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Review

REVIEW

Prevention of Relapse and Recurrence in Adults with Major Depressive Disorder: Systematic Review and Meta-Analyses of Controlled Trials

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Abstract

Background: Findings of substantial remaining morbidity in treated major depressive disorder (MDD) led us to review controlled trials of treatments aimed at preventing early relapses or later recurrences in adults diagnosed with MDD to summarize available data and to guide further research.
Methods: Reports (n = 97) were identified through systematic, computerized literature searching up to February 2015. Treatment versus control outcomes were summarized by random-effects meta-analyses.
Results: In 45 reports of 72 trials (n = 14 450 subjects) lasting 33.4 weeks, antidepressants were more effective than placebos in preventing relapses (response rates [RR] = 1.90, confidence interval [CI]: 1.73–2.08; NNT = 4.4; $p < 0.0001$). In 35 reports of 37 trials (n = 7253) lasting 27.0 months, antidepressants were effective in preventing recurrences (RR = 2.03, CI 1.80–2.28; NNT = 3.8; $p < 0.0001$), with minor differences among drug types. In 17 reports of 22 trials (n = 1 969) lasting 23.7 months, psychosocial interventions yielded inconsistent or inconclusive results.
Conclusions: Despite evidence of the efficacy of drug treatment compared to placebos or other controls, the findings further underscore the substantial, unresolved morbidity in treated MDD patients and strongly encourage further evaluations of specific, improved individual and combination therapies (pharmacological and psychological) conducted over longer times, as well as identifying clinical predictors of positive or unfavorable responses and of intolerability of long-term treatments in MDD.

Keywords: Antidepressants, depression, major depression, psychotherapy, recurrence, relapse

Introduction

Major depressive disorder (MDD) and other forms of clinical depression are characterized by persistent low mood with associated changes in behavior, cognition, sleep and appetite, impaired social and occupational functioning, increased risk of self-harm or suicide, and increased mortality due to co-occurring general medical disorders. Based on World Health Organization

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data (2012), there is an approximately 10% lifetime international prevalence of depression, with perhaps 350 million persons currently suffering from this leading worldwide illness burden. In 2000, adult depression cost the UK approximately £9 billion, with an estimated 110 million working days lost (Thomas and Morris, 2003). In the USA in the same year, depression accounted for costs totalling over $80 billion for treatment and disability (Greenburg et al., 2003). These considerations indicate that depression has a major, international, clinical, public health, and economic impact.

Currently, pharmacological and non-pharmacological treatments are relatively well established as having at least moderate efficacy for the short-term treatment of acute major depression (Undurraga and Baldessarini, 2012; Baldessarini, 2013; Bauer et al., 2015). Effective antidepressants include selective serotonin (SSRIs) and serotonin-norepinephrine re-uptake inhibitors (SNRIs), a growing number of other types of modern antidepressants (such as bupropion and mirtazapine), older tricyclic (TCA) and monoamine oxidase inhibitor (MAOI) antidepressants, electroconvulsive therapy (ECT; Baldessarini, 2013; Bauer et al., 2015), and a variety of psychotherapies, including prevalent cognitive-behavioral therapy (Bondolfi et al., 2010; Sheets et al., 2013).

Despite generally effective short-term treatments for acute episodes of major depression, many patients experience relapses (early return of symptoms within the expected duration of a current episode, of perhaps 3–12 months) or later recurrences (new episodes) following initial short-term improvement or remission (Georgotas 1985; Ferreri et al., 1997; Forte et al., 2015). Recurrence rates are over 85% within a decade of an index depressive episode, and average approximately 50% or more within six months of apparent clinical remission if the initially-effective treatment was not continued (Baldessarini, 2013). The median time to a new episode with antidepressant treatment continued has averaged approximately 40 months, compared to just over 1 year if treatment was discontinued (Baldessarini, 2013; Rosenthal et al., 2013). With such high rates of relapse and recurrence, it has become usual practice to continue initially-effective antidepressant treatments for at least 6–12 months following apparent clinical remission of acute depression, and often longer for patients who have experienced multiple recurrences (Baldessarini, 2013). Nevertheless, clinically-treated patients diagnosed with MDD in long-term observational studies are depressed 40–50% of the time at follow-up (Forte et al., 2015).

Earlier reviews and meta-analyses and recent treatment guidelines for long-term treatment of MDD are generally supportive of treatments continued for several months as well as more than a year, particularly pharmacotherapies (Geddes et al., 2003; Lam et al., 2009; Pilling et al., 2009; Williams et al., 2009; Glue et al., 2010; Bauer et al., 2015). In view of the clinical importance of evaluating the effectiveness of continued and long-term treatment to prevent relapses and recurrences of major depression, we updated and extended previous reviews of portions of available research findings by separately examining reports of research trials involving continuation (up to 12 months following initial treatment) or long-term treatments (more than a year), as well as long-term trials of psychotherapy, all aimed at prophylaxis or prevention of relapses and recurrences of depressive illness.

Methods

Search Strategy and Selection Criteria

References for this review were identified through searches of the National Centre of Biotechnology Information, Pubmed/Medline, Scieverse, SciDirect, and Web-of-Science databases for reports published up to February 2015. Search terms were combinations of: adult; depress; major depress; long-term; prevent; relapse; recurrence; treatment; and generic names of specific antidepressant drugs. We reviewed reports identified in these searches and in relevant references cited in identified articles.

Inclusion/Exclusion Criteria

A report was selected for inclusion if: (a) it examined relapse or recurrence of major depressive disorder in adults treated with pharmacological or non-pharmacological means; and (b) it was reported in English. Reports were excluded if they concerned: (a) bipolar depression; (b) seasonal depression; (c) juvenile depression; or (d) studied only adverse events or costs.

Data Extraction

For each included report two investigators (Drs J Sim and Lau) independently extracted relevant data, including numbers and types of subjects, study design, treatments and controls, definitions of relapse and recurrence, nominal duration of treatment, dropout rates, and outcomes as rates of relapse or recurrence. Discrepancies were resolved by discussions and consensus amongst all team members.

Data Analysis

Extracted data were organized in digitalized spreadsheets and then summarized in tables to guide assessments. We subjected comparisons of active and control treatments to random-effects meta-analysis to obtain relative response rates (RRs) for active treatments versus controls, with their 95% confidence intervals (CIs), as well as rate differences (RDs) and their reciprocals (1/RD = number-needed-to-treat [NNT]), both with CIs. Averaged data are presented as means ± standard deviation (SD) or with CI. Statistical analyses employed data spreadsheets based on *Statview.5* (SAS Institute) and *Stata.13* statistical software (StataCorp.).

