Review

Antidepressant responses in direct comparisons of melancholic and non-melancholic depression

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Abstract

Background: Efforts to develop less heterogeneous, more clinically useful diagnostic categories for depressive disorders include renewed interest in the concept of melancholia (Mel). However, clinical or biological differentiation of Mel from other (nonMel) episodes of depression has been questioned, and it remains unclear whether pharmacological responses proposed to be characteristic of Mel are supported by available research.

Methods: We carried out a systematic review seeking treatment trials reports comparing Mel and nonMel depressed subjects for meta-analyses of their differences in responses (a) to antidepressants overall, (b) to tricyclic (TCAs) or serotonin-enhancing agents (serotonin reuptake inhibitors/serotonin–norepinephrine reuptake inhibitors) and (c) with placebo treatment.

Results: We identified 25 trials in 16 reports comparing 2597 Mel with 5016 nonMel subjects. Overall, responses to antidepressant treatment did not differ between Mel (39.4%) and nonMel (42.2%) subjects. However, all subjects responded better to TCAs (50.6%) than SRIs (30.0%; $p<0.0001$). Mel subjects also responded less well with placebo, but also were significantly more severely depressed at intake.

Conclusions: Antidepressant responses were similar in Mel and nonMel depressed patients. Mel subjects responded 25% less with placebo but were more severely depressed initially, and there was preferential response to TCAs in both Mel and nonMel subjects. The findings provide little support for proposed differences in responses to particular treatments among Mel versus nonMel depressed patients, and underscore the need to match for illness severity in making such comparisons.

Keywords

Antidepressants, melancholia, serotonin-reuptake inhibitors, tricyclic antidepressants

Introduction

The current concept of major depressive disorder is complex and clinically heterogeneous, causing difficulties for biomedical research and limiting its clinical value for predicting future morbidity and treatment responses (Baldessarini, 2013; Sani et al., 2020; Shorter, 1997). Various proposals for defining subtypes of depressive disorders that might provide greater coherence, reliability and value for research and clinical needs have been advanced. One such subtype is the ancient concept of melancholic depression (Jackson, 1986; Sani et al., 2020; Shorter, 1997; Taylor and Fink, 2006). Over the centuries, the concept of melancholia evolved to have a strong association with severe depressive mental illness marked by changes in mood, cognition, autonomic functions and behaviour, notably including psychomotor retardation (Parker and Hadzi-Pavlovic, 1996; Paykel, 2008). Prior to the introduction of the concept of major depressive disorder with the DSM-III in 1980, melancholia represented the widely accepted concept of clinically important depressive illness (Hamilton, 1960; Shorter, 1997). Melancholia as a clinical concept of a particular type of depression that can occur in either major depressive disorder or depressive phases of bipolar disorder continues in DSM-5, as 'melancholic features' (APA, 2013) and is a category in ICD-11 (6A80.3: Current depressive episode with melancholia; WHO, 2018).

Melancholic depression is widely considered to be a relatively severe clinical expression of mood disorder and possibly a specific type of depression with an important 'endogenous' quality or relative independence of external stressors, possibly with a particular pathophysiology arising from genetic predisposition, and association with biological signs such as altered appetite, libido, motor activity and sleep, including circadian variations (Parker et al., 2010; Paykel, 2008; Taylor and Fink, 2006). Particular pathophysiological abnormalities proposed to be characteristic of melancholia include neuroendocrine functions (Arana et al., 1985; Carroll, 1985; Christiaens and Maes, 1992; Gitlin and Gerner, 1986; Orsel et al., 2010; Rush et al., 1997),

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circadian activity and other biorhythms (Armitage, 2007; Baglioni et al., 2016; Salvatore et al., 2012) and immunological responses (Simeonova et al., 2020; Zhao and Liu, 2019). However, a growing number of studies have questioned proposals about the pathophysiology of melancholic depression (Arana et al., 1985; Banki et al., 1986; Christiaens and Maes, 1992; Hadzi-Pavlovic and Boyce, 2012; Myers, 1988; Stetler et al., 2011; Tondo et al., 2020).

