Response of Depression to Electroconvulsive Therapy: A Meta-Analysis of Clinical Predictors

Aazaz U. Haq, MD[a,b]; Adam F. Sitzmann, BS[c]; Mona L. Goldman, PhD[a]; Daniel F. Maixner, MD, MS[a]; and Brian J. Mickey, MD, PhD[a,*]

ABSTRACT

Objective: Roughly one-third of individuals with depression do not respond to electroconvulsive therapy (ECT). Reliable predictors of ECT response would be useful for patient selection, but have not been demonstrated definitively. We used meta-analysis to measure effect sizes for a series of clinical predictors of ECT response in depression.

Data Sources: PubMed was searched systematically to identify studies published after 1980 that tested at least 1 clinical predictor of response to ECT.

Study Selection: Of 51 studies identified, 32 were compatible with meta-analysis.

Data Extraction: The weighted mean odds ratio (OR) or standardized mean difference (SMD) was computed for each of 10 clinical predictors, based on dichotomous outcomes (responder vs nonresponder). Statistical analyses examined robustness, bias, and heterogeneity.

Results: Shorter depressive episode duration predicted higher ECT response rate (SMD = –0.37, 7 studies, 702 subjects, $P = 4 \times 10^{-6}$). History of medication failure in the current episode was also a robust predictor: response rates were 58% and 70%, respectively, for those with and without medication failure (OR = 0.56, 11 studies, 1,175 subjects, $P = 1 \times 10^{-5}$). Greater age and psychotic features were weakly associated with higher ECT response rates, but heterogeneity was notable. Bipolar diagnosis, sex, age at onset, and number of previous episodes were not significant predictors. Analyses of symptom severity and melancholic features were inconclusive due to study heterogeneity.

Conclusions: Longer depressive episodes and medication failure at baseline are robust predictors of poor response to ECT, with effect sizes that are modest but clinically relevant. Patient characteristics used traditionally such as age, psychosis, and melancholic features are less likely to be clinically useful. More robust clinical and biological predictors are needed for management of depressed patients considering ECT.

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[a]Department of Psychiatry, University of Michigan, Ann Arbor
[b]Department of Psychiatry & Biobehavioral Sciences, University of California, Los Angeles (current affiliation)
[c]College of Literature, Science, & the Arts, University of Michigan, Ann Arbor
**Corresponding author:* Brian J. Mickey, MD, PhD, Department of Psychiatry, University of Utah School of Medicine, 501 Chipeta Way, Salt Lake City, UT 84108 (brian.mickey@utah.edu).

Personalized medicine is the tailoring of treatment based on an individual's characteristics. For patients with depression, clinicians strive to match an individual to one or more specific treatments, selected from an increasing variety of psychosocial interventions, medications, and brain stimulation therapies. Treatment-matching is especially important for electroconvulsive therapy (ECT). ECT is considered among the most effective treatments for depressive illness, but it is also associated with considerable costs and side effects.[1] Decades of clinical experience with ECT have led to its use for more severe and treatment-resistant forms of depressive illness, as reflected in current treatment guidelines,[2,3] but those guidelines are not based on evidence that more severe or treatment-resistant illness responds better to ECT. In fact, clinical response varies widely even among those with more severe or treatment-resistant disease.

Predictors of treatment response may be categorized into "clinical" predictors that are readily available from a clinical interview and examination, and "biological" predictors that require additional testing (biomarkers). While there is increasing interest in biological predictors of treatment response, a biological predictor will be clinically useful only if it adds predictive power above and beyond that of clinical predictors. Therefore, a fundamental question is whether clinical variables reliably predict response to ECT. Despite dozens of published studies of clinical predictors of ECT response, strong and consistent predictors have not yet emerged. For example, among the 5 largest studies of psychotic features, 2 reported that psychosis predicted better ECT response[4,5] and 3 found no significant association.[6–8] In a narrative review, Abrams[9(p49)] highlighted "endogenous or melancholic syndromes" as ECT responsive, but he concluded that for the majority of patients who do not neatly fit those categories "there is little help to be derived from the predictors." More recently, Kellner and colleagues[10] concurred that no useful clinical predictors have been demonstrated, although they hypothesized that greater symptom severity, family history of depression, and an episodic pattern of depression might predict better response to ECT. Thus, experienced clinicians have adopted strategies for recognizing clinical features that may be favorable for ECT, but published studies often appear inconsistent, so the true predictive power of those clinical features remains unclear.

The apparent inconsistency across studies may arise because individual studies are inadequately powered to detect the true effect size or because true heterogeneity exists between studies. Meta-analysis provides a method to compare effect sizes across studies and assess for heterogeneity. It also allows estimation of a pooled effect size, which can be expressed in clinically relevant terms. Our goal was to use meta-analysis to determine effect sizes for an array of clinical predictors of response to ECT.

Clinical Points

- Although electroconvulsive therapy (ECT) is the most effective treatment for depression, about one-third of patients do not respond. Predicting who is likely to respond is a clinical challenge.
- The patients most likely to respond to ECT are those with depressive episode durations of less than about 1 year and those without a failed adequate antidepressant medication trial in the current episode.

METHOD

Literature Search and Study Selection

We searched PubMed with combinations of terms including *electroconvulsive therapy*, *predictor*, *depression*, and *response* and terms describing 15 different clinical predictors (see below). All articles identified that tested any clinical predictor of ECT response were collected, and their references were manually searched for additional reports missed by the original search. We selected studies published after 1980 that tested at least 1 predictor. Studies published in 1980 and earlier (before *DSM-III*) were excluded because in those studies the diagnostic criteria for depressive illnesses differed significantly from modern criteria. Selected studies included patients with major depressive disorder or bipolar disorder as defined by standardized criteria (*DSM-III*, *DSM-IV*, RDC, *ICD-9*, or *ICD-10*). Both prospective and retrospective study designs were included, and design was examined as a study-level variable. We reasoned that prospective studies would be more likely to include standardized evaluations and treatment, whereas retrospective studies could potentially include patients more representative of real-world clinical practice and patients less likely to consent to research protocols (eg, suicidal, catatonic, psychotic). We were not able to include studies that categorized a continuous predictor (eg, binning of age). To be included in the meta-analysis, articles must have reported the effect size for statistical tests (or details sufficient to compute the effect size) with the clinical outcome as a dichotomous variable (ie, "responder" vs "nonresponder"). The exact definition of clinical response varied somewhat across studies, so we categorized each study's definition of response as high- or low-stringency (Table 1). Definition of response was considered as a potential source of between-study heterogeneity, as described below.

