



Major Depressive Disorders

Questions submitted for consideration by workshop participants

Prioritizing Comparative Effectiveness Research Questions:
PCORI Stakeholder Workshops

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1. For adults with co-morbid chronic illnesses and MDD, what are the essential elements of a triage analysis of the personal, clinical, and social variables for implementation of effective assessment and treatment of MDD?
2. What are the most effective manualized therapy approaches to treat MDD in adolescents, adult and older persons?
3. What is the comparative effectiveness of psychosocial, medication, and complementary/alternative interventions for improved outcomes in the areas of functioning (e.g., role, work/school/relationships) and stability (e.g., not requiring more intense intervention, reduced/lack of hospitalizations) for all populations (e.g., children, adolescents, adults, older adults, men, women, and different racial/ethnic groups) with major depressive disorder?
4. What is the comparative effectiveness of psychosocial, medication, and complementary/alternative interventions for long term/lasting outcomes (e.g., symptom reduction, remission, functioning, and stability) for all populations (e.g., children, adolescents, adults, older adults, men, women, and different racial/ethnic groups) with major depressive disorder?
5. Does adding peer support services to pharmacological treatment alone improve depression scores of adults living with depression? (Examples of peer support services may include a peer specialist delivered intervention to increase hope, decrease loneliness, etc.)
6. Do adults living with depression experience a higher wellness score (as defined by WHO-5 Wellbeing Index) when participating in one or more wellness strategy, such as meditation or increased exercise, in addition to pharmacological treatment?
7. Does long term involvement in peer-led support groups in addition to pharmacologic treatment decrease the number or severity of relapses in adults living with depression?
8. Post-myocardial infarction (MI) depression is an independent risk factor for increased mortality. What treatment approaches are most effective for adults who experience depression following a significant medical event such as MI or stroke?
9. Many adults seen in primary care settings where the IMPACT / Collaborative Care model for depression is applied present with other significant behavioral health issues such as anxiety and / or substance use. What is the comparative effectiveness of approaches that integrate screening and treatment for depression and other common behavioral health issues for adults receiving services in primary care settings?
10. What is the comparative effectiveness of various behavioral health integration models for addressing major depressive disorder among adult patients with multiple chronic conditions?
11. What are the comparative benefits and risks of non-pharmacologic treatments for major depressive disorder among minority patients (i.e. racially/ethnically diverse populations)?

12. What is the comparative effectiveness of different screening methods to identify major depressive disorder among vulnerable populations (i.e, those with poor SES, education levels, races/ethnicities)?
13. Does treatment adherence vary based on use or absence of SDM regarding therapy options for primary care patients with mild depression where treatment options include medication or psychotherapy or exercise?
14. Do clinical outcomes associated with differential treatment recommendations by primary care providers based on level of PHQ-9 exceed outcomes in usual care?
15. Do supports for depression treatment in primary care improve clinical outcomes?
16. What are the comparative tolerability and side effect profiles together with patient-relevant outcomes such as health related functioning and wellbeing for non-pharmacological and pharmacological interventions in adults with MDD and TRD?
17. How does risk of suicide change, and incidence of suicide vary with severity of MDD over time and/or with previous lines of treatment failures with non-pharmacological and pharmacological interventions in adults and children with MDD and TRD?
18. What are the comparative benefits and harms (risks) of pharmacological and non-pharmacological treatment interventions for adult patients with MDD judged to be at imminent risk for suicide? What are the healthcare delivery systems/ settings of care that contribute to producing positive outcomes?
19. What are the comparative benefits and harms (risks) of pharmacological and non-pharmacological treatment interventions for adolescent patients with MDD judged to be at imminent risk for suicide? What are the healthcare delivery systems/ settings of care that contribute to producing positive outcomes?
20. How can adult patients with MDD (or their caregivers where relevant) identify early signs of relapse and what will enable them to act upon them?
21. In elderly patients with major depressive disorder and cancer (note: we could select other comorbidities of interest), what is the comparative effectiveness of pharmacologic therapies (e.g., SSRIs vs. SNRIs vs TCAs), with or without antipsychotics, with or without psychotherapy* on depressive symptoms and health related quality of life**
 - *could include and test cognitive behavioral therapy, mindfulness based treatment or other behavioral interventions
 - **both disease specific (e.g., Quality of Life in Depression Scale – QLDS) and generic QoL (e.g., SF-36)
22. In adults with major depressive disorder who are in the work force, what is the comparative effectiveness of pharmacologic therapies (e.g., SSRIs vs. SNRIs vs TCAs), with or without antipsychotics, with or without psychotherapy* on depressive symptoms, health related quality of life** and work productivity***?

