Appendices

Appendix 1. Methods

Data sources

Medline was searched using PubMed (National Center for Biotechnology Information, U.S. National Library of Medicine) for reports published between January 1996 and May 2011. The search terms used are presented in Appendix 2. The search was limited to identify publications of studies that had primary data collection (e.g., "journal article") and to omit case reports, reviews, editorials, and letters. All other designs were included. Other limits included studies of humans and papers written in the English language. The search was augmented with additional PubMed search terms, with a search of economic outcomes through August 2013, and by using the Tufts Cost-Effectiveness Analyses (CEA) Registry (1), an online repository of cost-effectiveness studies. The search was also augmented by including the STAR*D trials. STAR*D, which used a more inclusive treatment-resistance criterion than this review (i.e. failure to remit), provided valuable comparators as the largest and longest study evaluating depression treatment.

Study selection

Two researchers screened each abstract of the retrieved references for potentially relevant studies (Appendix 3). Papers were included if the abstract referred to primary data collection as a part of the study; the endpoints were pertinent to clinical, societal, or economic outcomes; the study did not primarily assess pharmacokinetic or in vitro endpoints; the study dealt with an adult population (>18 years of age); and the target population had treatment-resistant depression. Teenagers' developing brains make adolescent depression a qualitatively different phenomenon, so studies of adolescents

were excluded to increase consistency of treatments, disease progression, and lifetime impact in an adult population. Two researchers then reviewed the full text of each potentially relevant study and independently recorded relevant data. These 2 extractions were subsequently reconciled into the final list of data for analyses.

This study's criterion for treatment-resistance was defined broadly to include studies with heterogeneous treatment-resistance definitions while conforming to accepted criteria: failure to respond to 1 or more adequate trials of drug therapy. An "adequate" trial was defined as being ≥6 weeks in duration (2, 3), with appropriate doses of treatment (4-7); response was defined as a ≥50% decrease in symptoms (8). In the absence of detailed descriptions of patient characteristics, "treatment-resistant" criteria were also fulfilled by any patient populations whose members were described as being "resistant" or "refractory" to treatment; this was done to avoid excluding possible treatment-resistant depression populations.

Data extraction and assessment of study quality

Extracted data included, where available, the following: author(s), year of publication, journal, study design (e.g., randomized control trial, observational), number of study arms and patients per arm, study duration, evidence grade, sample size, the percentage of women in the study, mean age, ethnic background, duration of illness at study entry, number of prior depressive episodes, and mean or median patient survival.

Data were also recorded on the names of antidepressant drugs reported in the study, their duration of use and cost, as well as the incidence and cost of medical and psychiatric hospitalizations, emergency department visits, and physician visits. Costs were reported in 2012 US dollars using the medical component of the Consumer Price Index for inflation. Rates of labor force participation, absenteeism, presenteeism (attending work while not healthy), homelessness, crime, and use of social services were documented. Data were extracted on incidence of treatment-resistant depression,

symptom severity, deaths, and comorbidities and adverse events that occurred during the study period. In the absence of qualifying data, any adverse event that resulted in discontinuation of a drug or hospitalization was classified as severe. Otherwise, adverse events not clearly specified as severe were assumed to be mild/moderate.

Mortality and suicide rates were recorded, including the number and prevalence of previous suicide attempts, suicidal ideation, self-injury, suicide attempts that resulted in death, and mortality due to different comorbidities. Mean baseline and changes in quality-of-life scales, utility scales, quality-adjusted life years, and disability-adjusted life years were obtained for patients and caregivers, if reported. Mean baseline and/or change in symptom severity of standardized assessment scales was recorded. Available data were extracted on the proportion of patients with treatment-resistant depression who had a treatment response, as defined by a ≥50% decrease in the HAM-D scores, QIDS-C16, or MADRS, or a HAM-D-17 score <10; and remission, as defined by a HAM-D-17 score of ≤7, a HAM-D-24 score of ≤8, a QIDS-C16 score of ≤5, or a MADRS score of ≤8 (8-19).