There have also been claims of particular responses to psychotropic drug treatments associated with melancholia (Brown, 2007; Georgotas et al., 1987; Perry, 1996; Peselow et al., 1992). For example, melancholic (Mel) patients may be less likely to respond to treatment with placebo (Fairchild et al., 1986) or with psychotherapy (Boschloo et al., 2019) than those with non-melancholic (nonMel) depression, and may respond relatively favourably to electroconvulsive treatment (Pinna et al., 2018), tricyclic antidepressants (TCA) and perhaps monoamine oxidase (MAO) inhibitors and combinations of antidepressants (Bobo et al., 2011; Dally and Rohd, 1961; Liebowitz et al., 1988; McGrath et al., 1984; Rush et al., 2011) more than to serotonin-enhancing antidepressants, including selective serotonin reuptake inhibitors (SRIs) and serotonin–norepinephrine reuptake inhibitors (SNRIs) with effects on neuronal reuptake of both serotonin and norepinephrine (Carroll, 2012; Parker et al., 2010; Taylor and Fink, 2006).

A major remaining question is whether proposed differences in responses to particular types of antidepressants between Mel and nonMel depressed patients is supported by available research. Among relevant recent findings, McGrath et al. (2008) found little difference in rates of clinical response or remission in DSM-IV Mel versus nonMel major depression subjects treated for 12 weeks with the SRI citalopram. Similarly, Bobo et al. (2011) found little difference in responses to single or combined antidepressants among DSM-IV Mel patients.

The preceding considerations raise questions about the clinical, research and theoretical value of the melancholia concept and, in particular, call for critical consideration of proposed differences in responses to specific treatments by people with Mel versus nonMel depression. To pursue this question, we made a systematic effort to identify trials of antidepressants involving direct comparisons of major depression patients with versus without melancholic features, and considered overall response to antidepressants, possible differences in responses with placebo and whether TCAs and SRI-like agents exerted differential effects in these diagnostic subgroups.

Methods

Search strategy

We searched for reports of treatment trials comparing medicines with antidepressant effects used to treat acute episodes of depression, in which Mel versus nonMel subjects were compared in the same trials. Systematic computerised searches of Medline and Cochrane Library research literature databases used the following search-terms: (‘melancholia’ or ‘melancholic depression’ [Text Word] OR ‘endogenous depression’ [All Fields]) AND (‘antidepressive agents’ [Pharmacological Action] OR ‘antidepressive agents’ [MeSH Terms] OR (‘antidepressive’ [All Fields] AND ‘agents’ [All Fields]) OR ‘antidepressive agents’ [All Fields] OR ‘antidepressant’ [All Fields]). In addition, we hand searched published reviews and research reports for additional relevant citations. Searching was limited to peer-reviewed reports of both randomised controlled trials (RCTs) and non-RCTs reported between 1970 and January 2020 in any language, with an English or Spanish summary.

Eligibility criteria

We included reports of double- or single-blind and open trials involving randomisation or non-randomised assignment to pharmacological treatment for adults in a major depressive episode with (Mel) or without (nonMel) melancholic features, based on diagnostic criteria provided in the DSM-III to DSM-5 (APA, 1980, 2013), or the International Classification of Diseases (ICD)-9 or -10 (WHO, 2018). We also included diagnoses of ‘endogenous depression’ as defined by Spitzer et al. (1978) in the Research Diagnostic Criteria and by the Newcastle Endogenous Depression Diagnostic Index (Davidson et al., 1984), assuming that ‘endogenous’ and ‘melancholic’ referred to the same or closely similar disorders (Parker, 2020; Stein et al., 2007). Drug doses could be fixed or flexible; their types were categorised as recommended by the Food and Drug Administration (2020). We excluded reports involving special populations, such as juveniles, or people with major general medical or neurological illnesses. We defined treatment of acute depression as trials of up to 16 weeks’ duration.