Clinical Predictors

On the basis of clinical practice and the relevant literature, we searched for 15 potential clinical predictors that are frequently obtained during a psychiatric evaluation: age, sex, severity of depressive symptoms, medication failure (ie, nonresponse to an adequate trial of antidepressant medication during the current episode), duration of the current episode, psychotic features, bipolar diagnosis (vs unipolar), age at onset of the illness, number of previous episodes, melancholic features, family history of depression, psychomotor disturbance, comorbid general medical conditions, substance use disorder, and personality disorder. As described in the Results, the latter 5 predictors were excluded due to a paucity of suitable studies. Dr Axel Nordenskjöld (Örebro University, Sweden) kindly provided unpublished summary data for age as a continuous predictor, because in the original publication[4] age was treated as a dichotomous variable.

Statistical Analysis

Each clinical predictor was analyzed separately using the "metafor" package (version 1.9–3, W. Viechtbauer) (http://cran.r-project.org/web/packages/metafor) and "meta" package (version 3.7–0, G. Schwarzer) (http://cran.r-project.org/web/packages/meta) with RStudio (version 0.97.551) in the R statistical computing environment (version 3.0.2, http://www.R-project.org/). For dichotomous variables (sex, medication failure, psychotic features, bipolar diagnosis, melancholic features), the effect size was represented as an odds ratio (OR = odds of response when predictor is present divided by odds of response when predictor is absent), and the Mantel-Haenszel method was used to calculate the pooled OR. For continuous variables (age, severity, duration of episode, age at onset, number of previous episodes), the effect size was represented by the standardized mean difference (SMD, mean value of the predictor among responders minus mean value of the predictor among nonresponders, divided by Hedges pooled standard deviation), and inverse-variance weighting was used to compute the pooled SMD. Fixed-effect and random-effects models were computed for each predictor. Forest plots and funnel plots were inspected for outliers and bias. Sensitivity analyses used the leave-one-out method to test for undue influence of single studies. For each predictor, we also used meta-regression and bubble plots to confirm that effect size was not associated with the prevalence or mean value of the predictor across studies.

When the heterogeneity test indicated nonsignificant heterogeneity across studies ($I^2 < 0.5$ and $P > .10$ as suggested[38]), we adopted the effect size from the fixed-effect model as our final estimate. When heterogeneity was suspected ($I^2 \geq 0.5$ or $P \leq .10$), studies that contributed most to the heterogeneity statistic were identified with Baujat plots,[39] and those studies were scrutinized to assess how they differed from other studies.

Rather than exclude studies based on study characteristics hypothesized to be important, we chose to include all eligible studies in our primary meta-analyses and explore potential sources of between-study variability using subgroup analyses and fixed-effect meta-regression. We considered 10 study-level variables that might contribute to heterogeneity: study design (prospective vs retrospective); method of diagnosis (structured vs unstructured interview); study size ($\log_{10}$ of the total number of subjects); study location (Europe vs North America vs other); year of publication; mean subject age; definition of clinical response (high vs low stringency); base rate of response; approximate mean number of ECT treatments delivered; and use of high ECT stimulus dose (all

Table 1. Studies Included in the Meta-Analysis of Clinical Predictors of ECT Response

Author	Year	Country	Design[a]	N	Mean Age, y	Diagnostic Criteria[b]	Base Rate of Response[c]	High Dose[d]	Mean No. of Treatments	Predictors Included[e]
Bailine et al[11]	2010	USA	Pro	220	53.4	MDD or BD (*DSM-IV*)[f]	79% (low)	Yes[g]	~6	B
Birkenhäger et al[12]	2003	Netherlands	Retro	55	50.4	MDD (*DSM-III-R*)	73% (low)	No[g]	~14	P
Daly et al[13]	2001	USA	Pro	228	57.7	MDD or BD (RDC)[f]	49% (high)	No[g]	9.3	B
de Vreede et al[14]	2005	Netherlands	Retro	53	59.0	MDD (*DSM-IV*)	44% (low)	Yes[g]	>5	F, P, S
Dombrovski et al[6]	2005	USA	Pro	328	57.4	MDD (RDC)[f]	56% (high)	No[g]	11.2	A, D, F, M, P, S
Fink et al[15]	2007	USA	Pro	489	55.5	MDD (*DSM-IV*)[f]	68% (high)	Yes[g]	7.2	M
Grunhaus et al[16]	2002	Israel	Retro	131	61.4	MDD or BD (unspecified)	56% (low)	No[g]	≥6	B
Gupta et al[17]	2000	India	Pro	22	44.3	Severe depressive episode (*ICD-10*)	50% (low)	Yes[h]	≤6	A, B, D, O, P, V
Heijnen et al[18]	2008	Netherlands	Pro	86	54.9	MDD (*DSM-IV*)	71% (low)	No[g]	>6	F
Husain et al[19]	2004	Scotland	Pro	50	49.8	MDD or BD (*ICD-10*, RDC)	60% (low)	Yes[i]	7.5	A, B, D, F, P, S, V
Kho et al[20]	2005	Netherlands	Retro	73	57.7	MDD or BD (*DSM-IV*)	66% (high)	No[g]	7.0	B, F, P, S
Kindler et al[21]	1991	Israel	Retro	52	56.5	MDD endogenous (RDC)	65% (high)	Yes[g]	11.3	A, B, D, E, P, S, V
Loo et al[22]	2011	Australia	Pro	75	46.2	MDD or BD (*DSM-IV*)	61% (low)	Yes[g]	9.7	A, B, M, P, V
Magni et al[23]	1988	Canada	Retro	30	73.3	MDD (*DSM-III*)	63% (low)	Yes[h]	>6	A, B, E, M, O, P, S
Nordenskjöld et al[4]	2012	Sweden	Retro	990	54.0	MDD or BD (*ICD-10*)[j]	80% (low)	No[g]	8.0	A, B, P, S
Okazaki et al[24]	2010	Japan	Pro	24	64.2	MDD or BD (*DSM-IV*)	71% (low)	Yes[g]	6.0	A, D, E, O, P, S, V
Pande et al[25]	1988	USA	Pro	48	61.0	MDD (RDC)	60% (low)	No[h]	7.5	V
Perugi et al[7]	2012	Italy	Pro	208	52.0	MDD or BD (*DSM-IV*)[f]	73% (low)	Yes[g]	7.2	A, B, D, E, O, P, S, V
Petrides et al[5]	2001	USA	Pro	253	56.0	MDD (*DSM-IV*)[f]	75% (high)	Yes[g]	7.8	P
Pluijms et al[26]	2002	Netherlands	Retro	41	51.5	MDD (*DSM-III-R*)	71% (low)	No[g]	NR	F
Prudic et al[27]	1990	USA	Pro	53	59.0	MDD endogenous (RDC)[f]	70% (high)	Yes[g]	9.8	F
Prudic et al[28]	1996	USA	Pro	100	62.2	MDD nonpsychotic (RDC)[f]	73% (high)	No[g]	9.6	F
Rasmussen et al[29]	2007	USA	Pro	226	54.5	MDD (*DSM-IV*)[f]	65% (high)	Yes[g]	~7	F
Sackeim et al[30]	2000	USA	Pro	80	57.0	MDD (RDC)[f]	65% (low)	No[g]	9.0	F
Sackeim and Prudic[31]	2005	USA	Pro	333	56.7	MDD or BD (*DSM-IV*)[f]	61% (high)	No[g]	7.2	B
Sienaert et al[32]	2009	Belgium	Pro	64	54.5	MDD or BD (*DSM-IV*)	78% (low)	Yes[g]	>7	B
Sivaprakash et al[33]	2000	India	Pro	30	33.1	MDD (*DSM-III-R*)	63% (low)	Yes[g]	6–10	V
Sobin et al[8]	1996	USA	Pro	143	57.4	MDD or BD (RDC)[f]	70% (high)	No[g]	9.5	P
Solan et al[34]	1988	USA	Retro	46	47.1	MDD (*DSM-III*)	85% (low)	Yes[g]	9.9	P
Tominaga et al[35]	2011	Japan	Pro	18	70.9	MDD or BD (*DSM-IV*)	39% (low)	Yes[g]	6.0	A, D, E, O, P, S, V
Tsuchiyama et al[36]	2005	Japan	Pro	24	53.1	MDD (*DSM-IV*)[f]	54% (high)	No[h]	11.8	M, P, S
van den Broek et al[37]	2004	Netherlands	Pro	85	54.8	MDD (*DSM-IV*)	71% (low)	No[g]	>6	F

