Poorer Long-Term Outcomes among Persons with Major Depressive Disorder Treated with Medication

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Major depressive disorder (MDD) is more often chronic or recurrent in clinical than in community samples. For example, perhaps 85% of patients but only 35% of persons in the community with MDD experience another depressive episode within 15 years [1]. Nonetheless, active treatments including antidepressant medication or cognitive therapy reduce depressive symptoms and delay relapse compared to inactive controls [2–4]. Follow-ups of treated and untreated persons in clinical trials have rarely exceeded 1–2 years, however.

Possible explanations for short-term treatment benefits but poorer long-term outcomes in clinical versus community samples include: (a) measurement differences between studies (e.g., perhaps patients were asses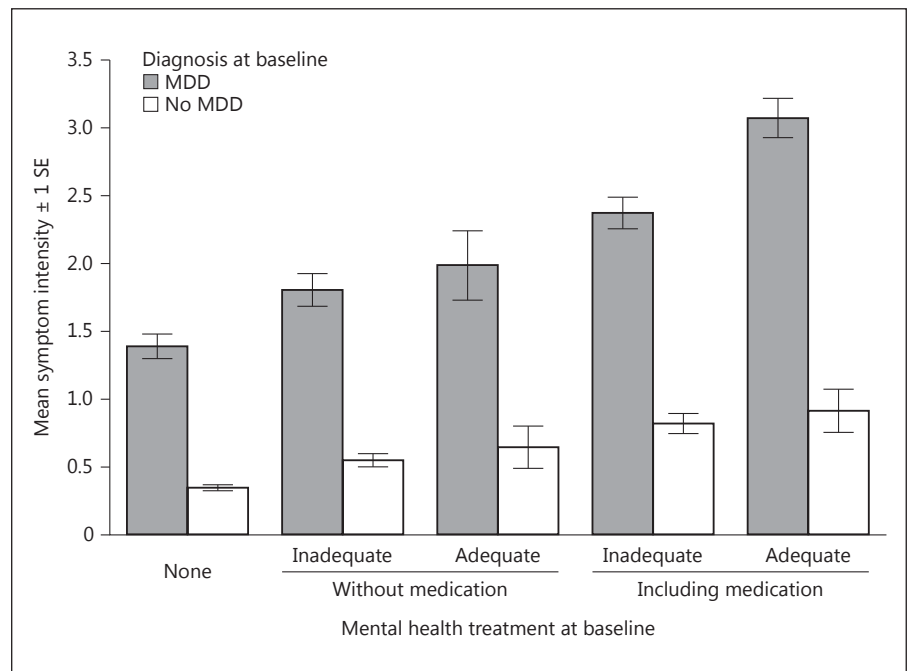sed more rigorously), (b) patients had severer MDD or other liabilities (e.g., intrapsychic, physical, social) that eventually outweighed treatment benefits, and/or (c) some depression treatments, such as medications, produced long-term harms [5].

The current analyses of a national sample with 9-year follow-ups clarified these possibilities. Using the same assessments for treated and untreated persons excluded the first possibility. Testing whether MDD severity and a wide range of demographic, psychosocial, and clinical variables accounted for long-term differences between treated and untreated persons estimated the second possibility, with remaining outcome differences more likely due to treatment.

The Midlife Development in the United States Survey conducted in 3 waves in the years 1995–1996 ($n = 7,108$), 2004–2006 ($n = 4,963$), and 2013–2014 ($n = 3,294$) provided data [6]. Participants were English-speaking, noninstitutionalized adults, residing in the coterminous United States, aged 25–74 at wave 1. Waves 2 and 3 attempted to reassess all living participants. Participants completed telephone interviews and mail-in questionnaires. Analyzed variables were collected at each wave unless noted.

The Composite International Interview short-form [7] assessed DSM-III-R MDD, generalized anxiety disorder, and panic disorder. Participants with 2 weeks of depressed mood and/or anhedonia during the past year completed assessment of 6 additional symptoms, yielding a 0–7 depression scale, and scores ≥ 4 also defined MDD.

Fig. 1. The presence of major depressive disorder (MDD) and receipt of mental health treatment predicted greater depressive symptoms 9 years later. Over the past year, treatment was "adequate" with ≥ 8 visits with a psychiatrist, psychologist, counselor, or social worker if not taking medication, or ≥ 4 visits with a psychiatrist or other medical doctor if taking medication; it was "inadequate" with fewer mental health visits or "none" with no visits and no medication.

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Participants reported mental health treatment visits with psychiatrists; other medical doctors; psychologists, counselors or social workers; and with religious/spiritual advisors over the past year; and use of prescription medicine for "nerves, anxiety, or depression" over the past month. "Adequate" treatment included ≥8 visits with a psychiatrist, psychologist, counselor, or social worker if not taking medication, or ≥4 visits with a psychiatrist or other medical doctor if taking medication [8]. "Inadequate" treatment included fewer mental health visits. Zero visits and no medication defined no treatment.

Illness and family history variables (wave 1 only) included globally rated mental health and parents' health (averaged across mother and father) when participants were aged 16, and a childhood maltreatment scale (emotional and physical abuse from mothers and fathers).

Current functioning scales included impairment in instrumental activities of daily living (e.g., carrying groceries, walking) plus social support and strain from friends and family. Personality scales included sense of control over personal circumstances, neuroticism, extraversion, and conscientiousness. Alcohol problems (by any of 4 screening items) and the count of 25 nonpsychiatric chronic illnesses during the past year were also analyzed.