Outcome measures

Response in treatment trials for major depressive episodes was considered as improvement in depressive symptoms between trial intake and end point, as defined in each report, typically basing ‘response’ on ⩾50% reduction of scores on established rating scales, including the Hamilton Depression Rating Scale (HDRS; Hamilton, 1960) and the Montgomery–Åsberg Depression Rating Scale (MADRS; Montgomery and Åsberg, 1979). For trials reporting only percentage change in depression ratings (Bobo et al., 2011; Mallinckrodt et al., 2005; Sneed et al., 2014; Uher et al., 2011), we used these percentages to estimate numbers of subjects responding, again comparing Mel and nonMel subjects treated in the same trials, as well as excluding such trials in subsequent sensitivity analyses.

Data analysis

Data were tabulated and pooled, usually as means with 95% confidence intervals (CIs). We employed random-effects meta-analysis to compare responses between major depression subjects with (Mel) versus without (nonMel) melancholic features, and reported resulting pooled odds ratios (ORs) with their CIs. Factors of interest were tested for association with response rates by multivariate linear regression modelling. Statistical software included StatView v5 (SAS Institute, Cary, NC) for spreadsheets, and STATA v13 (StataCorp, College Station, TX) for analyses.

Results

Study and subject characteristics

A systematic computerised search for reports of controlled trials with comparisons of patients diagnosed with major depression

with and without melancholic features yielded 16 reports from 1983 to 2020, with a total of 25 trials for analysis. The search process involved is summarised in Appendix Figure A1, and salient trial characteristics are provided in Table 1. We considered direct comparisons of Mel versus nonMel subjects for responses to any antidepressant as well as to TCAs or to SRIs pooled with trials of agents that inhibit neuronal reuptake of both serotonin and norepinephrine (SNRIs).

These 25 trials yielded data for 2597 Mel and 5016 nonMel subjects (N=7613). Trials lasted an average of 8.36 (95% CI 7.09–9.63) weeks, and involved 8.50 (95% CI 2.95–14.0) collaborating sites/study. Female subjects represented 61.2% (95% CI 57.3–65.1%) of all subjects. Initial depression severity ratings based on the percentage of the maximum attainable score with the rating scale employed averaged 14% higher among Mel (49.8; 95% CI 45.4–54.1) than nonMel (43.7; 95% CI 40.4–47.0) subjects (t=2.50, p=0.01).

Response rates in Mel versus nonMel subjects

We first compared responses to all types of drugs used to treat depression in all 25 trials with comparisons of Mel versus nonMel depressed subjects given the same treatment. The overall proportion of subjects responding to antidepressant treatment was similar among Mel (39.4%; 95% CI 37.5–41.3%) and nonMel (42.2%; 95% CI 40.9–43.6) subjects (χ^2=5.59, p=0.02). Random-effects meta-analysis indicated no significant overall difference between Mel and nonMel subjects in responses to various agents with antidepressant effects (Figure 1). The overall meta-analytically pooled OR and its 95% CI was 0.95 (0.78–1.15; z-score=0.55, p=0.58). Moreover, only 3/25 comparisons found a significant difference in treatment response between Mel and nonMel subjects (one trial each found: Mel>nonMel response with nortriptyline and with sertraline, and Mel<nonMel with various antidepressants; Figure 1).

Sensitivity analyses

We also considered only 21 randomised trials by omitting the four that did not employ randomisation (Bobo et al., 2011; Gili et al., 2012; McGrath et al., 2008; Uher et al., 2011 (two trials)). They yielded similar non-significant meta-analytic results (OR=1.06; 95% CI 0.84–1.37; z=0.57, p=0.57) to the results with all 25 trials included (Figure 1). In addition, omitting seven trials based on crude estimates of percentage responding from percentage improvement (Bobo et al., 2011 (two trials); Mallinckrodt et al., 2005; Sneed et al., 2014 (two trials); Uher et al., 2011 (two trials)) also yielded non-significant differences in responses between Mel and nonMel subjects (OR=0.93; 95% CI 0.70–1.24; z=0.48, p=0.63), further supporting the conclusion that Mel and nonMel subjects experienced similar treatment responses.