Results

Retrieved Studies

Initially, we identified 803 candidate reports, of which four represented second reports of the same study; of the 799 remaining citations, we excluded 653 as not meeting study inclusion/exclusion criteria. The remaining 146 full reports were reviewed in detail; 49 were excluded for having participants with diagnoses other than MDD, involving participants below 18 years old, or not specifying subject numbers and trial durations. This process left 97 reports for inclusion; two provided data for more than one of the following categories (Hollon et al., 2005; Segal et al., 2010). Reported study categories were: (a) intermediate-term (1–12 months) continuation trials of antidepressant treatment (n = 45); (b) long-term (≥12 months) trials of antidepressants (n = 35); and (c) long-term trials of psychosocial interventions (n = 17; supplementary Tables S1–S3). The screening and selection process is summarized in a Prisma flow chart (Figure 1).

Continuation Trials of Antidepressants

We identified 45 reports involving 72 placebo-controlled trials of different antidepressants, representing a total of 14 450 participants (Tables 1 and S1). Of these, four studies included two active treatments or two doses of one antidepressant versus a single placebo-treated group (Lauritzen et al., 1996; Montgomery et al.,

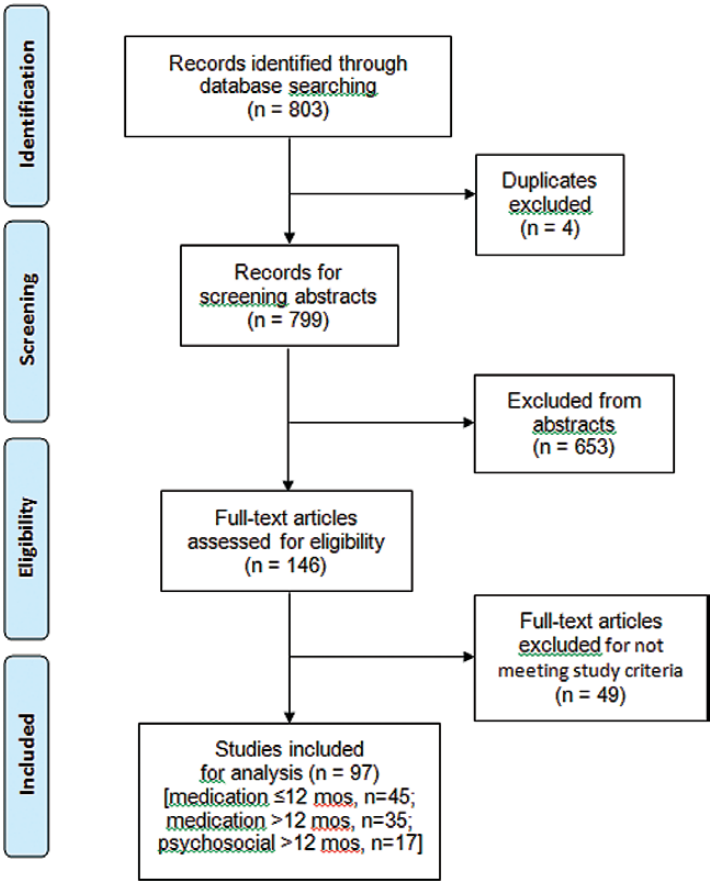

Figure 1. Flow chart of study selection process: 803 reports screened, 146 reviewed in detail, and 97 included for analysis, following Preferred Reporting Items for Systematic Reviews and Meta-Analyses recommendations (http://www.prisma-statement.org/statement.htm).

1998; Schimdt et al., 2000; Sackeim et al., 2001). Observed relapse rates in each randomized treatment arm of the trials, and other salient characteristics of each study, are shown in Table S1.

In these continuation trials, drug treatments continued for an average of 8.35 (CI 7.55–9.15) months. Risk of relapse within several months of initial remission averaged 23.3% with antidepressant continued versus 49.4% after discontinuing treatment, a 2.1-fold difference (Table S1). The meta-analytically computed, pooled relative, placebo/drug relapse rate was 1.90 (CI: 1.73–2.08), a highly significant decrease (z-score = 13.3, $p < 0.0001$; Table 1). Even when eight trials with unusually high drug-placebo differences (>5-fold; Table S1) were removed in a sensitivity re-analysis, the difference between continued antidepressant treatment and placebo remained highly significant. The overall computed number-needed-to-treat (NNT), or number of cases to be treated to obtain one responding better with drug than with placebo was low (4.4, CI 3.8–5.2).

Long-Term Antidepressant Treatment

We identified a total of 35 reports involving treatment with antidepressants continued for more than one year (2.27, CI 1.88–2.62 years) following an index episode of acute major depression, with a total of 7253 participants in 37 drug-control comparisons (Tables 2 and S2). All but one of these trials compared an antidepressant to a placebo; the single exception involved a small, 5.4-year comparison of antidepressant treatment alone versus with continued ECT, in which the addition of ECT yielded a significantly lower recurrence rate (27.6% vs. 82.8%; Gagne et al., 2000).

Based on random-effects meta-analysis (Table 2, Figure 2), all but five of the 37 (86.4%) drug-placebo comparisons trials yielded statistically superior benefits of active agents over placebo treatment in reducing recurrence risk. All but five trials (Maj et al., 1992; Rouillon et al., 2000; Wilson et al., 2003; Reynolds et al., 2006; Kasper et al., 2008) yielded statistically superior benefits of active agents over placebo treatments in reducing recurrence risk. These failed trials involved antidepressants such as tricyclic antidepressants (Maj et al., 1992), SSRIs (Wilson et al., 2003; Reynolds et al., 2006), the anxiolytic SNRI milnacipran (Rouillon et al., 2000), and a preparation of the plant *Hypericum perforatum* (St. John's Wort; Kasper et al., 2008). Overall, the long-term, controlled trials yielded significantly greater protection from recurrences with antidepressants versus placebo treatments (RR 2.03, CI 1.80–2.28; $z = 11.7$, $p < 0.0001$), with a low number-needed-to-treat (NNT 3.8, CI 3.3–4.6). That is, recurrence risk was reduced by 2.03-fold or 50.7% with long-term antidepressant treatment (Figure 2).

