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A quantitative review on outcome-to-antidepressants in melancholic unipolar depression

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ABSTRACT

The aim of this study was to explore outcome to antidepressants profile in melancholic unipolar depression. We conducted a systematic review of electronic databases and meta-analysis of randomized and nonrandomized trials comparing: 1) outcome to antidepressants and placebo between melancholic and non-melancholic depression; 2) outcome to different antidepressant classes in melancholic depression. Two outcomes were considered: clinical remission and response. Significant lower odds of remission to antidepressants in melancholic than in non-melancholic depressions were found. Although no significant differences were observed in the response to antidepressants between both subtypes of depression, those with melancholic features had lower odds of response to placebo. Finally, treatment of melancholic depression with serotonin reuptake inhibitors was associated with lower odds of remission compared with tricyclic antidepressants, and similar outcome compared with venlafaxine. Melancholia seems to show a differential pattern of outcome to antidepressants, which could be clinically valuable for a better implementation of personalized medicine of depression. Due to several limitations, further research is needed to support these preliminary findings.

1. Introduction

It has been proposed that major depressive disorder (MDD) is a heterogeneous condition in which different constituent subtypes could be identified (Baumeister and Parker, 2012; Ghaemi and Vöhringer, 2011; Østergaard et al., 2011). Nevertheless, studies have failed to find a consistent pattern of association between MDD subtypes and response to specific treatments. Consequently, current treatment guidelines do not recommend any individualized treatment for these subtypes of MDD (Bauer et al., 2013; Kennedy et al., 2016; NICE, 2009). Identifying subtypes of MDD with differential outcomes to treatments would be clinically valuable for a personalized medicine of depression (Simon and Perlis, 2010).

Melancholic (also named primary, endogenous, or endogenomorphic) depression, characterized by pervasive anhedonia with lack of mood reactivity, psychomotor disturbances, and typical vegetative symptoms (including early morning waking, diurnal variation with worse mood in the morning and weight loss), is one of the most comprehensively explored subtypes of major depression. Traditionally, melancholic depression has been associated with lower response to placebo and greater response to antidepressants and electroconvulsive therapy (Feinberg, 1992; Parker et al., 2010). Moreover, prior good response to somatic therapies was introduced as a diagnostic criterion for melancholic depression in DSM-III-R (APA, 1987). However, subsequent studies comparing efficacy of antidepressants between melancholic and non-melancholic depression showed controversial results and small size differences. (for review see Brown, 2007). Methodological factors such as the study design, the definition of melancholia employed, differences in baseline features and in response rate to placebo were mentioned as possible explanations for these inconsistent findings. For example, in the Sequenced Treatment Alternatives to Relieve Depression (STAR-D) study (McGrath et al., 2008) and in the International Study to Predict Optimized Treatment for Depression (Day et al., 2015) patients with melancholic unipolar depression had a decreased rate of remission with antidepressants compared to those without melancholic features, but differences became non-significant after adjusting for baseline characteristics. Regarding placebo, some studies showed a differential response between melancholic and non-melancholic depressions (Fairchild et al., 1986; Mazure et al., 1990; Nelson et al., 1990). Furthermore, placebo response, rather than

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antidepressant response, has been proposed as the main differential outcome between these patient groups by one literature review (Brown, 2007).

On the other hand, a second group of investigations focused on the outcome to different types of antidepressants in patients with melancholic depression through prospective designs or post-hoc analyses of samples of MDD patients. Although monoamine oxidase inhibitors (MAOIs) were initially discouraged for the treatment of melancholia, subsequent studies showed no differences when compared to tricyclic antidepressants (TCAs) (for a review see Lecrubier and Guelfi, 1990). Early studies with selective serotonin reuptake inhibitors (SSRIs) showed lower efficacy of these drugs in melancholic depression when compared to TCAs (for review see Perry, 1996; Amsterdam, 1998; Ayuso-Gutiérrez, 2005). It was suggested, however, that these early studies might have methodologically favoured TCAs given their short length allowing a non-specific symptom reduction due to anticholinergic and antihistaminic side-effects (Amsterdam, 1998). More recently, SSRIs-TCAs comparative studies in melancholic depression found both better outcomes with TCAs (Navarro et al., 2001), no differences (Sneed et al., 2014; Uher et al., 2011), or even better response to SSRIs in younger adult patients (Joyce et al., 2003). Similar inconsistencies were reported in studies comparing outcomes between SSRIs and newer antidepressants such as venlafaxine in patients with melancholic MDD (Clerc et al., 1994; Sheehan et al., 2009; Tzanakaki et al., 2000). In addition to the methodological factors mentioned above, the inconclusiveness of the results might be related to inadequate statistical power (Simon and Perlis, 2010).

In order to overcome sample-size limitations and gain some insight into the personalized medicine of depression, the aim of this study was to combine, by meta-analytic procedures, results of studies comparing: 1) the outcome to antidepressants and placebo between patients with melancholic and non-melancholic depression, and 2) the outcome to different antidepressant types in melancholic depression.

2. Methods

2.1. Search strategy and study selection criteria

The present systematic review and meta-analysis was conducted in accordance with the MOOSE and PRISMA guidelines (Liberati et al., 2009; Moher et al., 2009). A comprehensive search of the literature was performed using PubMed and PsycINFO databases covering the period from January 1980 (1980 was selected as a date limit considering that the publication of DSM-III enables to include studies with more precise diagnostic criteria) to January 2017, using the following search strategy: depressi* AND (melancholi* OR endogenous OR subtype) AND (treatment OR therap* OR antidepress* OR placebo). The reference lists of retrieved studies and systematic reviews on pharmacological treatment of MDD were cross-checked for further relevant investigations. No language restrictions were imposed on study selection; both English and non-English articles were reviewed.