Types of antidepressant treatments

We also carried out meta-analytic comparisons of Mel versus nonMel subjects to various types of treatments for depression, as listed in Table 1. There were eight trials with TCAs (DUAG, 1986, 1990; Joyce et al., 2003; Marcus and Mendels, 1996; Roose et al., 1994; Sneed et al., 2014; Stewart et al., 1983; Uher et al., 2011), and 11 with SRIs/SNRIs (Bobo et al., 2011; DUAG, 1986, 1990; Joyce et al., 2003; Mallinckrodt et al., 2005; Marcus and Mendels, 1996; McGrath et al., 2008; Roose et al., 1994; Sneed et al., 2014; Türkçapar et al., 1998; Uher et al., 2011). There were 11 with SRIs/SNRIs (Bobo et al., 2011; DUAG, 1986, 1990; Joyce et al., 2003; Mallinckrodt et al., 2005; Marcus and Mendels, 1996; McGrath et al., 2008; Roose et al., 1994; Sneed et al., 2014; Türkçapar et al., 1998; Uher et al., 2011). Finally, there were six trials with other agents (lamotrigine, mixed antidepressants, moclobemide, nefazodone). With none of these types of antidepressant treatments were there significant differences between Mel and nonMel subjects: (a) TCAs and SRIs/SNRIs (19 trials, p=0.75); (b) TCAs alone (8 trials, p=0.40); (c) SRIs/SNRIs alone (11 trials, p=0.40); and (d) other agents (6 trials, p=0.49; Table 2).

Responses with randomised placebo treatment

Five of the identified trials included placebo treatment in comparisons of Mel versus nonMel subjects (Mallinckrodt et al., 2005; Marcus and Mendels, 1996; Peselow et al., 1992; Peters et al., 2018; Stewart et al., 1983). Responses with placebo among Mel subjects averaged 40.1% (95% CI 36.6–43.7) versus 53.2% (95% CI 48.6–57.8) among nonMel subjects (for pooled ratios of responders/subjects, χ^2=20.1, p<0.001). Also, by random-effects meta-analysis, responses with placebo treatment were significantly greater among nonMel subjects (OR=0.50; 95% CI 0.39–0.64; z=5.49, p<0.001; Table 2), consistent with the already noted greater severity of depressive symptoms in the Mel subjects.

Factors associated with antidepressant responses

We evaluated factors of interest for their potential association with overall response rates in all 25 trials using multivariate linear regression modelling. The following factors were *not* significantly associated with response rate: (a) reporting year (β=−0.0003, r=0.008, p=0.96), (b) subject count (β=−0.007, r=0.135, p=0.35), (c) proportion of women subjects (β=0.137, r=0.060, p=0.68), (d) initial depression severity (β=−0.246, r=−0.095, p=0.67), (e) number of sites/trial (β=−0.486, r=0.274, p=0.13) and (f) trial duration (β=−1.19, r=0.187, p=0.19).

Improvement in depression ratings

In addition to reported or estimated response rates, 12 trials reported percentage improvement in symptom ratings of depression (Table 1). They also yielded no overall difference in percentage improvement with all antidepressant treatments: Mel (50.9%; 95% CI 45.6–56.2%) versus nonMel (49.5%; 95% CI 44.6–54.4%) subjects (t=0.65, p=0.53). Moreover, there was no difference in percentage improvement with TCAs in four trials: Mel (56.8%; 95% CI 43.7–69.9%) versus nonMel (51.9%; 95% CI 41.0–62.8%) subjects (t=1.25, p=0.30), nor to SRIs/SNRIs in four others: Mel (50.2%; 95% CI 35.7–64.7) versus nonMel (54.0%; 95% CI 42.0–66.0) subjects (t=0.92, p=0.42). These comparisons in four trials of each treatment type also indicated

Table 1. Characteristics of treatment trials for melancholic (Mel) and non-melancholic (nonMel) major depression.