[a]Design: Pro = prospective, Retro = retrospective. [b]Diagnostic criteria: *DSM = Diagnostic and Statistical Manual of Mental Disorders*, *ICD = International Classification of Diseases*, and RDC = Research Diagnostic Criteria. [c]Base rate of response: low = response defined with low stringency (≥ 50% improvement from baseline *or* a posttreatment depression score in the mild range or below *or* a global score in the mild range or below); high = response defined with high stringency (> 60% improvement from baseline *and* a posttreatment depression score in the mild range or below). [d]High dose: all patients treated with bilateral or with unilateral at 6 × threshold (see Method). [e]Predictors: A = age, B = bipolar diagnosis, D = duration of current episode, E = number of previous episodes, F = medication failure during the current episode, M = melancholic features, O = age at onset of the illness, P = psychotic features, S = sex, V = severity of depressive symptoms. [f]Structured interview used. [g]Brief or ultrabrief pulse stimuli. [h]Sine wave stimuli. [i]Stimulus waveform not reported. [j]Includes 5% schizoaffective disorder.

Abbreviations: BD = bipolar disorder, ECT = electroconvulsive therapy, MDD = major depressive disorder, NR = not reported.

Table 2. Studies Excluded From the Meta-Analysis

Author (year)	Reason for Exclusion
Coryell and Zimmerman (1984)[40]	Only continuous outcomes reported
Crow et al (1984)[41]	Only continuous outcomes reported
Brandon et al (1984)[42]	Only continuous outcomes reported
Rich et al (1984)[43]	Only ordinal outcomes reported
Rich et al (1986)[44]	Only continuous outcomes reported
Andrade et al (1988)[45]	Examined prognostic indices only, not raw predictors
Hickie et al (1990)[46]	Examined psychomotor disturbance only
Buchan et al (1992)[47]	Only continuous outcomes reported
O'Leary et al (1995)[48]	Only continuous outcomes reported
Hickie et al (1996)[49]	Only approximate *P* values reported; analyzed age as a categorical variable
Tew et al (1999)[50]	Analyzed age as a categorical variable
Lam et al (1999)[51]	Table internally inconsistent
Sivaprakash et al (2000)[33]	Raw data for predictors not reported
O'Connor et al (2001)[52]	Analyzed age as a categorical variable
Heikman et al (2002)[53]	Raw data for predictors not reported
Medda et al (2009)[54]	Data overlap with Perugi et al (2012)[7]
Birkenhäger et al (2010)[55]	Analyzed age as a categorical variable
Damm et al (2010)[56]	Analyzed age as a categorical variable
van Waarde et al (2013)[57]	Raw data for predictors not reported

patients treated with bilateral configuration at ≥ 1.5 times threshold or unilateral at ≥ 5 times threshold).