*could include and test cognitive behavioral therapy, mindfulness based treatment or other behavioral interventions

**both disease specific (e.g., Quality of Life in Depression Scale – QLDS) and generic QoL (e.g., SF-36)

***using a work scale like the Lam Employment Absence and Productivity Scale (LEAPS) or the Work Productivity and Activity Impairment questionnaire (WPAI), for example

23. In adolescents with major depressive disorder, what is the comparative effectiveness of pharmacologic therapies (e.g., SSRIs vs. SNRIs vs TCAs), with or without antipsychotics, with or without psychotherapy* on depressive symptoms, health related quality of life** and school productivity and social/family function****?

*could include and test cognitive behavioral therapy, mindfulness based treatment or other behavioral interventions

**both disease specific (e.g., Quality of Life in Depression Scale – QLDS) and generic QoL (e.g., SF-36)

****using the Sheehan Disability Scale for example (or other scales, if any, that assess school performance)

24. What are the best pharmacological treatments for older adults with major depression and comorbid medical conditions?
25. What are the best non-pharmacological approaches for older adults with major depression and comorbid medical conditions?
26. Which widely used diagnostic criteria/measure has the highest degree of accuracy in diagnosing depression among older adults, with a particular emphasis on those that can be administered by physicians?
27. The successful treatment of depressed mothers to remission has been shown to reduce the depression and anxiety in their children as well. What is the benefit for mother and baby of evidence-based psychotherapy compared to pharmacotherapy or the combination of medication and psychotherapy during pregnancy and the post-partum period? What information do women during child-bearing years need to make an informed decision about treatment? What barriers exist among physicians, nurse-midwives, nurse practitioners and other health professionals in recommending the most effective treatment for women during pregnancy and post-partum period?
28. For depressed patients who remain symptomatic despite initial first line pharmacotherapy (e.g. SSRI) what is the benefit of adding an evidence-based psychotherapy versus an alternate or augmentative pharmacotherapy intervention?
29. Despite admonitions regarding the use of benzodiazepines, these agents remain widely used in practice. For patients with anxiety and depression, what is the relevant benefit of treatment with an a



benzodiazepine compared to an antidepressant or combination pharmacological treatment or combination pharmacotherapies and psychotherapeutic treatments?

30. At least 50% of patients with major depressive disorder also have an anxiety disorder. Those with comorbid anxiety and depression are often the most treatment-resistant, and the presence of anxiety in untreated depression is a high risk factor for suicide. Patients often ask which disorder to treat first. Given the gaps in knowledge, how can clinicians most effectively treat both anxiety and major depressive disorder with pharmacotherapies, psychotherapies and combination treatments?
31. What are the comparative risks and benefits to treating people with Major Depressive Disorder with TMS and/or Deep Brain Stimulus?
32. What are the comparative risks and benefits to treating people with Major Depressive Disorder with TMS and/or Deep Brain Stimulus with additional treatment such as ADHD medications, specifically Vyvanse, which could have collateral effect on MDD?
33. What are the comparative risks and benefits to treating people with Major Depressive Disorder with TMS and/or Deep Brain Stimulus in combination with DBT (Dialectical Behavioral Therapy) for MDD?
34. What is the comparative effectiveness of [several interventions] for screening and treating at-risk caregivers of patients with MDD?
35. What is the comparative effectiveness of a highly-trained CBT therapist, a CBT therapist with fewer hours, telemedicine CBT, and an online program designed by a well-trained CBT therapist for patients with MDD?
36. What are the comparative cognitive effects of ECT and an intensive medication regimen on symptoms, function and memory for patients with MDD?
37. What is the comparative effectiveness of peer crisis respite versus TAU for persons in an acute episode of depression on future hospitalization and recovery?
38. What is the effectiveness of peer delivered WHAM (or related wellness coaching) versus non-peer delivered added to primary care treatment of depression on wellness and well-being outcomes?
39. What is the comparative effectiveness of peer delivered WRAP for youth in foster care versus non-peer WRAP on reduced medication reliance and recovery outcomes?
40. Given that both antidepressant medications and certain psychotherapies have been shown to be effective, how does a process of informed decision making affect the type of treatment(s) patients select and receive and their depression outcomes?
 - a. What factors (ie sex, level of education, SES, insurance status, age, racial and ethnic background, and medical comorbidities) affect the type of treatments patients' select and their outcomes?



