently with SNRI and antipsychotic medications. Our group of melancholic patients exhibited greater severity and at the same time lowers remission rates and more previous episodes. The combination of antidepressants plus antipsychotics drugs is currently one of the most evident strategies for resistant depression, and would appear to be preferentially provided by our clinicians to those with a melancholic depression.

A number of study limitations are offered in interpreting the results. First, the use of derived Hamilton and IDS-SR, item scores to capture melancholic and atypical patients risks being somewhat arbitrary. As melancholia requires some symptoms to be present, melancholic patients tend to score higher on severity scales [47,48], and it therefore remains unclear as to whether assigned melancholic patients therefore differed by type or by severity. It is difficult to differentiate between antidepressant drug response and clinical characteristics of the disorder. Second, baseline scores previous to pharmacological treatment were not assessed. Finally, TCAs and MAOIs are not currently used in clinical practice in our country while ECT was not prescribed by clinicians in our outpatient sample despite the published data on the efficacy of this treatment [49,50] and psychotherapy was not considered in data analyses. For that reason, conclusions on treatment differences between the groups needs further research clarification.

The main strengths of this study were its naturalistic design and large sample size, allowing differences between potential depressive sub-types to be pursued with some confidence.

In conclusion, our findings suggest important clinical pattern and remission differences in depressive outpatients with melancholic and atypical features. The clinical significance of these results is that it might be important to assess melancholic or atypical features in depressive patients prior to commencing treatment as such diagnostic decisions may contribute beneficially to treatment selection.

Author Contributions

Conceived and designed the experiments: MG MR JGC SA. Performed the experiments: SA DA. Analyzed the data: MG JGC. Contributed reagents/materials/analysis tools: MR SA. Wrote the paper: MG MR GP.

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