Trial (year)	Treatment	Drug type	Random	Blinded	Duration (weeks)	Women (%)	Initial severity (% of scale max)		Subjects (*n*)		Treatment responders (*n*)		Improvement (%)	
							Mel	nonMel	Mel	nonMel	Mel	nonMel	Mel	nonMel
Stewart et al. (1983)	Desipramine	TCA	Yes	Yes	6	51	–	–	16	29	11	16	–	–
DUAG (1986)	Clomipramine	TCA	Yes	Yes	5	70	–	–	40	17	25	9	–	–
DUAG (1986)	Citalopram	SRI	Yes	Yes	5	70	–	–	45	12	15	1	–	–
Georgotas et al. (1987)	Antidepressants	ADs	Yes	Yes	7	62	–	–	17	25	10	17	–	–
DUAG (1990)	Clomipramine	TCA	Yes	Yes	6	66	–	–	36	10	20	6	–	–
DUAG (1990)	Paroxetine	SRI	Yes	Yes	6	66	–	–	40	16	10	2	–	–
Peselow et al. (1992)	Antidepressants	ADs	Yes	Yes	4	–	55.2	48.4	76	76	19	2	46.4	46.7
Roose et al. (1994)	Nortriptyline	TCA	Yes	Yes	6	42	–	–	24	10	20	8	–	–
Roose et al. (1994)	Fluoxetine	SRI	Yes	Yes	6	42	–	–	10	8	1	4	–	–
Marcus and Mendels (1996)	Imipramine	TCA	Yes	Yes	7	62	51.0	48.0	96	70	41	36	47.0	50.0
Marcus and Mendels (1996)	Nefazodone	Atypical	Yes	Yes	7	64	51.0	48.0	129	118	75	81	50.1	38.3
Joyce et al. (2003)	Nortriptyline	TCA	Yes	No	6	57	–	–	51	43	22	14	64.0	62.0
Joyce et al. (2003)	Fluoxetine	SRI	Yes	No	6	57	–	–	62	35	31	21	62.0	64.0
Mallinckrodt et al. (2005)	Duloxetine	SNRI	Yes	Yes	8	70	44.6	41.0	759	379	305	152	40.2	40.2
McGrath et al. (2008)	Citalopram	SRI	No	No	12	64	52.0	41.0	675	2200	157	634	–	–
Türkçapar et al. (2008)	Moclobemide	MAOI	Yes	No	13	63	43.8	43.8	12	15	6	11	–	–
Türkçapar et al. (2008)	Sertraline	SRI	Yes	No	13	63	47.0	47.0	17	12	14	5	–	–
Bobo et al. (2011)	Venlafaxine+mirtazapine	SNRI+atypical	Yes	No	12	74	–	–	23	77	11	35	46.0	45.0
Bobo et al. (2011)	Escitalopram	SRI	Yes	No	12	74	–	–	83	23	36	12	43.0	52.0
Uher et al. (2011)	Nortriptyline	TCA	No	No	12	53	59.5	46.3	32	269	17	129	53.0	48.0
Uher et al. (2011)	Escitalopram	SRI	No	No	12	53	59.5	46.3	33	252	14	136	43.0	54.0
Gili et al. (2012)	Antidepressants	ADs	No	No	6	–	–	–	237	1218	118	733	–	–
Sneed et al. (2014)	Nortriptyline	TCA	Yes	Yes	12	55	41.7	35.8	20	32	13	15	63.2	47.4
Sneed et al. (2014)	Sertraline	SRI	Yes	Yes	12	60	42.0	35.1	18	40	8	20	52.9	45.9
Peters et al. (2018)	Lamotrigine	MS	Yes	Yes	8	70	–	–	46	30	25	20	–	–
Totals, means (95% CI)	–	**11 SRI/SNRI 8 TCA 5 other**	**21/25**	**15/25**	**8.36 (7.09–9.63)**	**61.2 (57.3–65.1)**	**49.8 (45.4–54.1)**	**43.7 (40.4–47.0)**	**2597**	**5016**	**1024**	**2119**	**50.9 (45.6–56.2)**	**49.5 (44.6–54.4)**

Of the 25 trials in 16 reports comparing melancholic (Mel) versus nonmelancholic (nonMel) subjects, nine involved two treatments. There were totals of 2579 Mel and 5016 nonMel subjects (N=7613). Mel subjects were 14% more severely depressed than nonMel subjects at intake: initial depression ratings were 49.8 (95% CI 45.1–54.1) with Mel and 43.7 (95% CI 40.4–47.0) with nonMel (t=2.50, p=0.01). Crude overall response rates: Mel (1024/2597=39.4%; 95% CI 37.5–41.3%); nonMel (2119/5016=42.2%; 95% CI 40.9–43.6); χ^2=5.59, p=0.02.