RESULTS

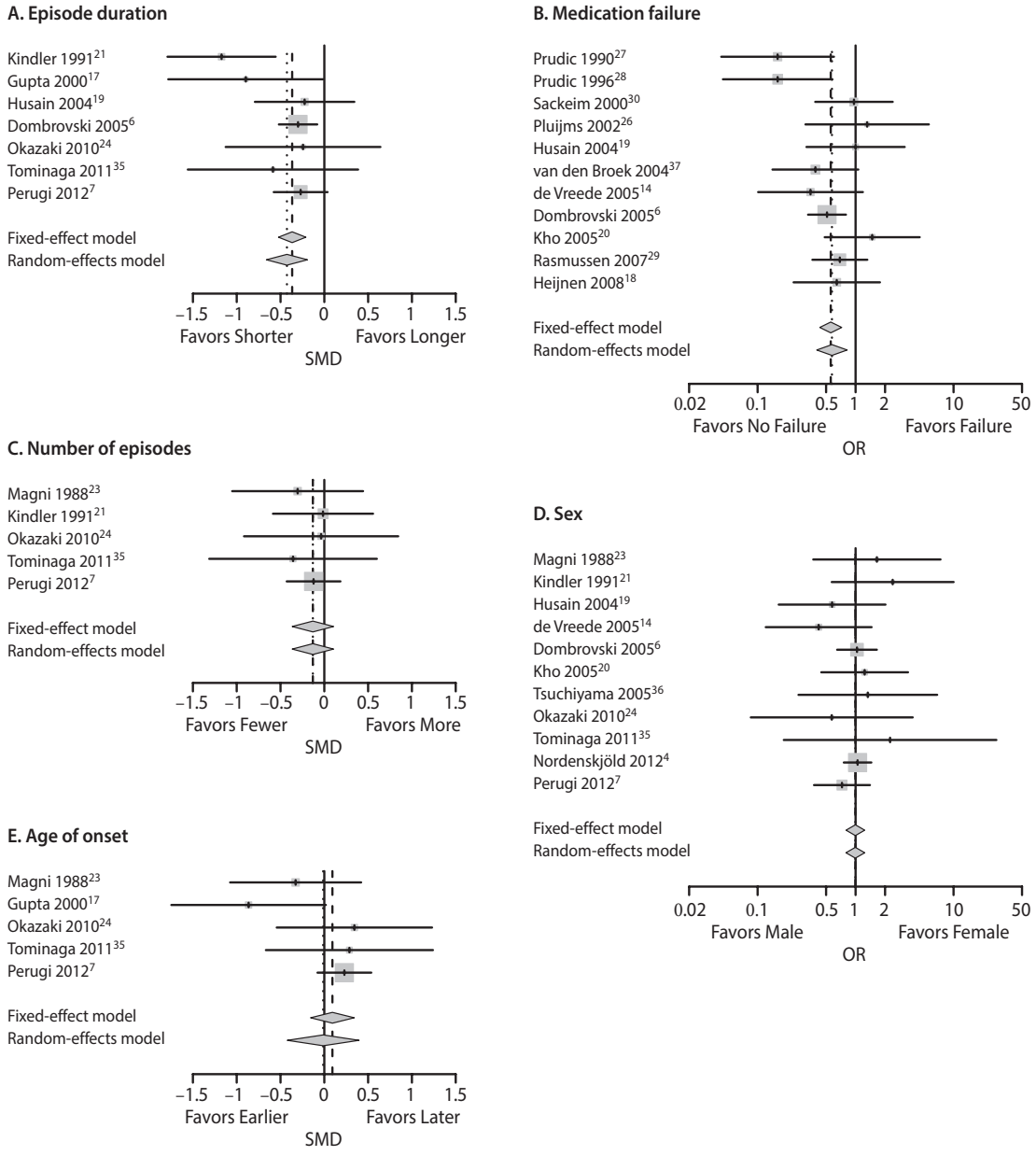
Study Characteristics

The literature search yielded 51 potential studies published after 1980. Thirty-two studies including a total of 4,658 subjects were compatible with meta-analysis (Table 1), and 19 studies were excluded (Table 2). Ten of the 15 clinical predictors were represented by at least 5 studies and were included in the analysis. The other 5 predictors (family history, psychomotor disturbance, general medical conditions, substance use disorder, personality disorder) were represented by fewer than 5 studies and were therefore excluded.

Episode Duration

Shorter duration of the current episode was associated with higher response rates for both fixed- and random-effects

Figure 1. Forest Plots of Effect Size for the 10 Predictors Tested[a]



(continued)

models (Figure 1A, Table 3). We found no evidence for heterogeneity or bias (Figure 2A, Table 3). Sensitivity analysis using the leave-one-out method indicated that the results were robust (all $P < .0001$). The weighted mean difference in episode duration between responders and nonresponders was 4.9 months (weighted mean duration of 6.6 months for responders, 14 months for nonresponders).

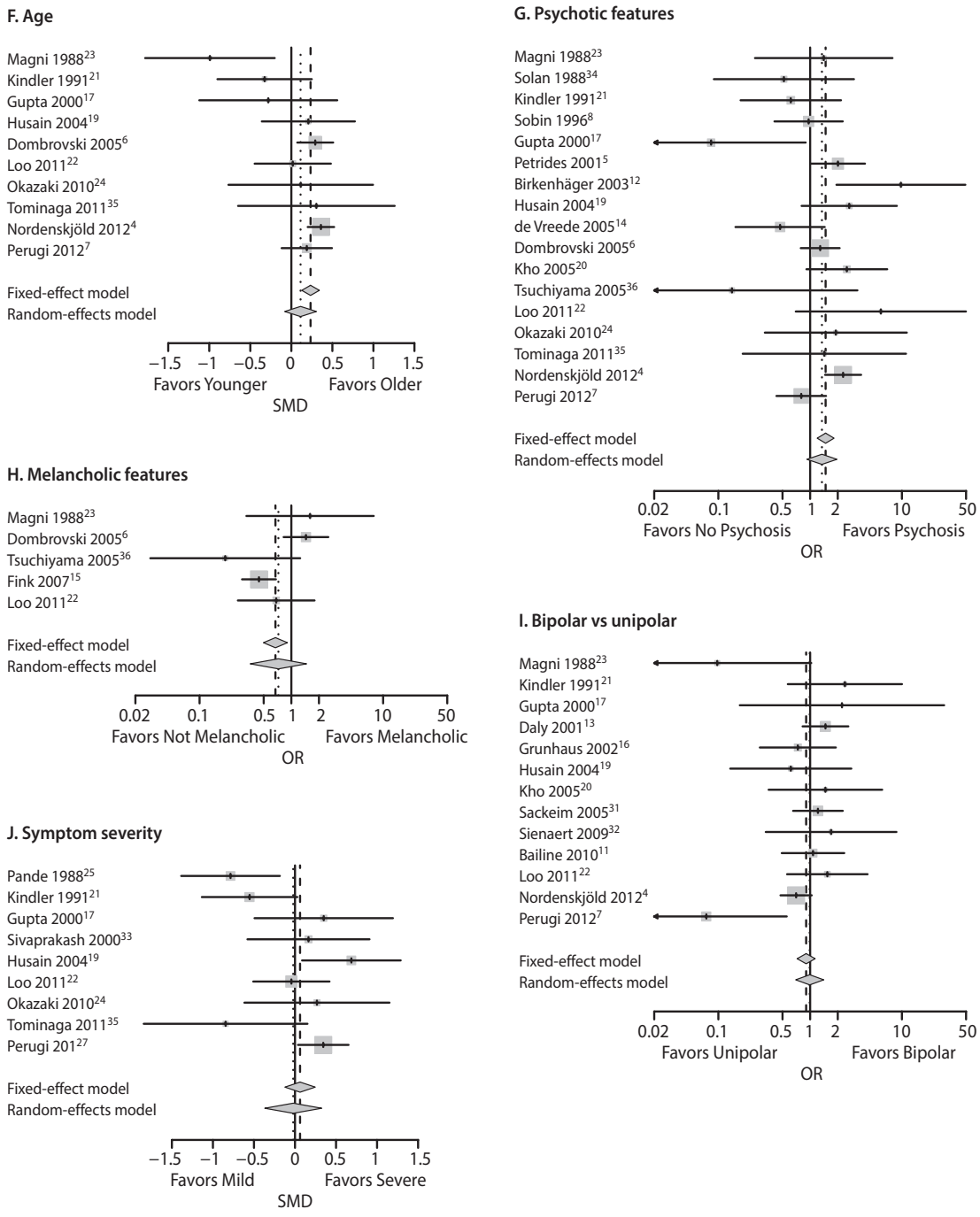
Medication Failure

Medication failure (ie, nonresponse to at least 1 adequate antidepressant medication trial during the current episode) was associated with poorer response to ECT for both fixed- and random-effects models (Figure 1B, Table 3). We found no evidence for heterogeneity or bias (Figure 2B, Table 3), and sensitivity analysis indicated that the results were robust (all $P < .001$). The rate of ECT response was 58% (424/728) among patients with medication failure, and 70% (314/447) among those without.