Randomized controlled trials and non-randomized trials published between January 1980 and February 2017 were included in the present review if they met the following criteria:

- Assessed patients older than 18 years old suffering from a major a depressive episode.
- With diagnosis of MDD according to a specified diagnostic system (i.e., International Classification of Diseases-ICD or the Diagnostic and Statistical Manual of Mental Diseases-DSM). Studies containing mixed samples of patients with unipolar and bipolar depression were excluded if they did not report the results separately. When the studies used the generic term “major depression” without specifying the underlying disease and no supplementary information could be gathered by contacting the authors, given the absence of explicit statement of bipolarity, the sample was considered as unipolar (Zaninotto et al., 2016).
- Trials included had to define melancholic depression using a validated scale – Research Diagnostic Criteria-RDC (Spitzer et al., 1978), DSM-III (APA, 1980), DSM-IV (APA, 1994), Newcastle Index (Carney et al., 1965), etc. –. For the purpose of this review, melancholia and endogenous depression were considered as synonyms. In the studies containing different diagnostic criteria of melancholic depression, those performed with specific diagnostic systems – i.e. CORE (Parker and Hadzi-Pavlovic, 1996), Newcastle Index – were prioritized.
- Compared outcome to antidepressants or placebo in patients with melancholic and non-melancholic depression, or outcome to different types of antidepressants in melancholic depression.
- Provided data to estimate between-group odds ratios (OR) for the outcome measure.

Non-randomized trials were included only if all melancholic and non-melancholic patients were assigned to the same antidepressant drug. Instead, non-randomized trials in which physicians could choose between various drug treatments were not considered for inclusion, as treatment selection might vary between melancholic and non-melancholic depression in clinical practice (Gili et al., 2012; Parker et al., 1992). If there were studies with overlapping content based on the same patient sample, only the data from the study with the largest sample were considered.

2.2. Data extraction and synthesis

Two independent reviewers (MPV and AGS) extracted data on each study, and a third investigator (DJM) resolved any discrepancies. Authors were contacted in case of any missing information.

Remission was selected as the main outcome for assessing the efficacy of antidepressant agents in depressive patients with and without melancholic features. Remission was proposed as the optimal outcome of acute-phase therapy, in terms of restoration of functioning (Lieberman et al., 2005). Given that there were only studies reporting response (and not remission) to placebo between melancholic and non-melancholic depression, the response to antidepressants among these subgroups was added as a secondary outcome for comparative purposes.

Regarding the comparative efficacy of different types of antidepressant agents in the treatment of MDD with melancholic features, again remission was used as the main outcome. Remission has the advantage over response that avoids the confounding effect of non-specific symptom reduction due to side effects of some antidepressants (Amsterdam, 1998). For purposes of these comparisons, MAOIs, TCAs, and SSRIs were each considered as a group, while newer antidepressants were considered individually. Furthermore, meta-analytic procedures were employed only when there were at least 3 studies comparing the same antidepressant.

We used remission and response as dichotomous measures. In line with previous recommendations (Rush et al, 2006), we defined remission using a total score threshold, and response as a percentage reduction in pre-treatment severity, using measures provided by individual studies (Tables 1 and 2). For remission, although individual studies used different cut-off points, there was some consistency between them, with 17/20 based on Hamilton Depression Rating Scale (HDRS) scores below 6 to 13 points. Similarly, 11/14 studies included in the response analysis were based on baseline HDRS score reduction greater than 50%.

2.3. Statistical analysis

All effect sizes were calculated as OR to indicate the risk of a positive or a negative outcome and were obtained together with their 95% confidence intervals (CI). The DerSimonian & Laird random effects

Table 1
Characteristics of studies assessing remission and response to antidepressants and placebo in melancholic and non-melancholic depression.

Study	Design	Diagnostic Criteria for Melancholia	Treatment (in mg/day)	Sample Mel/Non-Mel	Treatment duration in weeks	Mean Age	Concomitant Treatment	Setting	Response Definition	Remission Definition
Antidepressants Studies										
Bizière and Berger (1990)	Randomized trial	ICD-9	IMI (100–200) or MOC (300–600)	386/244	4–6	NA	NA	NA	HDRS score reduction ≥ 50%	NA
Bobo et al. (2011)	Randomized trial	IDS-C	ESC (10–20), or BUP-SR (150–400) + ESC (10–20), or VEN-XR (37.5–300) + MIR (15–45)	124/481	12	42.7	None	Outpatients	QIDS-SR score reduction ≥ 50%	QIDS-SR ≤ 5
Bouchard et al. (1987)	Randomized trial	NWC	CIT (40–60) or MAP (75–150)	35/55	6	44.7	BZD 85.6%	NA	MADRS score reduction ≥ 50%	MADRS ≤ 6
Day et al. (2015)	Randomized trial	CORE	ESC (10–20) or VEN-XR (75–225) or SER (50–200)	208/446	8	37.8	Only hypnotic or anxiolytic medications were allowed	Outpatients	HDRS score reduction ≥ 50%	HDRS ≤ 7
Danish University Antidepressant Group (1986)	Randomized trial	NWC	CIT (40) or CLO (150)	75/27	5	NA	Only BZD were allowed	Inpatients	NA	HDRS ≤ 7
Danish University Antidepressant Group (1990)	Randomized trial	NWC	PAR (30) or CLO (150)	76/26	6	NA	Only BZD and lithium (not started during the study) were allowed	Inpatients	NA	HDRS ≤ 7
Fava et al. (1997)	Non-randomized trial	DSM-IV	FLU (20)	47/143	8	39.0	None	Outpatients	NA	HDRS ≤ 7
Georgotas et al. (1987)	Randomized trial	NWC	NOR (50–180 ng/ml)[a] or PHE (70%)[b]	22/20	7	65.2	NA	Outpatients	NA	HDRS ≤ 10
Licht and Qvitzau (2012)	Randomized trial	DMS	SER (100) or SER (200) or SER (100) + MIA (30)	141/152	5	39.0	BZD/hypnotics 34.5%	Outpatients	HDRS score reduction ≥ 50%	NA
Lin et al. (2016)	Non-randomized trial	DSM-IV	FLU (20)	96/30	6	45.3	BZD 89.6%	Inpatients	HDRS score reduction ≥ 50%	NA
McGrath et al. (2008)	Non-randomized trial	IDS-C	CIT (20–60)	675/2200	12	40.8	Only anxiolytic, sedative and hypnotic medications were allowed	Outpatients	QIDS-SR score reduction ≥ 50%	HDRS ≤ 7
Mulsant et al. (2001)	Randomized trial	DSM-IV	PAR (20–40) or NOR (50–150 ng/ml)[a]	67/49	12	72.1	BZD 53.3%	Inpatients and outpatients	NA	HDRS ≤ 10
Navarro et al. (2001)	Randomized trial	NWC	CIT (30–40) or NOR (50–100)	13/43	12	70.7	BZD 38.0% AP 10.4%	Inpatients and outpatients	NA	HDRS ≤ 7
Nelson et al. (1990)	Non-randomized trial	DSM-III	DES (50–500)	20/29	4	46.0	NA	Inpatients	NA	HDRS ≤ 12
O'brien et al. (1993)	Randomized trial	ICD-9	TRA (10–30) or AMI (50–150) or TRA (50–150) + AMI (10–30)	32/29	6	41.4	Only BZD were allowed	NA	NA	HDRS ≤ 10
Peselow et al. (1992)	Randomized trial	DSM-III	FLU (5–60) or PAR (10–50) or CVX (100–350) or IMI (65–275)	76/76	6	NA	NA	NA	HDRS score reduction ≥ 50%	HDRS ≤ 6
Roose et al. (1994)	Non-randomized trial	DSM-III or DSM-III-R	FLU (40–60) or NOR (50–150 ng/ml)[a]	45/19	4	71.0	NA	Inpatients	NA	HDRS ≤ 7
Rush et al. (2008)	Randomized trial	IDS-C	BUP-SR (150–400) or SER (50–200) or VEN-XR (37.5–375)	121/606	12	NA	Only anxiolytic, sedative and hypnotic medications were allowed	Outpatients	NA	QIDS-SR < 6
Sandor et al. (1998)	Randomized trial	DSM-III	FLU (20–60) or DOX (150–225)	22/13	6	42.7	NA	Outpatients	HDRS score reduction ≥ 50%	HDRS ≤ 7
Sneed et al. (2014)	Randomized trial	NWC	SER (100–200) or NOR (80–120 ng/ml)[a]	38/72	12	64.6	NA	Outpatients	HDRS score reduction ≥ 50%	HDRS ≤ 11
Placebo Studies										