Twelve-month MDD prevalence at survey waves 1, 2, and 3 was 13.3, 10.5, and 9.9%, respectively. With MDD, 38.1% of participants received no treatment, 25.2% inadequate treatment including medication, 19.2% inadequate treatment without medication, 13.5% adequate treatment including medication, and 4.1% adequate treatment without medication during the past year.

Depressive symptom severity at 9-year follow-ups was predicted from prior MDD diagnostic status (present/absent), prior mental health treatment (none, inadequate including or without medication, adequate including or without medication), and their interaction, entered simultaneously as fixed effects in a time-lagged multilevel model (i.e., wave 1 → 2 and wave 2 → 3) using maximum likelihood estimation. The model controlled random effects of participant (repeated measures) and family (some participants were siblings).

Prior MDD status, $F(1, 7545) = 298.38$, treatment, $F(4, 7545) = 34.66$, and their interaction, $F(4, 7545) = 6.75$, $p_s < 0.001$, predicted subsequent depressive symptom levels (Fig. 1). Among persons with MDD, planned contrasts showed that symptoms were higher after inadequate treatment ($d = 0.36$), adequate treatment ($d = 0.59$), treatment without medication ($d = 0.26$), or treatment including medication ($d = 0.69$) compared to no treatment, and symptoms were higher after treatment including medication versus treatment without medication ($d = 0.43$), $p_s < 0.005$, two-tailed.

Depression severity and other variables predicted concurrent mental health treatment (Table 1). All variables in Table 1 were added to the multilevel model as covariates and contrasts recomputed. Among persons with MDD, symptoms were higher after inadequate treatment ($d = 0.25$), adequate treatment ($d = 0.40$), or treatment including medication ($d = 0.54$) compared to no treatment, and symptoms were higher after treatment including medication versus treatment without medication ($d = 0.43$), $p_s < 0.001$. However, symptoms after treatment without medication were no longer elevated compared to no treatment, $d = 0.11$, $p = 0.20$.

These results extended previously observed differences between clinical versus community samples [1]. Symptoms were more sharply elevated 9 years following treatment including medication than treatment without medication, and MDD severity plus other covariates did not account for increased depression after medication. Patient characteristics accounted for symptoms after treatment without medication, however. This pattern suggests possible long-term iatrogenic effects of antidepressants. For example, antidepressant medications may recruit processes that oppose and eventually overwhelm short-term benefits resulting in loss of efficacy, resistance to retreatment, paradoxical effects, and withdrawal syndromes [5], perhaps via disruption of homeostatic control of monoamine neurotransmitters [9].

Several limitations tempered the current findings. Because treatment was not randomized, additional unmeasured confounds possibly produced the observed group differences. Moreover, treatment details (e.g., clinical assessment/referral, which medications, doses, durations) were unknown. Better long-term outcomes may be possible with higher-quality care, such as sequential treatment with medication followed by cognitive therapy [10].

At best, treatment was insufficient to overcome liabilities among persons with MDD in the current sample. Moreover, treatment including medication may have worsened depression in the

Table 1. Baseline sample characteristics and concurrent correlations with mental health treatment

Variable	n	Mean	SD	Correlation
Age	7,049	46.38	13.00	−0.01
Female gender	7,027	51.7%		0.08**
White race	6,176	90.7%		0.00
Household income[a]	6,110	10.99	9.39	−0.02*
Level of education[b]	7,095	6.77	2.49	−0.01
Depressive symptoms[c]	7,108	0.79	1.93	0.26**
Generalized anxiety disorder	7,108	2.7%		0.12**
Panic disorder	7,108	6.6%		0.15**
Alcohol problem	6,239	6.8%		0.05**
Parental health at age 16[d]	6,218	4.37	1.08	−0.06**
Mental health at age 16[e]	7,095	4.11	1.00	−0.12**
Childhood maltreatment[f]	6,154	1.79	0.71	0.11**
Chronic illnesses[g]	6,308	2.06	2.18	0.19**
IADL dysfunction[f]	6,312	1.57	0.77	0.14**
Social support[f]	6,255	3.33	0.53	−0.05**
Social strain[f]	6,256	2.02	0.48	0.12**
Sense of control[h]	6,271	5.50	1.02	−0.17**
Neuroticism[f]	6,265	2.24	0.66	0.22**
Extraversion[f]	6,271	3.20	0.56	−0.06**
Conscientiousness[f]	6,270	3.42	0.44	−0.08**

Sample characteristics from survey wave 1; subsamples were reassessed 9 and 18 years later. Concurrent correlations between patient characteristics and mental health treatment (none = 0, inadequate = 1, adequate = 2) estimated in multilevel models including data from each survey wave. IADL, instrumental activities of daily living. * $p < 0.05$, ** $p < 0.001$, two-tailed. [a] $10,000 units adjusted for inflation to year 2015. [b] 1–12 scale. [c] 0–7 scale. [d] 1–6 scale. [e] 1–5 scale. [f] 1–4 scale. [g] 0–25 count. [h] 1–7 scale.

long run. Until mechanisms of benefits and harms are better understood, these findings argue for using antidepressant medication only if short-term benefits (e.g., reducing active suicide risk) are likely to outweigh delayed consequences.

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