Psychosocial Treatments

A variety of psychosocial methods were tested in 17 trials with 22 tested treatments, averaging 1.98 (CI 1.49–2.46) years and involving 1 969 participants (Tables 3 and S3). Treatment techniques included various forms of cognitive or cognitive-behavioral psychotherapy (CT or CBT), sometimes with a mindfulness orientation (MCT), and patient- or family-based psychoeducation, with or without antidepressant treatment. Controls typically involved treatment as usual (often involving continued use of antidepressants, or placebo controls for comparisons

Table 1. Meta-Analyses of Placebo-Controlled Trials of Continuation Treatments (≤12 months) for Major Depression

Trial	Treatment	Subjects	RR (95% CI)	NNT (95% CI)	Weight (%)
Mindham et al., 1973	Amitriptyline	61	2.83 (1.46–5.49)	2.3 (1.5–4.9)	1.15
Mindham et al., 1973	Imipramine	31	1.07 (0.25–4.49)	80 (3.4 to >100)	0.36
Klerman et al., 1974	Amitriptyline	50	2.33 (0.68–8.01)	6.2 (2.6 to >100)	0.46
Coppen et al., 1978	Amitriptyline	32	1.56 (0.45–5.43)	8.9 (2.4 to >100)	0.45
Stein et al., 1980	Amitriptyline	55	2.23 (1.22–4.06)	2.6 (1.6–7.3)	1.28
Van Praag and De Haan, 1980	Clomipramine	20	2.66 (0.98–7.22)	2.0 (1.1–8.1)	0.65
Bialos et al., 1982	Amitriptyline	17	12.4 (0.83–184)	1.2 (0.9–2.0)	0.11
Kane et al., 1982	Imipramine+Lithium	14	8.00 (1.28–50.0)	1.1 (0.8–1.8)	0.23
Kane et al., 1982	Lithium	13	3.50 (1.08–11.3)	1.4 (0.9–2.9)	0.50
Kane et al., 1982	Imipramine	12	1.50 (0.85–2.64)	3.0 (1.4 to >100)	1.37
Davidson and Raft, 1984	Phenelzine	15	6.12 (0.98–38.3)	1.4 (0.9–2.6)	0.23
Lendresse et al., 1985	Nomifensine	143	2.03 (1.17–3.52)	5.0 (2.9–18)	1.40
Cook et al., 1986	Tricyclics	15	4.90 (0.30–80.7)	3.0 (1.5 to >100)	0.10
Harrison et al., 1986	Phenelzine	12	5.00 (0.87–28.9)	1.2 (0.8–2.4)	0.25
Montgomery et al., 1988	Fluoxetine	182	2.20 (1.49–3.25)	3.2 (2.2–5.6)	1.88
Georgotas et al., 1989	Nortriptyline	36	1.21 (0.67–2.17)	8.8 (2.2 to >100)	1.32
Georgotas et al., 1989	Phenelzine	38	4.89 (1.30–18.4)	1.9 (1.3–3.9)	0.41
Quitkin et al., 1989	Imipramine	54	1.69 (1.10–2.60)	3.0 (1.7–11)	1.75
Quitkin et al., 1989	Phenelzine	53	1.93 (1.19–3.12)	2.6 (1.6–6.6)	1.59
Rouillon et al., 1989	Maprotiline	1 141	1.44 (1.13–1.84)	14 (8.2–45)	2.38
Doogan and Caillard, 1992	Sertraline	295	3.50 (2.29–5.36)	3.1 (2.3–4.5)	1.77
Montgomery et al., 1993b	Citalopram	155	3.05 (1.53–6.09)	4.6 (2.8–14)	1.09
Montgomery et al., 1993a	Paroxetine	135	2.68 (1.46–4.91)	3.7 (2.4–8.1)	1.27
Mynors-Wallis et al., 1995	Amitriptyline	61	3.10 (1.43–6.73)	2.5 (1.6–5.5)	0.94
Robert and Montgomery, 1995	Citalopram	226	1.76 (1.00–3.10)	9.5 (4.6 to >100)	1.37
Lauritzen et al., 1996	Paroxetine	58	6.33 (2.11–19.1)	1.8 (1.3–2.9)	0.56
Lauritzen et al., 1996	Imipramine	58	2.11 (1.16–3.86)	2.9 (1.7–9.7)	1.28
Cunningham, 1997	Venlafaxine	278	1.37 (0.99–1.90)	8.9 (4.3 to >100)	2.10
Stewart et al., 1997	Phenelzine	28	3.76 (1.36–10.3)	1.6 (1.1–2.9)	0.64
Stewart et al., 1997	Imipramine	32	1.13 (0.52–2.48)	18 (2.5 to >100)	0.92
M Fava et al., 1998	Paroxetine	73	1.00 (0.46–2.17)	>100	0.95
M Fava et al., 1998	Fluoxetine	74	0.72 (0.28–1.90)	>100	0.69
Montgomery et al., 1998	Mirtazapine	387	6.78 (3.32–13.9)	4.2 (5.9–6.8)	1.04
Montgomery et al., 1998	Amitriptyline	386	2.45 (1.56–3.86)	6.0 (4.1–11)	1.68
Feiger et al., 1999	Nefazodone	467	1.96 (1.39–2.75)	6.3 (4.2–12)	2.05
Silverstone and Ravindran, 1999	Fluoxetine	237	1.53 (1.05–2.23)	7.3 (3.9–52)	1.93
Silverstone and Ravindran, 1999	Venlafaxine-XR	240	1.39 (0.97–1.98)	9.0 (4.3 to >100)	2.00
Versiani et al., 1999	Reboxetine	283	2.57 (1.79–3.69)	3.1 (2.4–4.7)	1.98
Bauer et al., 2000	Lithium	28	1.50 (0.94–2.40)	2.0 (1.3–4.3)	0.11
Schmidt et al., 2000	Fluoxetine 90 mg	312	1.36 (1.05–1.76)	7.6 (4.1–51)	2.34
Schmidt et al., 2000	Fluoxetine 20 mg	311	1.93 (1.43–2.60)	4.2 (2.9–7.6)	2.19
Sackeim et al., 2001	Nortriptyline+Lithium	48	2.15 (1.25–3.68)	2.2 (1.4–4.9)	1.44
Sackeim et al., 2001	Nortriptyline	50	1.40 (0.97–2.01)	4.2 (2.1 to >100)	1.98
Thase et al., 2001	Mirtazapine	156	2.41 (1.45–4.00)	3.6 (2.4–7.3)	1.52
Bschor et al., 2002	Lithium	22	0.70 (0.17–2.81)	>100	0.38
Golden et al., 2002	Paroxetine-CR	423	0.62 (0.32–1.21)	>100	1.14
Golden et al., 2002	Paroxetine-IR	428	0.38 (0.21–0.70)	>100	1.27
Weihs et al., 2002	Bupropion	828	1.41 (1.20–1.64)	6.7 (4.6–12)	2.64
Fava et al., 2005	Hypericum	88	1.28 (0.81–2.03)	9.0 (3.1 to >100)	1.66
Fava et al., 2005	Fluoxetine	90	1.05 (0.69–1.58)	45 (4.4 to >100)	1.81
Amsterdam and Bodkin 2006	Selegiline-transdermal	312	1.95 (1.34–2.83)	5.2 (3.4–11)	1.94
Perahia et al., 2006	Duloxetine	269	1.63 (1.04–2.58)	9.1 (4.8–91)	1.67
van den Broek et al., 2006	Imipramine	26	4.40 (1.22–15.8)	1.6 (1.1–3.2)	0.43
Goodwin et al., 2009	Agomelatine	492	1.96 (1.48–2.59)	5.1 (3.5–8.9)	2.26
Rickels et al., 2010	Desvenlafaxine	374	1.77 (1.30–2.40)	5.4 (3.6–11)	2.17
Yildiz et al., 2010	Antidepressants	46	2.14 (1.08–4.26)	2.9 (1.6–13)	1.10
Rosenthal et al., 2013	Desvenlafaxine	548	2.08 (1.46–2.96)	6.8 (4.7–13)	2.01
Borges et al., 2014	Not stated	224	1.96 (1.29–2.97)	5.0 (3.1–14)	1.80
Borges et al., 2014	Not stated	258	1.78 (1.24–2.56)	5.4 (3.3–14)	1.97
Borges et al., 2014	Not stated	226	2.14 (1.60–2.88)	2.9 (2.1–4.7)	2.21
Borges et al., 2014	Not stated	147	2.14 (1.08–4.24)	6.6 (3.3 to >100)	1.10
Borges et al., 2014	Not stated	298	4.87 (2.85–8.30)	3.3 (2.4–5.0)	1.45
Borges et al., 2014	Not stated	125	2.72 (1.24–5.98)	5.1 (3.0–17)	0.92