(*continued on next page*)

Table 1 (*continued*)

Study	Design	Diagnostic Criteria for Melancholia	Treatment (in mg/day)	Sample Mel/Non-Mel	Treatment duration in weeks	Mean Age	Concomitant Treatment	Setting	Response Definition	Remission Definition
Davidson et al. (1998)	Randomized trial	DSM-III	Placebo	6/40	6	41.9	NA	Outpatients	CGI-I score of 1 or 2	–
Fairchild et al. (1986)	Non-randomized trial	RDC	Placebo	18/27	5	36.1	NA	Outpatients	HDRS score reduction ≥ 50%	–
Peselow et al. (1992)	Randomized trial	DSM-III	Placebo	44/35	6	NA	NA	NA	HDRS score reduction ≥ 50%	–
Stewart et al. (1985)	Randomized trial	DSM-III	Placebo	7/17	6	NA	NA	Outpatients	CGI-I score of 1 or 2	–

Mel = melancholic patients; No-Mel = non-melancholic patients; ICD-9 = International Classification of Diseases, Ninth Revision; IDS-C = Inventory of Depressive Symptomatology-Clinical Rating; NWC = Newcastle Diagnostic Scale; DMS = Diagnostic Melancholia Scale; DSM = Diagnostic and Statistical Manual of Mental Diseases; DSM-III-R = Diagnostic and Statistical Manual of Mental Diseases third edition revised; RDC = Research Diagnostic Criteria; IMI = imipramine; MOC = Moclobemide; ESC = escitalopram; BUP-SR = bupropion sustained release; VEN-XR = venlafaxine extended release; MIR = mirtazapine; CIT = citalopram; MAP = maprotiline; SER = sertraline; CLO = clomipramine; PAR = paroxetine; FLU = fluoxetine; NOR = nortriptyline; PHE = phenelzine; MIA = mianserine; DES = desipramine; TRA = tranylcypromine; AMI = amitriptyline; CVX = clovoxamine; DOX = doxepine; BZD = benzodiazepines; AP = antipsychotics; HDRS = Hamilton Depression Rating Scale; MADRS = Montgomery-Asberg Depression Rating Scale; QIDS-SR = Quick Inventory of Depressive Symptomatology self-report; CGI-I = Clinical Global Impression-Improvement Scale; NA = not available.

[a] Plasma level range.

[b] Platelet monoamine oxidase inhibition above 70%.

Table 2
Characteristics of studies assessing remission to different types of antidepressants in melancholic depression.