ADs: antidepressants; SNRI: serotonin–norepinephrine reuptake inhibitor; SRI: serotonin reuptake inhibitor; TCA: tricyclic antidepressant; CI: confidence interval.

no difference in responses of Mel subjects to the main antidepressant types (TCAs: 56.8%; 95% CI 43.7–69.9% vs. SRIs/SNRIs: 50.2%; 95% CI 35.7–64.7%; t=1.07, p=0.16), nor among nonMel subjects (TCAs: 51.9%; 95% CI 41.0–62.8% vs. SRIs: 54.9%; 95% CI 42.0–66.0%; t=0.41; p=0.65).

Discussion

The present meta-analytic review was based on 25 treatment trials from 16 reports comparing different types of antidepressant treatments to treat 7613 patient subjects with versus without melancholic features in a current major depressive episode. The findings indicate a lack of significant overall differences in responses to various antidepressant treatments between Mel and nonMel subjects (Figure 1 and Table 2). This conclusion based on meta-analysis of responder rates was sustained by analysis of outcomes based on improvement in depressive symptom ratings. We found no factors of interest that were associated significantly with response rates, including study size and duration, year of reporting and, notably, initial symptom severity (which was greater with Mel).

There was evidence of a greater response to TCAs than to serotonin-potentiating antidepressants (SRIs/SNRIs) overall, or among Mel or nonMel subjects considered separately. These findings may support the view that TCAs are superior in efficacy to many modern antidepressants, although the evidence on this question is conflicting (Anderson, 1998; Baldessarini, 2013; Undurraga and Baldessarini, 2012, 2017). Also, as expected, Mel subjects responded significantly less well during treatment with placebo than did nonMel subjects, possibly because of the greater initial severity of depressive symptoms in Mel subjects.

The present findings are in accordance with the conclusion that hypothesised treatment response differences between Mel and nonMel depressed patients have little support by treatment trials involving direct comparisons of both types. They add to other findings tending to question the potential clinical value of the diagnostic concept of melancholia. Previous studies have reported limited demographic, clinical, psychobiological or therapeutic differences in Mel versus nonMel patients (Arana et al., 1985; Christiaens and Maes, 1992; Hadzi-Pavlovic and Boyce, 2012; Myers, 1988; Tondo et al., 2020). Overall, these previous reports and the present findings provide limited support for differentiation by treatment response of major depression patients based on the presence of melancholic features, such as represented by the DSM-5 melancholic specifier.