Table 1. *Continued*

Trial	Treatment	Subjects	RR (95% CI)	NNT (95% CI)	Weight (%)
Borges et al., 2014	Not stated	213	1.72 (0.97–3.05)	9.9 (4.8 to >100)	1.34
Borges et al., 2014	Not stated	292	3.20 (1.86–5.50)	4.7 (3.3–8.1)	1.43
Borges et al., 2014	Not stated	156	1.49 (1.07–2.08)	5.2 (2.9–26)	2.08
Borges et al., 2014	Not stated	417	7.15 (2.56–20.0)	8.4 (5.9–15)	0.62
Borges et al., 2014	Not stated	312	1.93 (1.40–2.66)	4.3 (3.0–7.9)	2.12
Borges et al., 2014	Not stated	273	1.69 (1.22–2.34)	5.4 (3.3–15)	2.10
Borges et al., 2014	Not stated	269	2.22 (1.50–3.29)	4.1 (2.9–7.5)	1.87
Borges et al., 2014	Not stated	374	1.42 (1.11–1.82)	7.0 (4.1–23)	2.36
Borges et al., 2014	Not stated	548	1.93 (1.40 -2.66)	6.7 (4.5–13)	2.11
Pooled (72 comparisons)	——	14 450	1.90 (1.73–2.08)	4.4 (3.8–5.2)	100

By random-effects meta-analysis, pooled relative risk (RR 1.90; z = 13.3) and pooled number needed to treat (NNT 4.4; z = 12.7) were both highly significant, even in a sensitivity meta-analysis, omitting eight trials with RR ≥ 5.0 (RR 1.81, CI 1.66–1.97; z = 12.7; all $p<0.0001$); 23/72 trials (31.9%) individually yielded non-significant drug-placebo differences.

Table 2. Meta-analysis of long-term (>12 months) trials of antidepressants versus placebo in major depressive disorder

Trial	Treatment	Subjects	RR [95%CI]	NNT [95%CI]	% Weight
Bjork 1983	Zimelidine	38	2.67 [1.34–5.32]	1.9 [1.3–3.8]	1.83
Glen et al. 1984	Amitriptyline	67	1.41 [1.04–1.84]	3.9 [2.0–59]	3.67
Glen et al. 1984	Lithium	78	1.37 [1.03–1.92]	4.1 [2.1–139]	3.78
Prien et al. 1984	Amitriptyline±Lithium	150	1.91 [1.32–2.78]	3.5 [2.3–7.4]	3.28
Frank et al. 1990	Imipramine+IPT	51	2.72 [1.28–5.78]	2.4 [1.5–6.0]	1.64
Robinson et al. 1991	Phenelzine	47	2.80 [1.54–5.09]	1.9 [1.3–3.7]	2.17
Kupfer et al. 1992	Imipramine+IPT	20	7.33 [1.07–50.3]	1.7 [1.1–4.5]	0.35
Maj et al. 1992	Tricyclics±Lithium	72	1.22 [0.97–1.52]	6.3 [2.9 to >100]	4.17
OADIG 1993	Dothiepin	69	1.83 [1.01–3.32]	4.0 [2.1–37]	2.19
Kishimoto et al. 1994	Mianserin	22	2.25 [1.08–4.67]	1.8 [1.1–4.3]	1.71
Entsuah et al. 1996	Venlafaxine	448	1.69 [1.23–2.32]	7.2 [4.6–18]	3.61
Kocsis et al. 1996	Desipramine	129	4.79 [2.29–10.0]	2.4 [1.8–3.8]	1.68
Keller et al. 1998	Sertraline	161	3.48 [1.37–8.88]	6.2 [3.8–18]	1.20
Terra and Montgomery 1998	Fluvoxamine	436	2.75 [1.86–4.06]	4.4 [3.3–6.8]	3.20
Reynolds et al. 1999	Nortriptyline	107	2.42 [1.60–3.68]	2.2 [1.6–3.5]	3.04
Alexopoulos et al. 2000	Nortriptyline	43	2.88 [1.09–7.64]	2.9 [1.6–13]	1.13
Gagne et al. 2000	ECT+Antidepressants	58	3.00 [1.63–5.54]	1.8 [1.3–3.0]	2.11
Rouillon et al. 2000	Milnacipran	214	1.45 [0.83–2.50]	14 [5.6 to >100]	2.38
Gilaberte et al. 2001	Fluoxetine	253	2.02 [1.34–3.04]	5.0 [3.2–11]	3.07
Hochstrasser et al. 2001	Citalopram	264	3.45 [2.47–4.82]	1.9 [1.6–2.3]	3.51
Klysner et al. 2002	Citalopram	121	2.12 [1.41–3.20]	2.8 [1.9–5.3]	3.08
Gelenberg et al. 2003	Nefazodone	160	1.57 [1.05–2.37]	5.8 [3.1–40]	3.09
Wilson et al. 2003	Sertraline	113	1.18 [0.80–1.73]	13 [3.8 to >100]	3.24
Lepine et al. 2004	Sertraline	288	1.97 [1.29–3.00]	6.1 [3.7–18]	3.02
Montgomery et al. 2004	Venlafaxine	225	2.51 [1.70–3.70]	3.0 [2.2–4.7]	3.20
Hollon et al. 2005	Antidepressants	69	1.64 [1.10–2.44]	3.3 [1.9–12]	3.14
Keller et al. 2005	Gepirone	420	1.52 [1.12–2.07]	8.4 [4.9–30]	3.66
Kornstein et al. 2006	S-Citalopram	139	2.38 [1.57–3.59]	2.6 [1.9–4.5]	3.06
Reynolds et al. 2006	Paroxetine+CM	53	1.92 [1.11–3.31]	3.0 [1.8–11]	2.40
Reynolds et al. 2006	Paroxetine+PT	63	1.50 [0.82–2.72]	5.4 [1.8 to >100]	2.18
Keller et al. 2007a	Venlafaxine	131	5.89 [2.43–14.3]	2.7 [2.2–4.3]	1.31
Kocsis et al. 2007	Venlafaxine-ER	336	1.82 [1.31–2.52]	5.5 [3.5–11]	3.56
Kasper et al. 2008	Hypericum	426	1.42 [0.98–2.06]	13 [6.3 to >100]	3.29
Kelin et al. 2010	Duloxetine	514	2.53 [1.75–3.67]	5.3 [3.8–8.3]	3.30
Liebowitz et al. 2010	Quetiapine-ER	771	2.42 [1.83–3.20]	5.0 [3.8–7.0]	3.84
Segal et al. 2010	Antidepressants	58	2.60 [1.32–5.11]	2.3 [1.5–5.2]	1.88
Boulenger et al. 2012	Vortioxetine	639	1.97 [1.29–3.01]	7.8 [4.9–20]	3.00
Pooled (37 comparisons)	——	7253	2.03 [1.80–2.28]	3.8 [3.3–4.6]	100