Study	Design	Diagnostic Criteria	Treatment SSRI/TCA or VEN (in mg/day)	Sample SSRI/ TCA or VEN	Treatment duration in weeks	Concomitant Treatment	Setting	Remission Definition
Bobo et al. (2011)	Randomized trial	IDS-C	ESC (10–20)/VEN-XR (37.5–300) + MIR (15–45)	42/46	12	None	Outpatients	QIDS-SR ≤ 5
Bouchard et al. (1987)	Randomized trial	NWC	CIT (40–60)/MAP (75–150)	18/17	6	Only BZD were allowed	NA	MADRS ≤ 6
Danish University Antidepressant Group (1986)	Randomized trial	NWC	CIT (40)/CLO (150)	38/37	5	Only BZD were allowed	Inpatients	HDRS ≤ 7
Danish University Antidepressant Group (1990)	Randomized trial	NWC	PAR (30)/CLO (150)	40/36	6	Only BZD and lithium (not started during the study) were allowed	Inpatients	HDRS ≤ 7
Guillibert et al. (1989)	Randomized trial	NWC	PAR (30)/CLO (75)	40/39	6	Only BZD were allowed	NA	HDRS ≤ 13
Mulsant et al. (2001)	Randomized trial	DSM-IV	PAR (20–40)/NOR (50–150 ng/ml)[a]	38/29	12	Only BZD were allowed	Inpatients and outpatients	HDRS ≤ 10
Navarro et al. (2001)	Randomized trial	NWC	CIT (30–40)/NOR (50–100)	6/7	12	Only BZD and haloperidol were allowed	Inpatients and outpatients	HDRS ≤ 7
Roose et al. (1994)	Non-randomized trail	DSM-III or DSM-III-R	FLU (40–60)/NOR (50–150 ng/ml)[a]	13/32	4	NA	Inpatients	HDRS ≤ 7
Sandor et al. (1998)	Randomized trial	DSM-III	FLU (20–60)/DOX (150–225)	12/10	6	NA	Outpatients	HDRS ≤ 7
Sheehan et al. (2009)	Randomized trial	DSM-IV	FLU (60–80)/VEN (225–375)	99/91	6	Only chloral hydrate and zolpidem were allowed	Inpatients	HDRS ≤ 7
Sneed et al. (2014)	Randomized trial	NWC	SER (100–200)/NOR (80–120 ng/ml)[a]	18/20	12	NA	Outpatients	HDRS ≤ 11
Tzanakaki et al. (2000)	Randomized trial	DSM-IV	FLU (60)/VEN (225)	54/55	6	Only BZD were allowed	Inpatients and outpatients	HDRS ≤ 6

SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant; IDS-C = Inventory of Depressive Symptomatology-Clinical Rating; NWC = Newcastle Diagnostic Scale; DSM = Diagnostic and Statistical Manual of Mental Diseases; DSM-III-R = Diagnostic and Statistical Manual of Mental Diseases third edition revised; ESC = escitalopram; VEN-XR = venlafaxine extended release; MIR = mirtazapine; CIT = citalopram; MAP = maprotiline; CLO = clomipramine; PAR = paroxetine; NOR = nortriptyline; FLU = fluoxetine; DOX = doxepine; VEN = venlafaxine; SER = sertraline; BZD = benzodiazepines; QIDS-SR = Quick Inventory of Depressive Symptomatology self-report; MADRS = Montgomery-Asberg Depression Rating Scale; HDRS = Hamilton Depression Rating Scale; NA = not available.

[a] Plasma level range.

model (with the estimate of heterogeneity taken from the Mantel–Haenszel model) was used to pool data in all the analyses performed.

Heterogeneity between studies was assessed with the Q statistic (Cochran, 1954). The I^2 index (Higgins et al., 2003) was calculated to describe the percentage of total variation across reports due to heterogeneity rather than chance. I^2 values of 25%, 50%, and 75% indicate low, moderate, and high heterogeneity, respectively. We assessed the presence of publication bias first by visual inspection of funnel plots and, second, using Egger's regression asymmetry test (Egger et al., 1997).

In our analysis of outcome to treatment in depressive patients with and without melancholic features, to evaluate the potential effect of baseline severity on the results, we performed a meta-regression analysis considering the differences in baseline HDRS score between groups as a potential moderator.

A significance level of $p < 0.05$ was set for the random effects model and homogeneity analyses. All analyses were performed in STATA v. 14.1.

3. Results

We identified 6067 studies, of which 154 were shortlisted for full-text retrieval and 26 were finally included for the quantitative review (Fig. 1). In most studies, melancholic/endogenous status was assessed using DSM or similar criteria (i.e. RDC, Inventory of Depressive Symptomatology-IDS, ICD) (Bizière and Berger, 1990; Bobo et al., 2011; Davidson et al., 1988; Fairchild et al., 1986; Fava et al., 1997; Lin et al., 2016; McGrath et al., 2008; Mulsant et al., 2001; Nelson et al., 1990; O' Brien et al., 1993; Peselow et al., 1992; Roose et al., 1994; Rush et al., 2008; Sandor et al., 1998; Sheehan et al., 2009; Stewart et al., 1985; Tzanakaki et al., 2000). Fewer studies used other diagnostic systems instead of, or additionally to, DSM: Newcastle index (Bouchard et al., 1987; Danish University Antidepressant Group, 1990, 1986; Georgotas et al., 1987; Guillibert et al., 1989; Navarro et al., 2001; Sneed et al., 2014), Diagnostic Melancholia Scale (Licht and Qvitzau, 2002) and CORE system (Day et al., 2015) (Tables 1 and 2).

Analysis of depressed patients with and without melancholic features included 20 studies that assessed remission/response to antidepressant agents and 4 studies of response to placebo. Main characteristics of these studies are summarized in Table 1.

Analysis of efficacy of different types of antidepressants in patients with melancholic features included 9 studies comparing the efficacy of SSRI and TCA agents and 3 studies between SSRI agents and venlafaxine. Main characteristics of these studies are summarized in Table 2. No studies comparing other antidepressants met inclusion criteria.

3.1. Antidepressant remission rates according to depressive subtype

A total of 17 studies comprising 6,030 patients (1,696 presenting with melancholic features) were considered for the remission rates meta-analysis. Melancholic features were significantly associated with a lower likelihood of remitting from the depressive episode compared to patients without melancholic features (OR 0.71, 95% CI 0.56 to 0.88) during a weighted mean follow-up period of 10.6 weeks (Fig. 2). Heterogeneity was moderate (I^2 test = 43.1%). Because the patients from the study by Rush et al. (2008) were also included in the study by McGrath et al. (2008), (first and second phase of the STAR-D, respectively), to avoid overrepresentation of the STAR-D patients, we performed further analysis excluding the study by Rush et al. (2008). In this analysis, the differences in the odds of remission remained significant (OR 0.73, 95% CI 0.58 to 0.92).