Number of Episodes, Sex, and Onset Age

For each of these 3 variables—number of episodes, sex, and onset age, no significant effects were found under fixed- or random-effects models (Figure 1C–E, Table 3). There was no evidence for heterogeneity or bias (Figure 2C–E, Table 3). Sensitivity analyses indicated that the results were robust (all $P > .18$).

Figure 1 (continued). Forest Plots of Effect Size for the 10 Predictors Tested[a]



[a]Odds ratio (OR) is used for dichotomous variables, and standardized mean difference (SMD) for continuous variables. Each study is represented by a square and horizontal error bars (mean and 95% confidence interval). Square size represents fixed-effect study weight. For each predictor, the solid vertical line represents the null hypothesis (no effect of the predictor), the dashed vertical line is the fixed-effect weighted mean, and the dotted vertical line is the random-effects weighted mean. Diamonds represent means and 95% confidence intervals for fixed-effect and random-effects models.

Bipolar Versus Unipolar

Bipolar disorder was not a significant predictor under fixed- or random-effects models (Figure 1I, Table 3). Sensitivity analyses indicated that the results were robust (all $P > .12$). We found no evidence of bias, but heterogeneity was detected at a trend level ($P = .08$, Table 3, Figure 2I). The study by Perugi et al[7] contributed most to the heterogeneity. This study differed from other studies in the proportion of patients who were bipolar (85% vs 15%–33%), suggesting differences in recruitment. Exclusion of this study reduced the heterogeneity and left the effect size essentially unchanged (OR = ~ 1; Table 3).

Table 3. Meta-Analysis of Clinical Predictors of ECT Response

Predictor	No. of Studies	N	Random Effects SMD	Random Effects 95% CI	Random Effects *P*	Fixed Effect SMD	Fixed Effect 95% CI	Fixed Effect *P*	Heterogeneity Test *Q*	*df*	I^2	*P*
Continuous												
Duration of episode	7	702	−0.427	−0.662 to −0.192	.0004	−0.367	−0.524 to −0.211	.000004	9.2	6	0.35	.16
Age	10	1,743	0.112	−0.081 to 0.306	.25	0.234	0.126 to 0.342	.00002	18.0	9	0.50	.04
ex Magni et al[23]	9	1,713	0.244	0.124 to 0.363	.00006	0.257	0.149 to 0.366	.000004	8.5	8	0.06	.38
ex Magni et al,[23] Nordenskjöld et al[4]	8	777	0.172	0.024 to 0.319	.02	0.172	0.024 to 0.319	.02	5.7	7	0.00	.58
No. of episodes	5	332	−0.130	−0.367 to 0.106	.28	−0.130	−0.367 to 0.106	.28	0.6	4	0.00	.96
Onset age	5	302	−0.013	−0.423 to 0.397	.95	0.093	−0.157 to 0.342	.47	7.0	4	0.43	.14
Symptom severity	9	523	−0.022	−0.368 to 0.325	.90	0.062	−0.124 to 0.247	.51	23.4	8	0.66	.003
Dichotomous			OR	95% CI	*P*	OR	95% CI	*P*	*Q*	*df*	I^2	*P*
Medication failure	11	1,175	0.574	0.401 to 0.821	.002	0.558	0.431 to 0.722	.00001	15.4	10	0.35	.12
Psychotic features	17	2,328	1.344	0.922 to 1.960	.12	1.474	1.193 to 1.822	.0003	33.3	16	0.52	.007
ex Gupta et al,[17] Birkenhäger et al[12]	15	2,251	1.342	0.968 to 1.860	.08	1.460	1.175 to 1.814	.0006	22.4	14	0.37	.07
Female sex	11	1,796	0.994	0.797 to 1.241	.96	0.995	0.799 to 1.240	.97	6.5	10	0.00	.77
Bipolar	13	2,374	0.990	0.695 to 1.408	.95	0.905	0.721 to 1.135	.39	19.4	12	0.38	.08
ex Perugi et al[7]	12	2,166	1.034	0.781 to 1.369	.81	0.999	0.790 to 1.263	.99	12.9	11	0.15	.30
Melancholic features	5	946	0.723	0.357 to 1.465	.37	0.671	0.497 to 0.907	.009	13.6	4	0.71	.009
ex Dombrovski et al[6]	4	618	0.521	0.311 to 0.874	.01	0.489	0.338 to 0.705	.0001	3.7	3	0.20	.29
ex Fink et al[15]	4	457	0.925	0.444 to 1.925	.84	1.077	0.692 to 1.675	.74	5.4	3	0.44	.14

Abbreviations: CI = confidence interval, *df* = degrees of freedom, ECT = electroconvulsive therapy, ex = meta-analysis with specified studies excluded, N = total number of subjects, OR = odds ratio (predictor present/predictor absent), SMD = standardized mean difference (responders – nonresponders).

Age

Greater age was associated with higher ECT response rate under the fixed-effect model, but not under the random-effects model, and the heterogeneity test was significant (Figure 1F, Table 3). The study by Magni et al[23] contributed most to the heterogeneity. This study differed from other studies as it was a retrospective chart review of 30 elderly patients with high medical comorbidity, which was confounded with age. Exclusion of this study reduced the heterogeneity and aligned the fixed- and random-effects models, which yielded a pooled SMD of ~0.25 (Table 3). However, further analyses cast some doubt on this estimate. First, sensitivity analyses indicated that the large study by Nordenskjöld et al[4] dominated the results, and omitting this study reduced the SMD to 0.17 (Table 3). Second, meta-regression suggested an association of SMD with the dose of ECT delivered ($Q_1 = 5.1$, $P = .02$): greater age was associated with higher ECT response rate among the 2 studies in which low-dose ECT was used (SMD = 0.34; 95% CI, 0.21 to 0.47; $I^2 = 0\%$) but not among the 7 high-dose studies (SMD = 0.07; 95% CI, −0.13 to 0.27; $I^2 = 0\%$). Furthermore, the funnel plot revealed potential bias, with greater effect sizes among more precise studies ($t_8 = 3.1$, $P = .01$, linear regression test of funnel plot asymmetry; Figure 2F).