Based on 35 placebo-controlled trials (except for Gagne et al., with antidepressants-only as controls), with 37 drug/control comparisons, lasting >12 (14–60) months shown in eTable S2, with random-effects meta-analytic modeling. Total N includes 9 controls used twice (for Glen et al. 1984). The pooled RR (recurrence rate with placebo/drug) indicates highly significant overall superiority versus placebo (z=11.7, $p<0.0001$); 5/37 trials (13.5%) individually yielded nonsignificant drug-control differences. *Abbreviations*: *CM*, clinical management; *ECT*, electroconvulsive treatment; *ER*, extended release; *IPT*, interpersonal psychotherapy; NNT = number-needed-to-treat to yield a selective response to drug > placebo; *PT*, psychotherapy.

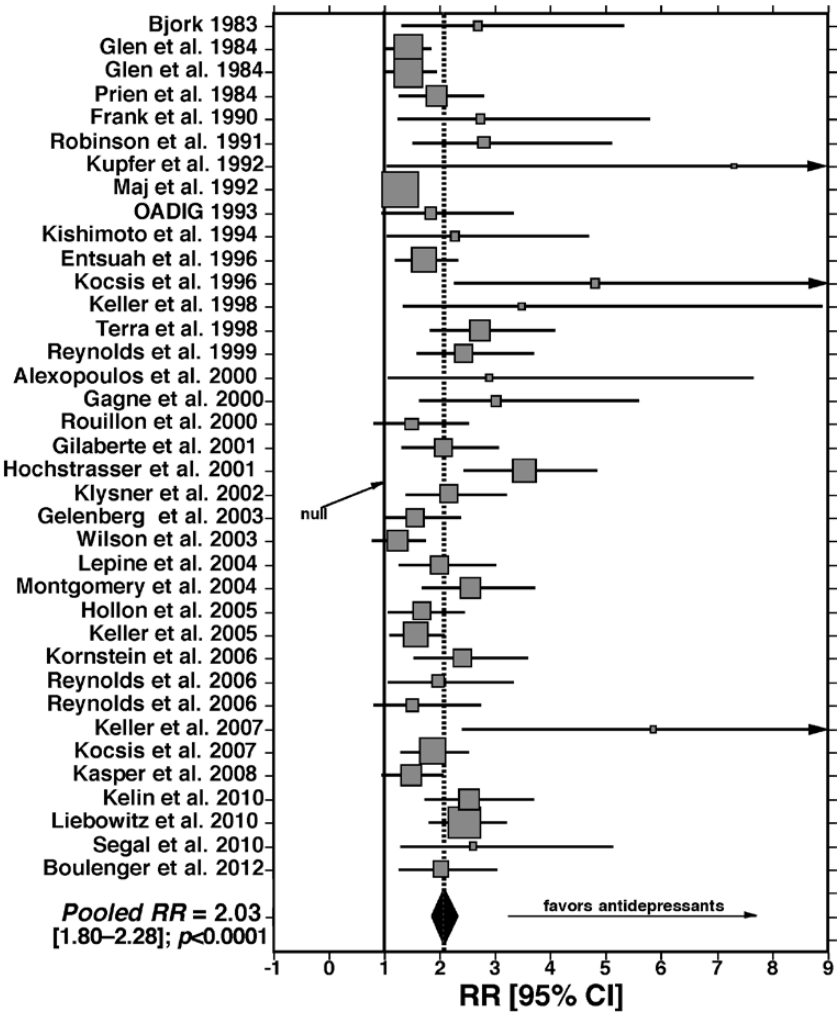

Figure 2. Findings from random-effects meta-analysis of 37 controlled, long-term trials (>12 months) of antidepressants vs. placebos in major depression. The pooled ratio (RR) of recurrence risk with placebo vs. antidepressants, of 2.03 [CI: 1.80-2.28]) is highly significant (z-score = 11.7, $p < 0.0001$).

in which antidepressants were involved). This heterogeneous group of studies yielded varied findings, as might be expected. Statistically nonsignificant results were reported in at least one component of 11 of the trials (50.0%; Tables 3 and S3). A notable finding in four of the trials (all involving CT or MCT) is that presumably more severely ill patients, with at least three or five pre-trial recurrences of depressive episodes, showed greater responses to treatment than subjects with fewer recurrences (Ma and Teasdale, 2004; Bockting et al., 2005, 2009; Teasdale et al., 2000).