Meta-regression analysis was used to adjust for the potential confounding effect on antidepressant remission rates of baseline differences in depressive symptoms severity between melancholic and non-melancholic patients. All the studies that assessed baseline severity, and were therefore included in this analysis, used the HDRS. Differences in baseline depressive symptom severity were not a statistically significant predictor of clinical remission in the meta-regression analysis (regression coefficient 0.10, 95% CI −0.37 to 0.21, $p = 0.51$).

3.2. Placebo and antidepressant response rates according to depressive subtype

Four studies comprising 204 depressive patients (75 presenting with melancholic features) were considered for the placebo analysis. Main

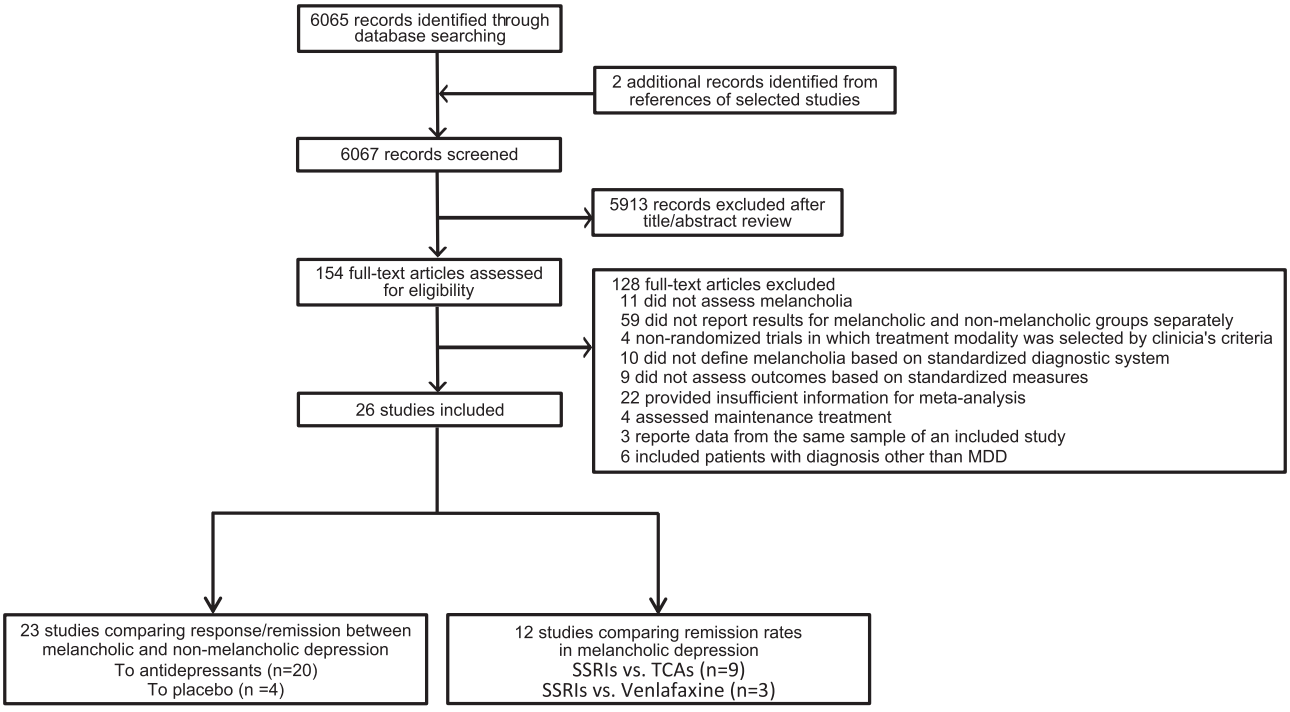

Fig. 1. Flowchart of the stepwise procedure for study selection.