Psychotic Features

Psychosis was positively associated with higher ECT response rate under the fixed-effect model, but not under the random-effects model, and the heterogeneity test was significant (Figure 1G, Table 3). The studies by Gupta et al[17] and Birkenhäger et al[12] contributed most to the observed heterogeneity. These studies were notable in that psychosis was confounded with longer episode duration[17] and shorter episode duration,[12] respectively. Given our finding that shorter episode duration is a robust predictor of ECT response (see above), these 2 studies are outliers in the expected directions. Exclusion of these studies reduced but did not eliminate the observed heterogeneity (Table 3). Unfortunately, meta-regression analyses using 10 different study-level variables revealed none that adequately accounted for the observed heterogeneity (data not shown). Few studies distinguished mood-congruent versus mood-incongruent symptoms, so we were unable to determine whether this was a source of heterogeneity. In summary, these findings indicate that the true odds ratio is not the same across studies of psychotic features (see Discussion) and that the distribution of true odds ratios is centered about 1.3.

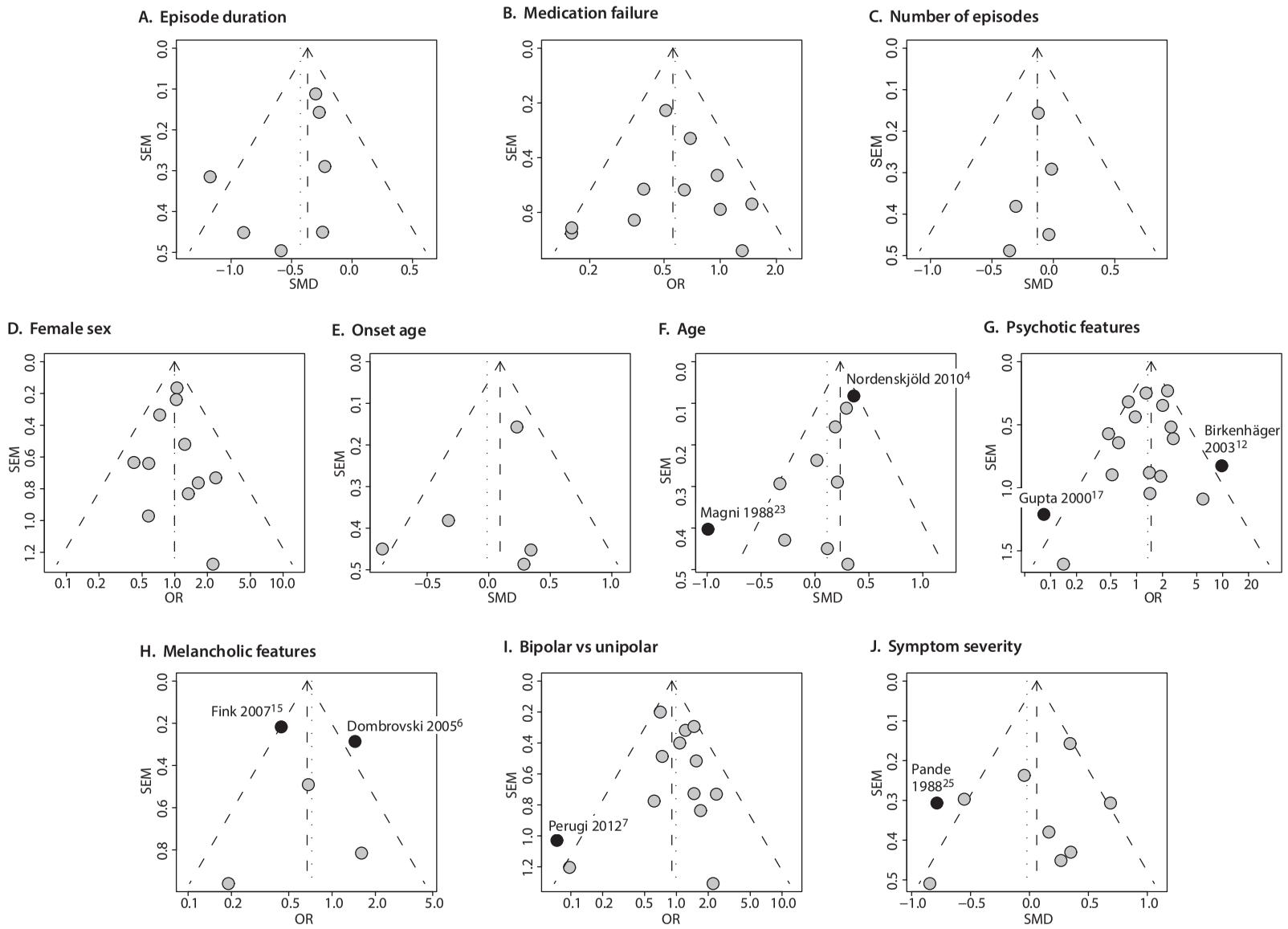
Melancholic Features

Presence of melancholic features was associated with ECT response rate under the fixed-effect model, but not under the random-effects model, and the heterogeneity test was significant (Figure 1H, Table 3). This heterogeneity was driven by opposite effects observed in the 2 largest studies: the presence of melancholic features was a nonsignificant predictor of response in the study by Dombrovski et al[6] and a significant predictor of nonresponse in the study by Fink et al.[15] Sensitivity analysis showed that the effect size estimate was strongly influenced by exclusion of either study (Table 3). Given the small number of studies, we conclude only that the true effect size is not the same across studies of melancholic features.

Severity

We found no significant association with baseline symptom severity under fixed- or random-effects models, but there was evidence of heterogeneity (Figure 1J, Table 3). The observed heterogeneity was not explained by the severity scale used (Montgomery-Asberg Depression Rating Scale vs Hamilton Depression Rating Scale; between-group $P = .65$, $Q_1 = 0.2$; within-group $P = .002$, $Q_7 = 23.2$). The study by

Figure 2. Funnel Plots of Study Precision (standard error of the mean, SEM) Versus Effect Size for the 10 Predictors Tested[a]



[a]Odds ratio (OR) is used for dichotomous variables, and standardized mean difference (SMD) for continuous variables. Each study is represented by a circle. For each predictor, the dashed vertical line is the fixed-effect weighted mean, and the dotted vertical line is the random-effects weighted mean. In the absence of heterogeneity and bias, 95% of studies are expected to fall below the dashed diagonal lines, evenly distributed about the mean. Studies referred to in the text are labeled by filled black circles with first author and year.

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Pande et al[25] contributed most to the observed heterogeneity, but exclusion of this study did not substantially alter the results (data not shown). We conclude that the true effect size varies across studies and that the distribution of true effect sizes is centered near 0.