The evidence grade for each study was assessed using the Quality Index developed by the Mental Disorders and Illicit Drug Use Expert Group (20). The Quality Index was developed to quantify and assess the representativeness of the studies and to ensure quality transparency for each reference. It includes items pertaining to completeness of reporting, ascertainment of cases, measurement instruments, diagnostic criteria, outcome, and follow-up. The maximum achievable score on the Quality Index is 19.

Data synthesis

Evidence tables were developed to facilitate data entry using Microsoft Excel worksheets. Analyses were performed using Stata™ version 9.2 (StataCorp, College Station, TX). Frequency distributions were generated for categorical variables (e.g., gender). For continuous variables (e.g., sample size), the distribution was summarized

using mean, median, standard deviations between studies, and minimum and maximum values across studies. A change in response rates was statistically analyzed using pooled estimates and by weighting studies with inverse-variance methodology (21). Summary statistics were weighted by sample size. Unless stated otherwise, results are reported for the treatment-resistant population, as mean ± standard deviation.

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Appendix 2. Detailed electronic search strategy

MAIN SEARCH TERMS

Treatment-resistant-depression-related

"major depressive disorder", "major depression", "MDD", "treatment-resistant", "TRD", "drug resistant", "refractory", "resistant"

Outcomes-related

"mortality", "morbidity", "survival", "quality of life", "adverse drug reaction", "ADR", "suicide"

Economic-related

"cost", "economic", "burden of illness", "cost of illness", "hospitalization", "decompensation", "work productivity", "workplace efficiency", "presenteeism", "absenteeism," "employment"

Society related

"crime", "homicide"

SUPPLEMENTAL PUBMED SEARCH TERMS

Treatment-resistant-depression-related

Same as above

Outcomes-related

"metabolic disease[MeSH]", "diabetes", "obesity", "lipid disorders", "diabetic", "metabolic syndrome", "insulin", "side effects", "adverse events", "tolerability", "tolerability[MeSH]", "toxicity", "toxicities", "induced mania", "QIDS", "quick inventory for depressive symptomatology"

Economic-related

"emergency", "ER", "emergency room", "emergency[MeSH]", "ED", "emergency department"

LIMITS

Subjects — Humans

Publication types — Journal Article, Clinical Trial, Randomized Controlled Trial, Clinical Trial, Phase I, Clinical Trial, Phase II, Clinical Trial, Phase III, Clinical Trial, Phase IV, Comparative Study, Controlled Clinical Trial, Multicenter Study

