King's Research Portal

DOI:

[10.1056/NEJMcp1712493](https://doi.org/10.1056/NEJMcp1712493)

Document Version

Publisher's PDF, also known as Version of record

[Link to publication record in King's Research Portal](#)

Citation for published version (APA):

Moulton, C., & Young, A. (2019). Depression in the primary care setting. *New England Journal of Medicine*, 380(6), 559-568. <https://doi.org/10.1056/NEJMcp1712493>

Citing this paper

Please note that where the full-text provided on King's Research Portal is the Author Accepted Manuscript or Post-Print version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version for pagination, volume/issue, and date of publication details. And where the final published version is provided on the Research Portal, if citing you are again advised to check the publisher's website for any subsequent corrections.

General rights

Copyright and moral rights for the publications made accessible in the Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognize and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the Research Portal

Take down policy

If you believe that this document breaches copyright please contact librarypure@kcl.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.

Depression in the Primary Care Setting

TO THE EDITOR: In the Clinical Practice article by Park and Zarate (Feb. 7 issue)¹ on depression in the primary care setting, the authors do not address the considerable financial barriers and stigma that many patients with depression encounter with regard to accessing psychotherapy. We would like to call attention to a promising model that we are using in our practice — the collaborative care model — that allows us to embed a behavioral health care manager into our usual clinical care.²

The Centers for Medicare and Medicaid Services recently introduced billing codes for services provided by a behavioral health care manager working collaboratively with primary care providers within their own practice.³ In this model, patients in primary care settings are screened for depression with the use of a validated instrument such as the Patient Health Questionnaire 9 (PHQ-9). If the results are positive, the patients undergo consultation with a psychiatrist, are enrolled in a registry, receive a brief course of evidence-based psychotherapy such as cognitive behavioral therapy, and are monitored with the use of measurement-based targets. Numerous randomized, controlled trials have shown the effectiveness of this approach as compared with usual liaison psychiatry.⁴ Such innovative approaches will allow more patients to access expanded mental health services within their own primary care practice, which is both cost-efficient for the patient and sustainable for the practice.

Peter Ellis, M.D., M.P.H.
Brandon Kitay, M.D., Ph.D.
Caroline J. Schmidt, Ph.D.

Yale School of Medicine
New Haven, CT
peter.ellis@yale.edu

No potential conflict of interest relevant to this letter was reported.

1. Park LT, Zarate CA Jr. Depression in the primary care setting. *N Engl J Med* 2019;380:559-68.
2. Unützer J, Katon W, Callahan CM, et al. Collaborative care management of late-life depression in the primary care setting: a randomized controlled trial. *JAMA* 2002;288:2836-45.
3. Press MJ, Howe R, Schoenbaum M, et al. Medicare payment for behavioral health integration. *N Engl J Med* 2017;376:405-7.
4. Archer J, Bower P, Gilbody S, et al. Collaborative care for depression and anxiety problems. *Cochrane Database Syst Rev* 2012;10:CD006525.

DOI: 10.1056/NEJMc1903259

TO THE EDITOR: As Park and Zarate discuss, non-response to first-line antidepressants is common. The authors comment that, “Although improvement may be noted as early as 2 weeks, full relief of symptoms may not be seen for 8 to 12 weeks.” Unfortunately, this does little to challenge the commonly held belief that antidepressants take longer than 2 weeks to take effect. In a meta-analysis of 47 randomized, controlled trials, 35% of clinical improvement was seen during the first week and a further 25% during the second week.¹ Furthermore, clinical improvement by 2 weeks is a powerful predictor of subsequent response and remission.² In line with a 2015 guideline,³ we would therefore advocate reassessment 2 weeks after the initiation of antidepressant therapy to assess efficacy, side effects, and suicide risk. If there is no improvement 4 weeks after initiation, despite adherence to the regimen and an absence of coexisting substance use, it would be prudent to consider a medication change. Given that protracted depression causes suffering, functional decline, and even structural brain changes,⁴ clinicians may minimize this burden by making proactive changes to ineffective therapy.

Calum D. Moulton, M.A., M.R.C.Psych.
Allan H. Young, Ph.D., F.R.C.Psych.

King's College London
London, United Kingdom
calum.moulton@kcl.ac.uk

No potential conflict of interest relevant to this letter was reported.