Meta-Regression

For each predictor, we used meta-regression to examine whether effect size was associated with prospective versus retrospective study design, approximate mean number of ECT treatments delivered, or use of high ECT stimulus dose (bilateral or unilateral > 5 × threshold). With the exception of age and ECT dose (see Results: Age), meta-regression revealed no significant associations (all $P > .05$).

DISCUSSION

We performed meta-analyses of modern studies of ECT that reported associations of acute depression outcomes with baseline clinical features. To our knowledge, this is the first published attempt to comprehensively quantify effect sizes for a full range of clinical features. We found that 2 variables—longer duration of the current episode and medication failure in the current episode—were robust predictors of lower response rates. For both of these predictors, the null hypothesis was rejected with $P < .0001$, which survives correction for testing of 10 predictors. We detected weaker associations of ECT response with greater age and with psychotic features, but for those predictors, confidence in effect-size estimates was limited by observed heterogeneity and bias. We found fairly clear evidence that 4 variables—sex, onset age, bipolar disorder, and number of previous episodes—are not associated with outcome. Finally, analyses of melancholic features and symptom severity were inconclusive due to heterogeneity across studies.

It is important to contextualize these findings within the well-established fact that ECT is the most effective treatment available for depression.[1,58] In our analysis, for example, even patients with at least 1 failed medication trial had a response rate of 58%, which by most standards would be considered highly effective. This raises the question of whether a "ceiling effect" might limit the power of a clinical feature to predict outcomes. We believe not, based on medical testing considerations. The predictive value of a test is optimal when the pretest probability is .5, and predictive power remains above 80% as long as the pretest probability is above ~ .25 (assuming 95% sensitivity and 95% specificity).[59] For a clinical predictor of ECT nonresponse, that means the predictive power remains high when the prior probability of nonresponse is above ~ 25%. Across all 32 studies that we analyzed, the rate of nonresponse was 32%, so we conclude that clinical predictors are potentially useful for predicting ECT response.

The strengths and limitations of our study largely mirror those of meta-analysis in general. One strength is that, unlike narrative reviews, which often deal with *P* values only, meta-analysis quantifies and compares effect sizes across studies. Meta-analysis allows testing of the null hypothesis (in this case, that the clinical variable does not predict treatment response), but it also permits inclusion of underpowered studies, allows rigorous assessment of whether a result is robust or variable across studies, and produces a summary effect size that can be cast in clinically relevant terms.[38]

Several limitations are also notable. The results of meta-analysis depend on the studies that are included and their quality. We found several relevant studies that could not be included because effect sizes (or data sufficient to compute effect sizes) were not reported, or because dichotomous outcomes were not reported, or because continuous predictors were reported as discretized variables. Furthermore, despite our best efforts, we may have overlooked relevant studies. The most severely ill patients (eg, suicidal, catatonic, or psychotic) may not be well represented in the included studies. Finally, the majority of included studies were based in academic medical centers in North America and Europe, so it is possible that the findings would not hold in other settings. Any of the above issues may lead to systematic bias. To evaluate for bias and inconsistency across studies, we used heterogeneity tests, funnel plots, and sensitivity analyses, but even these approaches are limited, especially for analyses that included a small number of studies (eg, onset age, number of previous episodes, and melancholic features).[38]

One of our most robust findings was that longer depressive episodes predicted lower ECT response rates. The estimated standardized mean difference of −0.37 indicates a small-to-medium effect, with substantial overlap in the distributions of responders and nonresponders. It is notable that the groups are differentiated by duration on a scale of months, rather than weeks or years: we calculated weighted mean episode durations of approximately 7 months and 14 months for responders and nonresponders, respectively. It is instructive to compare this time window to previous studies of recovery from depression. For depressed patients followed naturalistically in the National Institute of Mental Health (NIMH) Collaborative Depression Study, average rates of recovery declined from 15% per month in the first 3 months, to 7% per month at the end of the first year, to less than 3% per month beyond 1 year.[60] In the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, the remission rate was 31% for patients with episode durations < 6 months and approximately 24% for those with episodes > 6 months.[61] These convergent observations suggest that episode durations of approximately 6 months to 1 year may represent a general inflection point at which the rate of recovery from depression drops substantially.

It remains unclear whether response to ECT is reduced by episode duration per se or by factors associated with episode duration. Analyses of STAR*D data indicated that the association between episode duration and remission could be fully accounted for by a series of demographic and clinical characteristics (most of which were not easily modifiable), suggesting that episode duration is a marker of multiple factors that cause poor outcomes.[61] Our finding suggests that ECT response may depend on similar factors. If ECT

response depends on unmodifiable risk factors associated with episode duration, then earlier intervention with ECT is unlikely to increase response rates. On the other hand, if episode duration per se is a causal risk factor, then early intervention should be a high priority. Further studies including individual-level data are needed to resolve this question. Regardless of the causal mechanisms, the association of episode duration and ECT response could be relevant to patients and clinicians considering ECT. Patients with episode durations greater than about 1 year should expect a modestly lower response rate. Perhaps the clearest message for patients and clinicians is to avoid chronicity: delaying ECT treatment will not increase, and may in fact decrease, the likelihood of recovery.

A second robust finding was that medication failure during the current episode predicted poorer ECT response. Our analysis of 11 studies confirms and expands on a 2010 meta-analysis of 7 studies.[62] The effect size we observed (odds ratio of 0.57) is often described as small or medium and is likely to be clinically relevant. Across studies, response rates were 70% and 58% for patients without and with (respectively) a history of medication failure. There is considerable evidence that nonresponse to an antidepressant medication in the current episode reduces the chance of subsequent response to another antidepressant, suggesting some degree of generalization across medications. For example, in the STAR*D trial, the remission rate with citalopram was 37% during step 1 treatment, but nonresponders treated subsequently experienced remission rates of only 31% on step 2 and ~13% on steps 3 and 4.[63] We found strong evidence that response to ECT is also predicted by medication failure. Considering that ECT is a unique treatment, with mechanisms of action that are most likely very different from current antidepressants, our result suggests that medication failure is a rather general marker of poorer response to antidepressant therapies.

Medication failure is likely to correlate with other potential risk factors, which could include episode duration. In our analyses, we were unable to evaluate whether medication failure and episode duration are independent clinical predictors, since data for the 2 predictors were not available within the same subjects. To our knowledge, only 2 published studies have jointly analyzed these 2 predictors, and both studies found that medication failure and episode duration were independent predictors of ECT response.[6,28] Similar analyses of larger samples or pooled individual-level data are needed to replicate that finding.