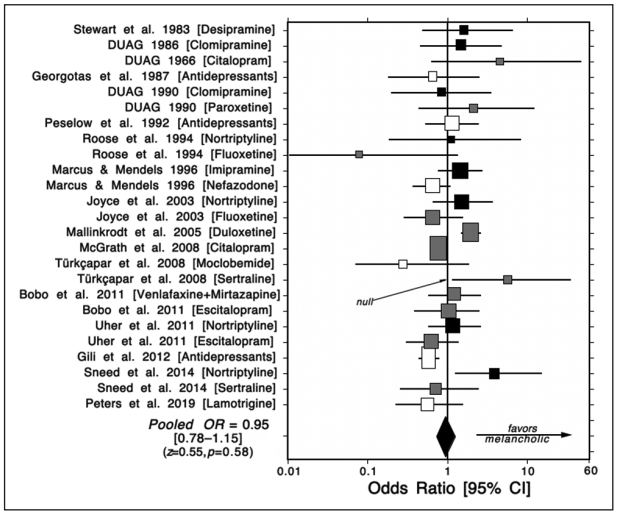

Figure 1. Meta-analysis of direct comparisons of 25 trials of treatments for melancholic versus non-melancholic subjects in an acute major depressive episode. Drug types are: tricyclic antidepressants (TCAs; black squares), serotonin or serotonin–norepinephrine reuptake inhibitors (SRIs/SNRIs; grey squares) or others (various antidepressants, lamotrigine or moclobemide; white squares). There is no overall difference in response to the various antidepressant or mood-altering agents between the diagnostic subgroups (pooled OR=0.95; 95% CI 0.78–1.15; z-score=0.55, p=0.58). Heterogeneity is moderate (I^2=37.6%). OR: odds ratio; CI: confidence interval.

Study limitations

This study has important limitations. It is based on relatively few direct comparisons of treatment responses in Mel and nonMel depressed subjects, and with varied criteria for the presence of melancholic features. Indeed, some criteria may well overlap and fail to provide sharp distinctions of Mel from nonMel subjects (Parker, 2020; Parker et al., 2010; Taylor and Fink, 2006). In

Table 2. Results of meta-analyses of direct comparisons of antidepressant treatment responses in Mel versus nonMel depressed subjects.

Trials (n)	Treatment	Responder rate (%) (95% CI)		Pooled OR (95% CI)	z-Score	p-Value
		Mel	NonMel			
25	All agents	39.4 (37.5–41.3)	42.2 (40.9–43.6)	0.95 (0.78–1.15)	0.55	0.58
19	TCAs and SRIs/SNRIs	50.6 (41.4–60.3)	45.8 (37.7–53.8)	0.97 (0.78–1.19)	0.32	0.75
8	TCAs	53.6 (48.0–59.3)	48.5 (44.0–53.1)	1.16 (0.83–1.62)	0.85	0.40
11	SRIs/SNRIs	34.1 (31.9–36.4)	33.5 (31.8–35.2)	0.89 (0.67–1.17)	0.84	0.40
6	Other agents	48.9 (44.5–53.3)	58.3 (55.7–60.8)	0.82 (0.46–1.45)	0.69	0.49
5	Placebo	40.1 (36.6–43.7)	53.2 (48.6–57.8)	0.50 (0.39–0.64)	5.49	<0.001

Five trials reported responses on subjects randomised to placebo treatment (Mallinckrodt et al., 2005; Marcus and Mendels, 1996; Peselow et al., 1992; Peters et al., 2018; Stewart et al., 1983). Responses were greater to TCAs versus SRIs/SNRIs among Mel (53.6% vs. 34.1%; χ^2=108) and nonMel subjects (48.5% vs. 33.5%; χ^2=41.2), as well as overall (50.6%; 95% CI 47.0–54.1% vs. 30.0%; 95% CI 28.8–31.2%); χ^2=132; all $p<0.0001$).

Mel: melancholic; NonMel: nonmelancholic; SNRI: serotonin–norepinephrine reuptake inhibitor; SRI: serotonin reuptake inhibitor; TCA: tricyclic antidepressant; CI: confidence interval.

addition, some trials involved non-randomised treatment assignments and reported changes in depression ratings rather than the percentage of subjects who responded to treatment, although both types of outcome measures yielded similar findings. Importantly, Mel and nonMel subjects were not matched for initial depression severity, which was greater with Mel. Nevertheless, the findings are quite consistent based on multiple methods of comparison and analysis.

Conclusion

The present findings indicate that depressed patients with (Mel) and without (nonMel) melancholic features differed very little in their responses to a variety of antidepressants. Mel subjects responded somewhat better to TCAs than to SRIs/SNRIs, but similar differences were found among nonMel subjects and overall, suggesting that TCAs might have somewhat superior efficacy. Responses to placebo were also greater among nonMel than Mel subjects, as expected, but Mel subjects were significantly more severely depressed at intake. Finally, the present findings add to the growing impression that the value of the concept of a melancholic subtype of major depression may be quite limited.

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Supplemental material

Supplemental material for this article is available online.

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