Meta-Regression Analyses

Following random-effects meta-analyses, we used meta-regression modeling to test for associations of outcomes of trials reported in Tables 1–3 and S1–S3 with available potential covariates. These factors included: (a) year study was reported; (b) trial size (total number of subjects); (c) mean age of subjects; (d) proportion of women participants; (e) estimated counts of previous depressive episodes; (f) initial weeks of treatment prior to randomization; (g) month duration of continuation or long-term trials; (h) type of antidepressant (older agents [TCAs, the atypical agents dothiepin and mianserin, or MAO inhibitors] vs. newer agents [SSRIs or SNRIs, mirtazapine, or bupropion]).

Regarding meta-analysis of intermediate-term continuation trials (Tables 1 and S1), meta-regression found only one of the eight stated factors to be significantly associated with efficacy of active treatments over placebo. It was the duration (weeks) of initial treatment and clinical stabilization of subjects presenting in acute depressive episodes prior to randomization into a continuation phase of each trial. That is, longer initial treatment was associated significantly with a larger drug-placebo contrast (greater effect size, whether based on placebo/drug RR or the difference in relapse rates between placebo and antidepressant, RD) during continuation treatment (β slope function = +0.048; CI 0.024–0.073; z = 3.90, $p < 0.001$).

Meta-regression analysis for long-term medication maintenance trials (Tables 2 and S2) also found only one factor to be significantly associated with outcomes in meta-analysis. That is, longer duration (months) had a positive effect on drug-placebo contrasts (β slope function = +0.104; CI 0.044–0.163; z = 3.44, $p < 0.001$). In addition, with linear regression modeling, recurrence rates with both drug and placebo increased with longer exposure time, as expected, although recurrence risk with placebo grew much more than with drug (r = +0.57 vs. +0.30, respectively). It follows that both their RR and RD grew larger, with longer treatment indicating greater effect size (r = +0.47 and +0.41, respectively, both t-scores ≥2.56, with $p \leq 0.01$), consistent with the meta-regression analysis.

Table 3. Meta-Analysis of Controlled, Long-Term Trials of Psychosocial Treatments for Major Depression

Trials	Subjects	Treatment	Controls	RR (95% CI)	NNT (95% CI)	Weight (%)
Shea et al., 1992	37	CBT	Pbo	0.92 (0.37–2.26)	>100	3.06
Shea et al., 1992	36	IPT	Pbo	1.00 (0.39–2.55)	>100	2.93
GA Fava et al., 1998	40	CBT+AD	AD	3.20 (1.45–7.05)	1.8 (1.2–3.4)	3.58
Gortner et al., 1998	151	CBT	CM	0.73 (0.50–1.08)	>100	6.06
Teasdale et al., 2000[a]	73	MCT (high)	TAU	1.64 (1.04–2.59)	3.8 (2.1–25)	5.63
Teasdale et al., 2000[b]	72	MCT (low)	TAU	0.55 (0.31–0.98)	>100	4.82
Jarrett et al., 2001	156	CBT	TAU	3.00 (1.44–6.26)	4.9 (3.1–12)	3.86
Katon et al., 2001	386	PsychoEd	TAU	0.98 (0.75–1.29)	>100	6.85
Klein et al., 2004	82	CBT	TAU	3.25 (1.15–9.14)	4.6 (2.6–20)	2.58
Ma & Teasdale, 2004[a]	38	MCT (high)	TAU	0.98 (0.68–1.26)	1.4 (1.1–1.9)	0.98
Ma & Teasdale, 2004[b]	38	MCT (low)	TAU	0.40 (0.15–1.06)	>100	2.81
Bockting et al., 2005[a]	71	CT (high)	TAU	1.54 (1.02–2.32)	4.1 (2.1–41)	5.92
Bockting et al., 2005[b]	101	CT (low)	TAU	0.93 (0.68–1.26)	>100	6.66
Hollon et al., 2005	70	CT	Pbo	2.45 (1.46–4.13)	2.2 (1.5–4.0)	5.16
Dobson et al., 2008	79	CT	AD	2.19 (1.08–4.42)	3.6 (2.1–14)	4.03
Dobson et al., 2008	76	BA	AD	2.00 (1.00–4.02)	3.8 (2.1–23)	4.09
Kuyken et al., 2008	123	MCT	AD	1.26 (0.90–1.75)	8.2 (3.4 to >100)	6.46
Bockting et al., 2009[a]	86	CT (high)	TAU	1.28 (1.06–1.53)	11 (2.8–16)	7.33
Bockting et al., 2009[b]	86	CT (low)	TAU	0.97 (0.79–1.20)	>100	7.22
Bondolfi et al., 2010	60	MCT	TAU	1.19 (0.56–2.50)	18 (3.4 to >100)	3.81
Segal et al., 2010	54	MCT	Pbo	2.45 (1.30–4.60)	2.4 (1.5–5.6)	4.46
Shimazu et al., 2011	54	FamPsychoEd	TAU	6.00 (1.52–23.7)	2.4 (1.6–4.8)	1.71
Pooled (22 comparisons)	1 969	—	—	1.39 (1.13–1.70)	6.0 (3.8–14)	100

Based on random-effects meta-analysis of data in Supplementary Table S3, omitting drug arms and trials lacking separate control arms. The pooled RR of 1.39 is statistically significant ($z = 3.15$, $p = 0.002$), although 11 of 22 (50.0%) comparisons involved non-significant differences between experimental psychosocial treatments and controls.

In four studies, differences were found among subgroups with relatively [a]high (≥3 or ≥5) vs. [b]lower numbers of previous depressive recurrences. With high recurrences, pooled RR = 1.63 (1.04–2.57; $z = 2.14$, $p = 0.03$); with low recurrences, RR = 0.80 (0.58–1.09; $z = 1.41$, $p = 0.16$).

AD, antidepressants; BA, behavioral activation therapy; CBT, cognitive behavioral therapy; CI, confidence interval; CT, cognitive psychotherapy; FamPsychoEd, family psychoeducation; IPT, interpersonal psychotherapy; MCT, mindfulness-oriented cognitive therapy; Pbo, placebo; PsychoEd, psychoeducation; RR, recurrence rate; TAU, treatment as usual.

Meta-regression modeling for findings in long-term psychotherapy trials (Tables 3 and S3) indicated that none of the factors listed above was significantly associated with larger effect-sizes in random-effect meta-analysis. However, when trials involving high (≥3 or ≥5) versus low counts of previous depressive episodes were pooled for random-effects meta-analysis, there was a much greater effect of psychosocial interventions after higher recurrence counts.