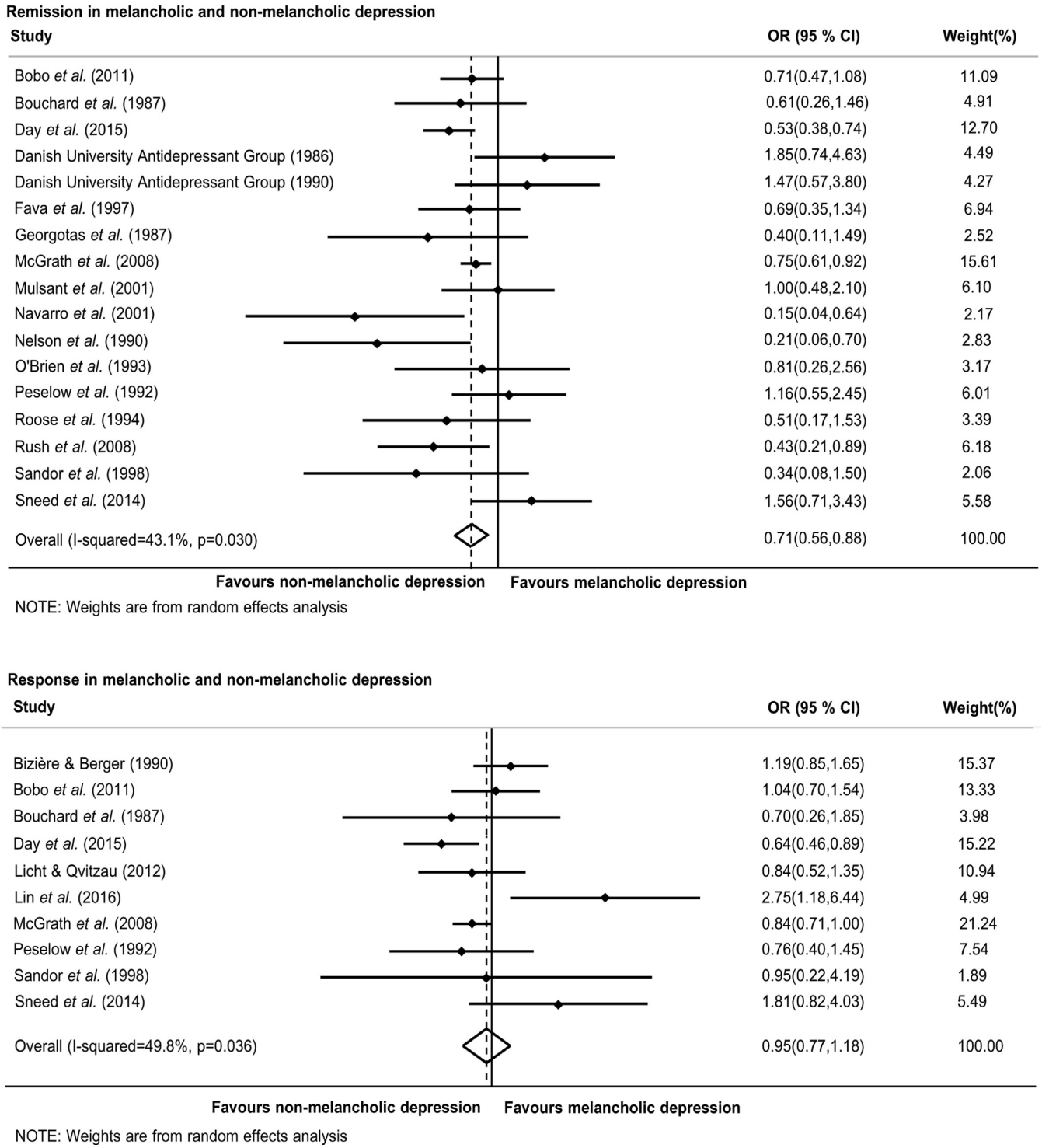

Fig.2. Forest plots for clinical remission and clinical response in trials comparing outcome to antidepressants in melancholic and non-melancholic depression. Note: weights are from random effects analysis.

characteristics of these studies are summarized in Table 1. Patients with melancholic features were less likely to show response to placebo than patients without melancholic status (OR 0.17, 95% CI 0.04 to 0.68) during a weighted mean follow-up period of 5.8 weeks. Heterogeneity was low (I^2 = 23.3%).

A total of 10 studies comprising 5,570 patients (1,801 presenting with melancholic features) were considered for the antidepressant response rates meta-analysis. Melancholic features were not associated with diminished likelihood of responding to antidepressant treatment (OR 0.95, 95% CI 0.77 to 1.18) during a weighted mean follow-up period of 10 weeks (Fig. 2). Heterogeneity was moderate (I^2 = 49.8%). Differences in the odds of response remained non-significant (OR 0.89, 95% CI 0.75 to 1.06) after reducing heterogeneity by the exclusion of the study by Lin et al. (2016) (I^2 = 27.8%; Q-Test p = 0.20).

Differences in baseline depressive symptom severity between melancholic and non-melancholic depression were not a statistically significant predictor of clinical response to antidepressants in the meta-regression analysis (regression coefficient 0.07, 95% CI −0.11 to 0.25,