We expected that psychotic features would be a robust clinical predictor of ECT response, but our analysis did not support this notion. Although psychosis was associated with better ECT response, the heterogeneity we observed indicates that the true effect size varies across studies. Such variability may arise from differences in study procedures, ECT technique, or patient characteristics. Meta-regression was used to test for influence of many such covariates, but none accounted for the observed heterogeneity. On the basis of examination of outlier studies, and on the robust effects we found for episode duration and medication failure, we speculate that the heterogeneity across studies arises from variation in the degree to which psychosis is confounded with episode duration and medication failure. It seems likely that, in some settings, patients with psychotic features receive ECT earlier in their course of illness, which would result in those with psychosis having shorter episodes and less medication resistance. Of the 17 studies we analyzed, only 3 provided enough detail to determine whether psychosis was confounded with episode duration or medication failure. Future studies are needed to determine whether the presence of psychotic features is valuable as an independent predictor.

Greater age was also associated with better ECT response, but the magnitude of the effect may not be clinically relevant. The estimate of effect size varied depending on which studies were included in the analysis, and we found evidence of larger effect sizes among studies using less effective forms of ECT and among more precise (larger) studies. It is possible that our effect size estimate is biased by exclusion of several relatively large studies, which we were unable to include because they did not treat age as a continuous variable.[49,50,52,55,56] However, because some of those studies found no effect, and others found a positive association of age and ECT response, it seems unlikely that their exclusion strongly biased our results. Even if we were to adopt the largest effect sizes as valid (SMD ~ 0.25), this estimate is small relative to those for episode duration and medication failure, so the clinical relevance is doubtful. Furthermore, it remains unclear whether age would be useful as a predictor independent of episode duration, medication failure, and psychotic features.

We found consistent evidence that sex, bipolar disorder, age at onset, and number of previous episodes are not predictive of ECT response. Our analysis of 13 studies on bipolar disorder expands on and confirms the findings of a 2012 meta-analysis of 6 studies, which also found no difference in response between bipolar and unipolar patients.[64] These results may be particularly important for individuals with bipolar disorder who respond poorly to antidepressant medications. In contrast to the robust findings for sex, bipolar disorder, age at onset, and number of previous episodes, we were unable to draw strong conclusions about melancholic features or symptom severity because of heterogeneity across studies.

Our results carry implications for future research. Few studies collected and reported effect sizes for family history of mood disorder, psychomotor disturbance, *DSM-IV* melancholic features, or classic melancholia.[65] Many studies failed to report effect sizes or exact *P* values, and some studies reported results only after discretizing a continuous variable. Fuller assessment of clinical features and more complete reporting of exact statistics would greatly facilitate future meta-analyses. An even more powerful approach is the expansion of large registries or databases that include individual-level data. Such registries could be developed through national or international consortia (eg, National

Network of Depression Centers [nndc.org], Canadian Network for Mood and Anxiety Treatments [canmat.org]). Such databases would allow univariate analyses (as in the current study) but also multivariate approaches, which might identify configurations of clinical features (syndromes) that predict response to ECT. Finally, our findings suggest a minimal criterion for future development of biological predictors (biomarkers) of ECT response. Specifically, any clinical biomarker should usefully predict ECT response after accounting for duration of depressive episode and history of medication failure.

In conclusion, we found that longer episode duration and medication failure in the current episode predicted poorer acute response to ECT, with small-to-medium effect sizes that are clinically significant. We are optimistic that discovery of other robust clinical predictors and biomarkers of ECT response will ultimately make possible more personalized treatment and prognosis for patients with depression.

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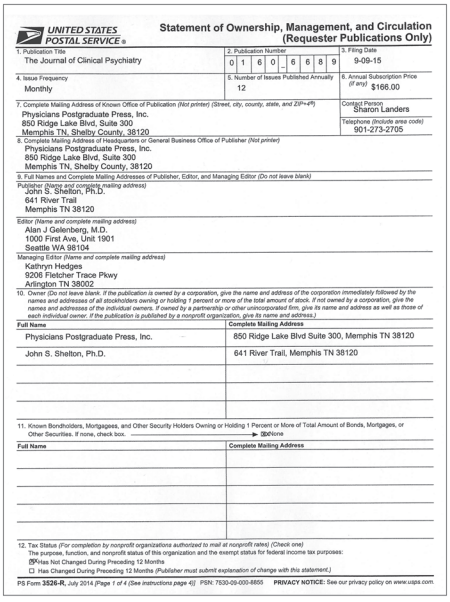

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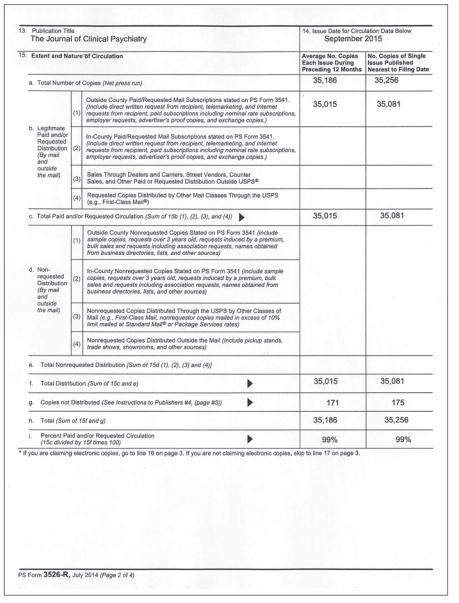

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f. Total Distribution (Sum of 15c and e)			35,015	35,081
g. Copies not Distributed (See Instructions to Publishers #4, (page #3))			171	175
h. Total (Sum of 15f and g)			35,186	35,256
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* If you are claiming electronic copies, go to line 16 on page 3. If you are not claiming electronic copies, skip to line 17 on page 3.

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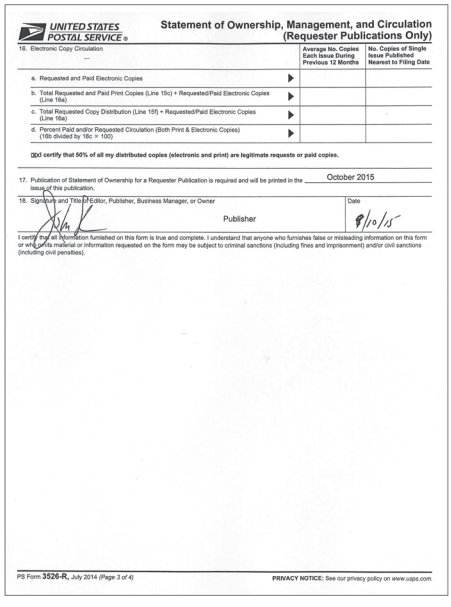

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