41. Psychotherapy can be provided online, by phone or face to face in a one on one or group setting. For a given type of therapy (eg cognitive behavior therapy), how does the modality through which the therapy is provided affect depression related outcomes?
 - a. Does providing this type of psychotherapy through different combinations of modalities (eg telephone and online, face to face and telephone, face to face and online) affect these outcomes?
42. In the real world most patients who receive psychotherapy receive a combination of different types of therapies. How do different combinations of therapies affect their outcome? How does providing education about the types of therapies available and facilitating patient choice affect psychotherapy outcomes?
43. Many depressed primary care patients do not receive a minimally effective dose of evidence-based treatment (antidepressant medication, psychotherapy) for depression. How does primary care providers' communication styles affect treatment recommendations, shared-decision making, treatment adherence and depression related outcomes?
 - a. Can PCP communication training improve depression treatment uptake and adherence and outcomes?
 - b. How does communication training affect the type of treatment(s) patients select and receive and their depression outcomes?
44. African Americans and Hispanics are less likely to receive effective treatment for depression than Caucasians. Can culturally tailored interventions to engage and treat these two minority populations reduce these disparities?
45. Has anyone commissioned a study on the impact telemedicine can have on improving outcomes of major depressive disorder?
46. Which provider organizations have separated from the pack in producing significantly better than normal outcomes? If yes, who?
47. Is there a region or state across the US that reports better outcomes than normal?
48. What is the single BIGGEST factor in our ability to better treat patients (i.e. great psychiatrists, poor referral program, lack of psychotherapy, stigma/embarrassment, lack of understanding of the disease by medical community, etc.)?
49. What are the three most innovative ideas/approaches that provider organizations have tried implementing in 2012-2014? Why?
50. What are the comparable benefits and risks of (a) combination pharmacotherapy, smart-phone guided therapy and disease management, (b) combination psychotherapy and pharmacotherapy, and (c) smartphone-guided therapy and disease management for adolescents with depression?

51. What are the comparable benefits and risks of exercise and diet and nutritional strategies as an augmentation to evidence-based therapy for adults with depression and comorbid chronic physical illnesses?
52. What are the comparable benefits and risks of evidence-based pharmacotherapy and psychotherapy for depression, alone, or in combination, for youth and adult cancer survivors with co-occurring depression?
53. How does TMS compare with standard antidepressant treatment for the treatment of adolescents and adults with major depressive disorder?

Rationale: extensive interest among the public in TMS, as an alternative, non-pharmacological intervention, but no effectiveness trials addressing its benefits and risks compared with traditional treatments. Need for cost-effectiveness evaluation.

54. How does an algorithmic approach to treating treatment-resistant depression (defined as lack of remission after 2 evidence-based interventions) compare with naturalistic community treatment?

Rationale: treatment-resistant depression is prevalent, but, despite a number of trials of specific interventions, there is no established systematic strategy that is accepted by clinicians and patients.

55. For severe treatment-resistant depression (defined as lack of response after at least 3 evidence-based interventions), how does ECT compare with combined pharmacotherapy which includes antipsychotic medication?

Rationale: Severe treatment-resistant depression is a chronically impairing condition that frequently leads to disability. ECT is effective in severe depression, but alternative pharmacological interventions have been more recently developed. The comparative effectiveness of these different strategies have not been evaluated, especially on functional outcomes.

56. Antidepressants are an effective treatment for Major Depressive Disorder (MDD) and can be readily delivered in primary care where the majority of antidepressants are prescribed, but antidepressant adherence is poor, with 40% discontinuing in the first month and 75% within 3 months. What is the comparative effectiveness of antidepressant adherence strategies for individuals prescribed antidepressants for MDD in primary care?
57. Cognitive behavioral therapy (CBT) for Major Depressive Disorder (MDD) is highly effective but not widely available (due to a lack of providers trained in CBT), while online CBT can be effectively delivered online at low cost and is highly scalable. What is the comparative effectiveness of online CBT coupled with various forms of online support for the treatment of MDD in primary care?
58. What is the comparative effectiveness of brief, practical strategies for detecting major depressive disorder in primary care patients and engaging them in evidence-based depression care?



59. What are the “active” ingredients in evidence-based psychosocial interventions for depression (eg, psychotherapies or collaborative care), and can measures of these be validated (ie, shown to be associated with clinical and functional improvements) as fidelity and quality metrics?
60. Which patients respond to particular depression treatments, and is prospectively assigning treatments using these characteristics more effective than usual care?
61. What is the comparative effectiveness of particular combinations of newer (eg, rTMS, mindfulness training, ketamine) as well as more traditional (eg, CBT and antidepressants) modalities for treatment-resistant depression?
62. People: Primary care patients with co-morbid substance abuse and depression. Options: Treatment in primary care or referral to specialty substance use disorder treatment. Outcomes: People may prefer to receive treatment in the familiar confines of primary care but we have little evidence about the effectiveness of conjoint depression/SUD treatment in primary care.
63. People: Primary care patients with co-morbid anxiety and depression. Options: Treatment in primary care with a collaborative care model vs. referral to mental health treatment provider. Outcomes: Co-morbid depression and anxiety may be depression alone, depression plus an anxiety disorder, or masked bipolar disorder. The treatments may be complex. Can they more conveniently but just as effectively be approached in primary care with team based care?
64. People: Primary care patients with chronic medical illness(es) and significant chronic mental illness(es) that include depression. Options: Treatment via collaborative care in a primary care site or referral to specialty mental health provider with continued medical treatment in primary care. Outcomes: Collaborative treatment in primary care may provide more continuity and integration of care but treatment in a specialty mental health setting may provide more intensive psychological and psychopharmacologic management