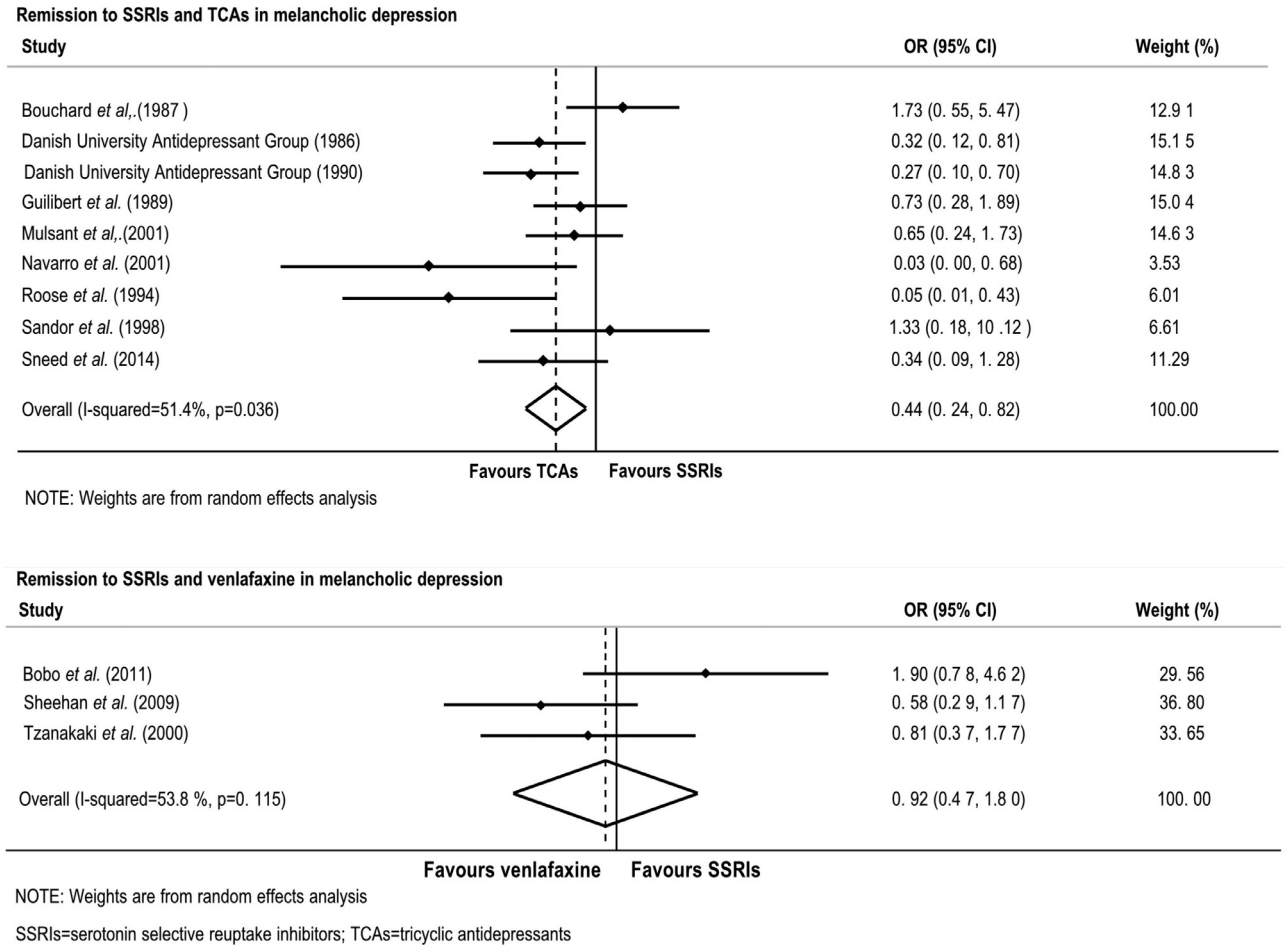

Fig.3. Forest plots for clinical remission in trials comparing outcome to antidepressants in melancholic depression.
Note: weights are from random effects analysis.
SSRIs = serotonin selective reuptake inhibitors; TCAs = tricyclic antidepressants.

$p = 0.39$).

3.3. Efficacy to different antidepressant agents in patients with melancholic features

Nine studies comprising 450 melancholic patients (223 receiving a SSRI agent and 227 receiving a TCA agent) compared the efficacy of SSRI and TCA drugs in the treatment of depressive patients with melancholic features. Melancholic patients receiving a SSRI agent were significantly less likely to achieve remission when compared to melancholic patients receiving a TCA agent (OR 0.44, 95% CI 0.24 to 0.82) during a weighted mean follow-up period of 7.2 weeks (Fig. 3). Heterogeneity was moderate ($I^2 = 51.4\%$). After removal of 2 outliers (Navarro et al., 2001; Roose et al., 1994) heterogeneity diminished significantly ($I^2 = 32.8\%$; Q-test $p = 0.18$) and differences remained significant (OR 0.55, 95% CI 0.33–0.93).

Three studies comprising 387 melancholic patients (195 receiving SSRI agent and 192 receiving a venlafaxine) compared the efficacy of SSRI agents and venlafaxine in melancholic patients. No significant differences between these two groups of antidepressant agents were found (OR 0.92, 95% CI 0.47 to 1.80) during a weighted mean follow-up period of 7.4 weeks (Fig. 3). Heterogeneity was moderate ($I^2 = 54\%$), however the null hypothesis of homogeneity was not rejected (Q-test $p = 0.12$).

3.4. Publication bias

Due to the nature of our analyses, publication bias assessment was only performed for studies evaluating comparative efficacy of SSRI and TCA or venlafaxine. We found evidence of publication bias in none of both analyses (Egger's test $p = 0.52$ and 0.09, respectively).

4. Discussion

This study meant to explore outcome-to-antidepressants profile in melancholia. In order to achieve a more valid pattern of results, we tried to conduct our study based on Consensus Guidelines for Evaluating Quantitative Reviews of Antidepressant Efficacy (Lieberman et al., 2005). However, some recommendations were not followed (e.g. minimum number of patients per arm) as a result of the scarcity of studies on treatment efficacy in melancholia. Additionally, further issues must be considered when interpreting the findings. First, a major concern is the variability of the criteria used to define melancholic depression across included studies, some based on cross-sectional symptomatology (i.e. RDC, DSM-III, DSM-IV), whereas other focused on psychomotor disturbances (i.e. CORE scale), and others, as DSM-III-R or Newcastle Index, also consider features of previous course, precipitating factors, and previous response to treatment. Thus, it can be seen how prevalence of melancholic depression varies within one study (Georgotas et al., 1987), or between different studies based on the same sample of patients (Arnow et al., 2015; Day et al., 2015), depending on the diagnostic criteria used. Furthermore, DSM criteria for melancholic

features have been criticized for overlapping with major depression criteria, providing improper differentiation of those melancholic and non-melancholic patients (Parker, 2011). Leaving aside controversies regarding what the best way to define melancholia is (Fink and Taylor, 2007; Parker and Paterson, 2014), it is important to note that the different criteria may contribute to the heterogeneity of the results on the efficacy of antidepressants. The use of a polydiagnostic approach has been proposed as a useful tool to control for the variance due to differences among diagnostic schedules (Maier et al., 1989). Second, most studies found greater baseline severity of depressive symptoms in melancholic patients, which tends to be solved statistically adjusting the outcome to antidepressants for this measure (Bobo et al., 2011; Day et al., 2015; Fava et al., 1997; Georgotas et al., 1987; McGrath et al., 2008; Nelson et al., 1990). Nevertheless, this procedure could lead to a misinterpretation of the results as a consequence of the structure of scales commonly used to assess symptomatic severity, such as the HDRS or the Montgomery-Asberg Depression Rating Scale (Cusin et al., 2010; Stewart et al., 2007). In fact, many of the items that contribute to depression severity represent melancholic features themselves (i.e. insomnia, decreased appetite and weight, as well as psychomotor disturbances) while reversed symptoms, more prevalent in non-melancholic depression (i.e. hypersomnia, increased appetite, weight gain) are under-represented in these scales. Therefore, adjusting for differences in baseline symptomatic severity is, at least in part, adjusting for those features that distinguish melancholic from non-melancholic depressions, with the consequent risk of nullifying valid results. Thus, it would be advisable for further studies to use scales with a balanced number of items of melancholic and non-melancholic depression or, alternatively, a sub-score of non-melancholic items to measure baseline symptomatic severity. Finally, to summarize the literature data, we grouped all antidepressants in the analysis by comparing remission/response in melancholic and non-melancholic depression, and then by drug class (i.e. SSRIs, TCAs) to compare the efficacy in melancholic depression. However, some data indicate that neither all SSRIs (Amsterdam, 1998) nor all TCAs (Anderson, 1998; Perry, 1996) could be equally effective in the treatment of melancholia. On the whole, there is an important source of heterogeneity in the individual studies included in our quantitative review, and the paucity of research on this topic prevents us from using more homogeneous study groups. Therefore, the results of our study, based on the literature available to date, should be considered preliminary and as a source of questions for future research, rather than as firm conclusions regarding this subject.