1. Posternak MA, Zimmerman M. Is there a delay in the antidepressant effect? A meta-analysis. *J Clin Psychiatry* 2005;66:148-58.
2. Szegedi A, Jansen WT, van Willigenburg APP, van der Meulen E, Stassen HH, Thase ME. Early improvement in the first 2 weeks as a predictor of treatment outcome in patients with major depressive disorder: a meta-analysis including 6562 patients. *J Clin Psychiatry* 2009;70:344-53.
3. Cleare A, Pariante CM, Young AH, et al. Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 2008 British Association for Psychopharmacology guidelines. *J Psychopharmacol* 2015;29:459-525.
4. Oluboka OJ, Katzman MA, Habert J, et al. Functional recovery in major depressive disorder: providing early optimal treatment for the individual patient. *Int J Neuropsychopharmacol* 2018;21:128-44.

DOI: 10.1056/NEJMc1903259

TO THE EDITOR: In their review article about depression, Park and Zarate mention that a Lyme

titer should be obtained as clinically appropriate. It is somewhat unclear why Lyme disease was singled out. The vast majority of patients with untreated Lyme disease (at least 70%, but more likely closer to 90%) present with the skin lesion erythema migrans.¹ A recent systematic study involving adult patients with erythema migrans showed no evidence that such patients were significantly more likely than matched healthy controls to have a major depressive disorder on presentation.² The mildly elevated Beck Depression Inventory–II scores at baseline strongly and directly correlated with the total number of somatic symptoms and, as in another study,³ were more likely to be attributable to somatic symptoms rather than to affective depressive symptoms.

Overall, no convincing evidence has supported the notion that any psychiatric illness might be the primary manifestation of untreated Lyme disease.⁴ If all patients with depression were tested for Lyme disease, thousands of misdiagnoses would occur owing to false positive tests as well as background seropositivity from earlier resolved infections.

Gary P. Wormser, M.D.

New York Medical College
Valhalla, NY
gwormser@nymc.edu

Afton L. Hassett, Psy.D.

University of Michigan
Ann Arbor, MI

Dr. Wormser reports receiving research grants from Immunetics, Institute for Systems Biology, RareCyte, and Quidel, owning equity in Abbott–AbbVie, being an expert witness in malpractice cases involving Lyme disease, and being an unpaid board member of the American Lyme Disease Foundation; and Dr. Hassett, receiving consulting fees from AbbVie and Precision Health Economics. No other potential conflict of interest relevant to this letter was reported.

1. Shapiro ED, Wormser GP. Controversies about Lyme disease — reply. *JAMA* 2018;320:2482-3.
2. Wormser GP, Park K, Madison C, et al. Evaluation of prospectively followed adult patients with erythema migrans using the Beck Depression Inventory Second Edition. *Am J Med* 2019; 132:519-24.
3. Bechtold KT, Rebman AW, Crowder LA, Johnson-Greene D, Aucott JN. Standardized symptom measurement of individuals with early Lyme disease over time. *Arch Clin Neuropsychol* 2017; 32:129-41.
4. Nadelman RB, Herman E, Wormser GP. Screening for Lyme disease in hospitalized psychiatric patients: prospective serosurvey in an endemic area. *Mt Sinai J Med* 1997;64:409-12.

DOI: 10.1056/NEJMc1903259

TO THE EDITOR: Park and Zarate provide helpful guidance on antidepressant use in primary care,

but they mention the antidepressant discontinuation syndrome — sometimes considered to be a withdrawal syndrome — only in Table 2 of their article. They correctly identify the agents with a short half-life, paroxetine and venlafaxine, as being more likely than other antidepressants to provoke the discontinuation syndrome.¹ However, their statement that controlled-release or extended-release formulations of these drugs “may decrease risk” of the discontinuation syndrome is not well supported. Extended-release formulations slow the rate of drug entry and reduce peak plasma levels but do not extend the elimination half-life of the drugs. Thus, sudden discontinuation of extended-release venlafaxine may provoke adverse effects in as many as 78% of patients within 3 days.²

Although most instances of discontinuation syndrome are of mild-to-moderate severity and last days to weeks, some cases are more severe and prolonged.³ Besides the avoidance of agents with a short half-life, discontinuation syndrome is probably best prevented by using a very long tapering schedule of 2 to 6 months, especially in patients who have been taking antidepressants for more than a year.⁴ Careful monitoring of the patient’s response to dose reduction is essential.

Ronald W. Pies, M.D.

SUNY Upstate Medical University
Syracuse, NY
ronpies@massmed.org

No potential conflict of interest relevant to this letter was reported.