Effect of Type of Treatment

We also summarized meta-analytic results for comparisons of specific types of antidepressants versus placebo controls in long-term trials summarized in Table 2. Only TCAs (n = 10) and the pool of SSRIs (n = 11) and SNRIs (n = 7) provided at least 10 trials for meta-analysis, and all yielded similar RR values (2.09, 2.10, and 2.17, respectively). Overall, computed RR values (relative recurrence with placebo/antidepressant: greater, better) ranked: ECT (RR = 3.00) > MAO inhibitor (2.80) > SSRIs (2.17) ≥ SNRIs (2.10) ≥ TCAs (2.09) > various standard antidepressants (1.91) > atypical agents (gepirone, hypericum, mianserin, nefazodone, or quetiapine-ER; 1.72) > lithium (1.39), but all active agent types were significantly superior to placebo.

Summary of Findings

Finally, salient characteristics of the information found regarding: (a) continuation of antidepressant treatment up to 12 months (72 trials with 14 450 subjects) after an acute depressive episode; (b) long-term maintenance treatment with antidepressants (37 trials with 7253 subjects); and (c) long-term use or addition of psychosocial treatments (22 trials with 1 969 subjects) are summarized in Table 4. By trial-type, meta-analytically computed values of effect-size (RR) ranked: b, long-term antidepressants (2.02) > a, continuation of antidepressants (1.90) > c, long-term psychosocial treatments (1.39). Similarly, computed NNT values ranked inversely in the same order (b, 3.8 < a, 4.4 ≤ c, 6.0), as did the rate of trials finding superior outcomes with test treatment versus controls (b, 86.5% > a, 68.1% > c, 50.0%).

Discussion

Most pharmacotherapy trials for MDD patients found significant reductions of early relapse (up to 12 months) or of long-term recurrence rates with active drugs compared to placebo controls (Tables 1, 12, S1, and S2, Figure 2). Differences between specific types of treatments or specific agents were insufficiently studied except for TCA, SSRI, and SNRI antidepressants, all of which appeared to provide similar long-term benefits. Long-term trials of psychotherapy for depression were relatively fewer and have yielded variable findings (Tables 3 and S3). Family psychoeducation appeared to be useful long-term in two studies reported from Japan (Shimazu et al., 2011; Shimodera et al., 2012).

Continuation and Long-Term Pharmacological Treatments

In most continuation and long-term maintenance trials, antidepressant drugs proved to be more effective than placebo controls (Tables 1 and 2). Of the total of 109 such trials of efficacy

Table 4. Summary of Meta-Analytic Findings from Controlled Trials for Continuation or Maintenance Treatments for Recurrent Major Depression

Measures	Drug Continuation	Drug Maintenance	Psychosocial Maintenance
Reports	45	35	17
Controlled trials	72	37	22
Years	1 973–2 014	1 983–2 012	1 992–2 011
Subjects			
Total	14 450	7253	1 969
Per trial	189 (138–239)	188 (131–245)	124 (92.1–156)
Mean age	48.3 (46.0–50.6)	47.5 (42.5–52.1)	44.6 (44.0–48.2)
% Women	60.4 (56.4–64.4)	69.5 (37.3–71.7)	69.6 (64.7–75.5)
Duration (mos)	8.35 (7.55–9.15)	26.8 (25.5–31.1)	23.7 (18.4–29.0)
RR (95% CI)	1.90 (1.73–2.08)	2.03 (1.80-2.28)	1.39 (1.13–1.70)
z-score (*p*-value)	13.3 (<0.0001)	11.7 (<0.0001)	3.15 (0.002)
NNT (95% CI)	4.4 (3.8–5.2)	3.8 (3.3–4.6)	6.0 (3.8–14)
Trials with significant superiority of test treatment (%)*	49/72 (68.1%)	32/37 (86.5%)	11/22 (50.0%)

Recurrence rate (RR) is meta-analytically pooled risk of new depression with placebo or control treatment vs. active experimental treatment. Data are derived from Tables 1–3 and Supplementary Tables S1–3. *Success-rate is significantly greater for drug vs. psychosocial maintenance treatments ($\chi^2 = 6.29$, $p = 0.01$) and for all drug vs. psychosocial treatments ($\chi^2 = 4.72$, $p = 0.03$), but not between continuation and maintenance drug treatment ($\chi^2 = 2.80$, $p = 0.09$).
CI, confidence interval; NNT, number needed to treat to yield a selective response to drug > placebo.

in preventing relapses or recurrences of major depression, 81 (74.3%) yielded statistically significant differences favoring a variety of types of antidepressants (68.1% of continuation trials and 86.5% of maintenance trials). The most frequently studied antidepressants were SSRIs and SNRIs, which outperformed placebo controls in 11 of 20 (55.0%) continuation trials and 13 of 15 (86.7%) maintenance trials. Based on the results of meta-analysis, the relative risk of new episodes of depression with these modern drugs and TCAs was very similar, and the numbers of trials of other types of treatments was too limited to support secure conclusions about comparative efficacy. These findings appear to support the clinical value of extending antidepressant treatment for up to 12 months after initial improvement or remission of acute depression, as well as the value of long-term antidepressant treatment, at least when indications based on the demonstrated risk of recurrences, and of probable benefit, are present.

Non-Pharmacological Treatments

The effects of psychosocial treatments, with or without antidepressants, yielded inconsistent and largely inconclusive findings (Table 3). Among these, notably, family psychoeducation continued for up to 10 months was examined in two Japanese studies and found to be clinically effective and cost-effective in reducing recurrence risks in major depressive disorder patients (Shimazu et al., 2011; Shimodera et al., 2012). Mindfulness-based cognitive psychotherapy aims at teaching patients to disengage from cognitive processes that are proposed to increase vulnerability to depression, by improving awareness and acceptance of negative thoughts and feelings. Several trials of this treatment method did not provide superior protection against recurrences of depression than control conditions (Kuyken et al., 2008; Bondolfi et al., 2010; Mathew et al., 2010). However, one trial found it to be about as effective as long-term treatment with an antidepressant (Segal et al., 2010), and others found beneficial effects among patients with at least three previous depressive episodes (Teasdale et al., 2000; Ma and Teasdale, 2004). Widely clinically employed cognitive-behavioral therapy was associated with significantly lower long-term recurrence rates of depression than with a control condition involving treatment as usual or nonspecific clinical management, again, but the benefits appeared to be limited largely to patients with three or more previous episodes (GA Fava et al., 1998; Bockting et al., 2005, 2009). There is also some evidence that use of CBT during an index episode of acute depression may have long-lasting beneficial effects in limiting risks of relapse or recurrences for up to 2 years after initial remission (Hollon et al., 2005; Dobson et al., 2008).