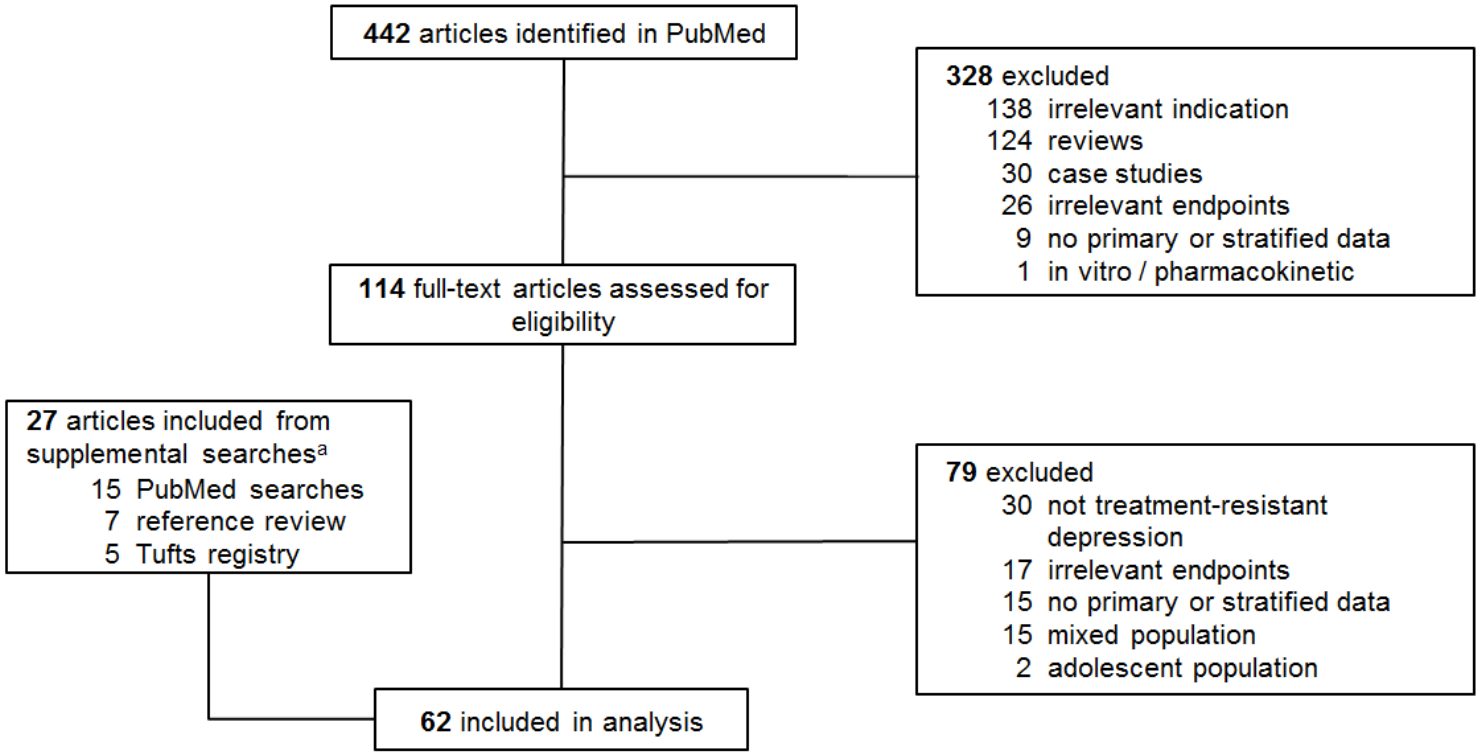
Language — English

Publication Date — January, 1996 to May, 2011[a]

Abbreviations: MeSH - Medical Subject Heading.

[a] Additional supplemental search conducted using treatment-resistant-depression-related search terms and all economic-related search terms for publications between May 2011 and August 2013.

Appendix 3. Flow diagram of literature search



[a]*Tufts CEA registry search, reference review of cost articles, and PubMed search on adverse events, emergency room costs, costs through August 2013, and Quick Inventory of Depressive Symptomatology severity scale.*

Appendix 4. Identified studies on the burden of illness of treatment-resistant-depression

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6 Benedict A, Arellano J, De Cock E, et al: Economic evaluation of duloxetine versus serotonin selective reuptake inhibitors and venlafaxine XR in treating major depressive disorder in Scotland. J Affect Disord 120:94-104, 2010

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Appendix 5. Study design, subgroups, length, and quality of evidence[a]

Variable	Patients per study			% of total studies (out of 49)
	Mean	±	SD	
Study design				
Phase III RCT	122	±	118	14%
Phase II RCT	20	±	9	10%
Comparative randomized trial (no control)	246	±	232	6%
Non-randomized comparative trial	104	±	126	12%
Non-randomized single arm trial	168	±	395	18%
Retrospective cohort study	5521	±	9603	20%
Cross sectional study	72	±	107	10%
Case series	35	±	32	8%
Case report	0	±	NA	0%
Total	1239	±	4756	100%
Number of treatment arms per study				
1	1878	±	6134	50%
2	353	±	1075	32%
3	28	±	NA	2%
>3	483	±	NA	4%

	Mean	±	SD	% of total studies reporting data
Study duration (months)	93	±	21	46%
Quality of evidence score[b]	13	±	3	100%

Abbreviations: NA - not applicable; RCT - randomized controlled trial; SD - standard deviation.

The SD was not reported when only one study provided results.

[a] Table summarizes 49 studies from 56 articles; the 6 utility weight studies based on models were not included in other analyses.

[b] Evaluated based on the Quality Index developed by the Mental Disorders and Illicit Drug Use Expert Group (20).