1. Jha MK, Rush AJ, Trivedi MH. When discontinuing SSRI antidepressants is a challenge: management tips. *Am J Psychiatry* 2018;175:1176-84.
2. Fava M, Mulroy R, Alpert J, Nierenberg AA, Rosenbaum JF. Emergence of adverse events following discontinuation of treatment with extended-release venlafaxine. *Am J Psychiatry* 1997; 154:1760-2.
3. Fava GA, Gatti A, Belaise C, Guidi J, Offidani E. Withdrawal symptoms after selective serotonin reuptake inhibitor discontinuation: a systematic review. *Psychother Psychosom* 2015;84: 72-81.
4. Pies R. Are antidepressants effective in the acute and long-term treatment of depression? Sic et non. *Innov Clin Neurosci* 2012;9:31-40.

DOI: 10.1056/NEJMc1903259

THE AUTHORS REPLY: Ellis and colleagues highlight the role of financial barriers and stigma as obstacles to psychotherapy and describe the delivery of mental health care by means of a collaborative care model with an embedded behav-

ioral health manager. We acknowledge the difficulty in accessing psychotherapy, applaud their efforts, and strongly advocate for innovative approaches to mental health care delivery.

Moulton and Young describe a developing view in the field that response to first-line antidepressants may occur earlier than previously thought, and they advocate for a more aggressive pharmacologic approach that considers a medication switch within 4 weeks. We are sympathetic to this approach but believe that it may be better suited to patients with urgent or refractory presentations than to those with mild-to-moderate depression. In the meta-analysis of clinical trials cited by Moulton and Young,¹ 60% of the improvement was seen within the first 2 weeks, but a substantial amount (40%) was seen after this time. In addition, the final end point of the analysis was 6 weeks, so abatement of symptoms after this time was not captured. Real-world assessments of antidepressant effects — such as the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial² — suggest that greater improvement may be seen after 8 weeks.

Wormser and Hassett question whether Lyme disease should be considered as a cause of or contributor to depressive symptoms. We agree that erythema migrans is not significantly associated with depression; moreover, we are not suggesting that Lyme disease causes depression. Rather, we believe that the neuropsychiatric symptoms of Lyme disease (e.g., fatigue, sleep disturbance, and somatic depressive symptoms³) may manifest in a manner similar to depressive syndrome and thus that Lyme disease should be a diagnostic consideration. For the same reasons that Wormser and Hassett provide, we do not recommend screening for Lyme disease in all patients with depression but only when clinically appropriate.

Finally, Pies contends that “controlled-release or extended-release formulations . . . do not

extend the elimination half-life of the drugs.” At face value this seems logical. However, pharmacokinetic studies of venlafaxine have shown an overall lower maximum concentration and more gradual and narrower range of plasma concentration changes per equivalent dose with the extended-release formulation than with the immediate-release formulation.⁴ This suggests that missed doses or abrupt discontinuation may result in fewer side effects in the short term with the extended-release formulation than with the immediate-release formulation. Although the analysis by Fava and colleagues⁵ showed that 78% of the patients discontinuing extended-release venlafaxine reported adverse events, no events were judged to be severe, and there was no immediate-release comparator. Still, for either formulation, it seems prudent to be aware of discontinuation symptoms and to use a gradual taper.

Lawrence T. Park, M.D.

Carlos A. Zarate, Jr., M.D.

National Institute of Mental Health
Bethesda, MD
lawrence.park@nih.gov

Since publication of their article, the authors report no further potential conflict of interest.

1. Posternak MA, Zimmerman M. Is there a delay in the antidepressant effect? A meta-analysis. *J Clin Psychiatry* 2005;66:148-58.
2. Trivedi MH, Rush AJ, Wisniewski SR, et al. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. *Am J Psychiatry* 2006;163:28-40.
3. Bechtold KT, Rebman AW, Crowder LA, Johnson-Greene D, Aucott JN. Standardized symptom measurement of individuals with early Lyme disease over time. *Arch Clin Neuropsychol* 2017;32:129-41.
4. Troy SM, Dilea C, Martin PT, Rosen AS, Fruncillo RJ, Chiang ST. Bioavailability of once-daily venlafaxine extended release compared with the immediate-release formulation in healthy adult volunteers. *Curr Ther Res* 1997;58:492-503.
5. Fava M, Mulroy R, Alpert J, Nierenberg AA, Rosenbaum JF. Emergence of adverse events following discontinuation of treatment with extended-release venlafaxine. *Am J Psychiatry* 1997;154:1760-2.

DOI: 10.1056/NEJMc1903259

Teamwork in Medicine

TO THE EDITOR: In her article in the February 21 issue,¹ Rosenbaum convincingly argues that effective team collaboration is crucial in today's

complex health care system. One underutilized approach to improving clinicians' ability to collaborate is to start early in their professional