In the present findings, notably, some trials found that psychosocial methods outperformed or significantly added to benefits of pharmacotherapies (e.g. GA Fava et al. 1998; Dobson et al. 2008; Kuykun et al. 2008; Table 3). Such findings encourage additional, well-designed, larger trials to test for long-term benefits of psychosocial methods, including their potential additional benefits when combined with antidepressants.

Finally, studies of effects of long-term ECT remain scarce. Two were identified that examined patients who had responded to ECT in an acute episode of major depression. Participants were then randomized to continue ECT with or without antidepressant medication, compared to other treatments that included an antidepressant plus lithium. Their findings favored ECT added or compared with medicinal treatments (Gagne et al., 2000; Kellner et al., 2006). A small "mirror-image" study found that maintenance ECT was associated with fewer and shorter psychiatric hospitalizations over 8 years compared to similar periods of illness before use of maintenance ECT (Gupta et al., 2008).

Effect of Multiple Depressive Recurrences

Several of the studies reviewed found that treatment effects appeared to be superior among patients with multiple (especially ≥3) previous episodes of depression (Montgomery et al., 1993; Teasdale et al., 2000; Lepine et al., 2004; Ma and Teasdale, 2004; Kelin et al., 2010). This relationship was more likely with psychotherapy (Teasdale et al., 2000; Ma and Teasdale, 2004; Bockting et al., 2005, 2009) than with pharmacotherapies (Montgomery and Dunbar, 1993; M Fava et al., 1998; Lepine et al., 2004; Keller et al., 2007a; 2007b; Kocsis et al., 2007; Kuyken et al., 2008; Bondolfi et al., 2010; Kelin et al., 2010; Mathew et al., 2010; Thase et al., 2011). Mechanisms involved are not clear, but more recurrent depressive disorders may be particularly responsive to efforts to apply psychological methods to modify demoralization and adverse patterns of thinking and behavior proposed to contribute to a risk of depression (Bockting et al., 2005). An

alternative possibility is that multiple previous recurrences may select for cases with particularly high future risks of recurrence, and so provide a statistical advantage in controlled trials.

Effect of Duration of Initial and Later Treatment

In meta-regression analyses, the only factors that appeared to be associated with greater drug-placebo differences were a longer initial treatment of index episodes of acute depression and a longer duration of long-term treatment that followed. Presumably, longer initial treatment places antidepressant-treated patients at an advantage in terms of adequate recovery from an acute depressive episode, with greater stabilization and resistance to relapses within several initial months, and longer treatment is disadvantageous for placebos. We also found recently that shorter duration of initial treatment with an antidepressant, especially less than 4–6 months, is followed by higher relapse risks with a placebo (Baldessarini et al., 2015). The possibility that such effects influenced the outcome of continuation trials could not be tested since data on the duration of initial placebo treatment in index depressive episodes were not available.

Limitations

This review has several noteworthy limitations. First, there were relatively few well-designed studies involving non-pharmacological treatments, and very few involving specific combinations of treatment methods that are commonly employed clinically on an empirical basis. Second, follow-up periods ranged from several months to five years (average: up to 2 years), with a probable excess of new episodes within the early months, although the actual times to new episodes usually were not reported. That is, not all trials are likely to represent fair testing of protection against recurrences (not contaminated by relapses) of major depression, which probably requires several years given the natural history of the illness, in which episodes typically reoccur less than yearly (Baldessarini, 2013). Third, many studies involve "enriched" designs, in which patients were required to respond favorably to short-term treatment of an initial episode of acute major depression. Such case selection is likely to limit potential generalization of findings to broader clinical populations. Fourth, many intermediate- or long-term trials involve discontinuation of an active treatment in patients barely recovering from an acute episode of depression. Such treatment discontinuation itself may contribute to inferior outcomes in the placebo arms of trials, especially if treatment discontinuation is abrupt or rapid (Baldessarini et al., 2010, 2015; Baldessarini, 2013). Fifth, we did not include studies of juvenile depression or study mainly geriatric depression. However, recent reviews of maintenance trials in these groups indicate that the evidence available is encouraging, but much less abundant than in adult MDD (Kok et al., 2011; Cox et al., 2012; Wilkinson and Izmeth, 2012). Additional limitations include the need to reuse single placebo arms in some trials that compared more than one active treatment; however, we carried out sensitivity analyses based on including only one treatment/control comparison from each of such studies, and found very minor effects on the meta-analytically pooled outcomes (not shown). In addition, there is a general lack of relevant clinical details concerning previous depressive episodes in many studies, and little consideration of subjective wellness and improved functioning as clinically relevant components of outcomes, and we found very little evidence that specific clinical or biological characteristics were considered that might contribute to predicting the likelihood of accepting, tolerating, and benefitting from particular long-term treatments.

Conclusions

Most of the pharmacotherapy trials reviewed showed significantly lower rates of relapse or recurrence of depressive episodes among adult patients diagnosed with MDD compared to placebos. These treatments involved the use of SNRIs, SSRIs, and other agents with demonstrated short-term efficacy in acute major depressive episodes (Undurraga and Baldessarini, 2012; Baldessarini, 2013). ECT also had some benefit in recurrence prevention, but remains inadequately tested in the long term. Fewer long-term, monotherapy trials of psychotherapies have been reported; most involve cognitive-behavioral techniques, sometimes with antidepressants continued. Nevertheless, most psychotherapy trials have found some evidence of long-term benefit, especially in patients with three or more previous episodes of major depression. Despite the evidence of efficacy of antidepressants, and suggestive support for some forms of psychosocial interventions compared to placebos or other controls, the present findings underscore the substantial rates of long-term unresolved morbidity in treated MDD patients (Forte et al., 2015); with treatment, relapse rates averaged 23.3% (in 8.4 months), and recurrences averaged 24.6% to 36.8% (in 24–27 months; Tables S1–3). That conclusion strongly encourages further efforts to develop more effective and better-accepted treatments and evaluations of the effects of dosing and of specific combination therapies, conducted over periods longer than a year, and efforts to design trials so as to limit biases associated with case selection and artifacts associated with treatment discontinuation, especially soon after initial apparent clinical recovery, as well as to examine predictors of positive or unfavorable outcomes and of nonadherence to long-term treatments.

Supplementary Material

For supplementary material accompanying this paper, visit http://www.ijnp.oxfordjournals.org/

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Statement of Interest

No author or immediate family member has financial relationships with commercial organizations that might represent the appearance of potential conflicts of interest with the material presented here.

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