A first aim of this review was to compare outcomes to antidepressants and placebo between melancholic and non-melancholic depression. Regarding antidepressants, patients with melancholic depression showed lower odds of remission. As mentioned above, a greater severity of baseline depressive symptomatology could contribute to this finding, especially in studies with short follow-up periods. Eight of the studies included in the remission analysis (Bobo et al., 2011; Day et al., 2015; Fava et al., 1997; McGrath et al., 2008; O'Brien et al., 1993; Peselow et al., 1992; Sandor et al., 1998; Sneed et al., 2014) reported baseline severity of depressive symptomatology, with a mean difference of 3.55 (95% CI 2.36–4.74) points higher in melancholic depressions. However, the results of our meta-regression analyses suggest that these differences do not entirely account for the lower odds of remission in melancholic depression. An alternative explanation is that a longer time to remission with antidepressants may be an intrinsic feature of melancholic depression (Parker et al., 2013). A recent study using latent class analysis reported that depressions with melancholic features took significantly longer time to remission (11.3 weeks) than the other types of depression identified (6.6–8.6 weeks) even when influence of baseline symptoms was controlled (Bühler et al., 2014).

On the other hand, there was no difference in the odds of response to antidepressants between melancholic and non-melancholic depressions. Differences in our results between response and remission to antidepressants might be partly explained by the lesser influence of baseline severity on chances of achieving response, as it is defined as a proportional change in this measure (Tedlow et al., 1998). Likewise, even when melancholic depression takes longer until remission, the mean time of trials (usually 5–8 weeks) may be sufficient for a 50% reduction in baseline depressive symptomatology, thus equating the odds of response to antidepressants between both depression subtypes. It is worth noting that, unlike the case of response to antidepressants, our results showed that there is a lower response to placebo in melancholic depression. This result agrees with 2 observational studies reporting lower response rates to 1–2 weeks of hospitalization without active-drug treatment after controlling for baseline severity of depressive symptoms in melancholic compared to non-melancholic patients (Maier et al., 1988; Nelson et al., 1990). It has been proposed that the extent to which antidepressants outperform placebo (which controls for non-pharmacological aspects) can be used to index the “true” pharmacological effect of these medications in clinical settings (Fournier et al., 2010). Unfortunately, almost none of the original studies include a placebo arm, which prevents us from making a more accurate discernment of the effect of the active drug. A notable exception is the study by Peselow et al. (1992), in which patients with melancholic and non-melancholic depression had relatively similar rates of response to antidepressants (54% and 61%, respectively), although they differed in response to placebo (23% and 43%, respectively). Similarly, in another study conducted on a mixed sample of unipolar and bipolar II patients (Heiligenstein et al., 1994), response rates were significantly higher in the antidepressant arm than in the placebo arm in depressed patients with melancholic features (71% and 30%, respectively) but not in patients without those features (50% and 60%, respectively). These results, together with those in our review, provide preliminary evidence that the "true" effect of antidepressants may be greater in patients with melancholic depression. Likewise, it suggests the need to evaluate the differential rate of response to active drug/placebo rather than the raw score of response to antidepressants in studies comparing melancholic and non-melancholic depression. Again, these studies should employ an adequate measure of baseline symptomatology in order to rule out that severity instead of depression subtypes, accounted for the differential rate of response to antidepressant-placebo (Fournier et al., 2010; Kirsch et al., 2008). In any case, our findings might suggest that the variability of results among RCTs evaluating the efficacy of antidepressants in MDD may depend, at least in part, of the proportion of patients with melancholic features included. If this were the case, reporting the proportion of patients with melancholic features included in RCTs on MDD could improve the comparability of the results between studies.

The second aim of this review was to compare the odds of remission to different types of antidepressants in melancholic depression. This analysis could be performed only by comparing SSRIs vs. TCAs and SSRIs vs. venlafaxine, as there were not enough studies to compare other antidepressants. First, melancholic patients treated with SSRIs had significantly lower odds of achieving remission than patients treated with TCAs. Since remission was used as the main outcome, it is unlikely that this result could be attributed to the non-specific symptom reduction of TCAs due to anticholinergic and antihistaminic side effects. This result agrees with those of early studies (Anderson, 1998; Perry, 1996) and suggests that melancholic MDD patients may benefit more from treatment with TCAs than with SSRIs. Despite this general pattern, it is important to re-emphasize that our analysis does not allow us to distinguish efficacy among different TCAs. Some authors have suggested that among TCAs, the tertiary amines could be more effective than the secondary amines for melancholic MDD (Anderson, 1998; Perry, 1996) which could be the focus of future studies. In contrast to TCAs, there were no differences in the odds of remission between SSRI and venlafaxine. It is important to note that this result is based on the analysis of only 3 studies, in one of which venlafaxine was used

concomitantly with mirtazapine (Bobo et al., 2011). Nevertheless, our results are consistent with those of the second step of STAR-D study, in which melancholic features were not associated with differences in remission between patients randomized to sertraline or venlafaxine-extended release (Rush et al., 2008), and with those of another recent large study in which melancholia was not a significant differential moderator of remission to venlafaxine-extended release (relatively low dose), escitalopram, or sertraline in patients with MDD (Day et al., 2015).

In summary, there is a relative paucity of studies that have focused on melancholia despite several decades of research in the antidepressant treatment of MDD. The preliminary results of our review suggest that melancholic unipolar depression could distinguish a subtype of MDD with a differential pattern of outcome to antidepressants: lower rate of remission and greater rate of differential response to active drug/placebo. Moreover, our preliminary results show that not all antidepressants may be equally effective for this depressive subtype, with TCAs showing higher efficacy than SSRIs. Therefore, melancholia appears as an interesting target to improve our knowledge about personalized medicine of MDD. Future studies on outcome-to-treatment between melancholic and non-melancholic depression may not be restricted to antidepressants but extended to other drugs commonly used in the treatment of MDD such as mood stabilizers and antipsychotics.

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Conflict of interest

None.

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