Major Depressive Disorder:

Topic Brief

June 9, 2015

High-Level Research Question

What is the comparative effectiveness of pharmacologic treatment and behavioral interventions in managing major depressive disorders (MDDs) in adolescents and adults in diverse treatment settings?

Assignment for Workgroup Participants

- Based on your perspective (patient, clinician, payer, etc.), what is the most relevant comparative effectiveness research (CER) question focusing on major depressive disorders in adolescents and adults that would address current gaps in knowledge?
- Submitted questions will be used to generate the agenda for the workgroup meeting.

Opportunity Snapshot

As part of PCORI's efforts to fund high-impact and useful research on critical patient-centered health and healthcare issues, PCORI is hosting a multistakeholder workgroup to discuss high-priority topics that focus on the comparative effectiveness of MDD. PCORI intends to use feedback from the workgroup to conduct further gap analyses and to develop a funding announcement in this area. The objective of the workgroup is to create a set of comparative research questions that have the potential to produce findings that will improve patient-centered outcomes.

1. Overview

MDD is a serious mental illness that causes significant distress and interferes with a person's basic functioning. MDD can cause both emotional distress and somatic symptoms. It is characterized by depressed mood, diminished interest or pleasure, sleeping problems and tiredness, and negative thoughts. MDD can include a single episode or be recurrent. In serious cases, MDD also can be associated with frequent thoughts of suicide, overt suicide attempts, and psychotic features. A 2006 study conducted by the Substance Abuse and Mental Health Services Administration (SAMHSA) found that an estimated 30.4 million adults (13.9 percent of the US adult population) suffered from at least one major depressive episode in their lifetime.

Various treatments and treatment categories (behavioral, pharmacological, somatic) are used for MDD. Given the disorder's impact on functional status, productivity, quality of life, and mortality, research to compare the effects of treatments and treatment combinations on symptoms and functioning should be a high priority. Different providers and healthcare systems (therapists, primary care providers, psychiatrists, pharmacy, hospital) may be involved in care delivery to patients with MDD; therefore, CER on features of the health systems delivering care has the potential to inform stakeholders' decisions.

As many as one-third of people diagnosed with MDD have severe symptoms or fail to respond to at least two successive trials of an antidepressant medication. These individuals are classified as having "treatment resistant depression." The clinical approach to these patients includes intensification of follow-up by providers, combinations of medications, and a variety of modalities in addition to antidepressants.

2. Patient Centeredness

An episode of MDD is a period lasting at least two weeks, with five or more of the following symptoms:

- Depressed mood
- Loss of interest or pleasure in any activities (i.e., anhedonia)
- Insomnia or excessive sleeping
- Significant weight loss or weight gain
- Agitation
- Fatigue or low energy
- Decreased ability to concentrate, think, or make decisions
- Thoughts of worthlessness or excessive or inappropriate guilt
- Recurrent thoughts of death or suicidal ideation, or a suicide attempt

MDD has an impact on many physical, emotional, and social aspects of patients' lives, including:

- Emotions (e.g., depressed mood, feeling worthless, excessive guilt)
- Employment issues (e.g., difficulty obtaining or keeping a job)
- Interpersonal problems (e.g., relationship problems)
- Quality and quantity of sleep
- Increased risk of mortality, including suicide
- Drinking or drug problems
- Unhealthy weight (obesity or severe underweight)
- Decreased physical functioning and pain (headaches, digestive disorders, chronic pain)
- Slower recovery from physical illnesses

3. Impact (Burden) of the Condition on the Health of Individuals and Populations

- Major depression accounts for 8.3 percent of all US years lived with disability.[1]
- Major depression, particularly recurring MDD, is highly associated with cardiovascular disease and related comorbidities.
- Major depression accounts for more than two-thirds of the 30,000 reported suicides in the United States each year.[2]
- African Americans and Hispanics are less likely to receive effective treatment for depression than are Caucasians and non-Hispanic Caucasians.
- Up to 80 percent of those treated for depression show an improvement in their symptoms within 4 to 6 weeks of beginning medication, psychotherapy, attending support groups, or a combination of these treatments.[3]
- Nearly two out of three people suffering with depression do not actively seek or receive treatment.

4. Evidence Gaps

Pharmacologic Management of Major Depression—Interventions with Good Evidence:

- Antidepressant medications, particularly selective serotonin reuptake inhibitors (SSRIs), have a long history of efficacy in the treatment of major depression. Research has found that none of the individual SSRIs has a substantially higher rate of initial response, and most patients require dosage escalation or a change to a different agent. Side effects can sometimes be a barrier to the use of higher dosages. [4]
- Evidence suggests that second-generation antipsychotics[5]—quetiapine, aripiprazole, olanzapine, and risperidone—showed beneficial effects, compared with placebo, when used as an adjunct to antidepressants. These agents are associated with a moderate risk of additional side effects.
- In a study of amitriptyline versus placebo,[6] high-quality evidence suggests that amitriptyline is effective as an antidepressant, but it is also associated with multiple side effects.
- Available evidence suggests that St. John's Wort is superior to placebo but has an undefined role in the management of refractory or treatment-resistant depression.[7]

- The addition of benzodiazepine to antidepressant treatment improves medication adherence and increases immediate symptom reduction, but this combination also has the potential to lead to dependence and accident proneness.[8]

Nonpharmacologic Management of Major Depression—Interventions with Strong Evidence:

- There is strong evidence to support the efficacy of cognitive behavioral therapy (CBT), both in group and individual forms, in the treatment of major depression.[9]
- Preventive CBT and mindfulness-based treatment for depression have shown promise as strategies to prevent depression recurrence. [10, 11]

Nonpharmacologic Management of Major Depression—Interventions with Weak Evidence:

- There is some evidence, although sparse, in the use of psychotherapy for treatment-resistant depression. Most of the trials to date are of low quality.[12]
- There is a growing number of neurological treatments for depression, including repetitive transcranial nerve stimulation, cranial electrotherapy stimulation, and electroconvulsive therapy. These are primarily used in treatment-resistant depression. The evidence is limited for the efficacy of these treatments, with small studies to date.[13]
- In terms of interventions to improve return to work in depressed people, there is currently no evidence of the comparative effectiveness of various antidepressant medications in affecting sickness absence.[14]

Depression with Other Diseases/Health Conditions/Populations—Interventions with Weak Evidence:

- For psychosocial and psychological interventions for treating antenatal depression, current evidence is inconclusive, with small sample sizes and low generalizability.[15]
- In terms of psychosocial and psychological interventions for treating postpartum depression, there is low methodological quality in the current studies and the long-term effectiveness of these interventions is unclear.[16]
- A Cochrane review notes the low-quality evidence on the effectiveness and safety of antidepressants in Parkinson's patients.[17]
- There is no evidence on the effectiveness of psychotherapy for incurable cancer patients with depression.[18]
- In terms of antidepressants for treating depression in dementia, the few studies on this topic have small sample sizes.[19]
- The current studies on using antenatal psychosocial assessment for reducing perinatal mental health morbidity are small, and further studies with better sample sizes are needed.[20]

Depression in Children and Adolescents—Interventions with Weak Evidence:

- There is limited evidence for the effectiveness of psychological therapies versus antidepressant medication—alone and in combination—for treating depression in children and adolescents.[21]
- Due to the diversity in the designs of trials, it is difficult to compare outcomes across studies that explore interventions for preventing relapse and recurrence of a depressive disorder in children and adolescents.[22]

Systems-Level Interventions for Depression:

- There is good evidence that antidepressant therapy can be effectively managed in primary care settings. Collaborative care for depression has a strong evidence base, showing improvements over usual care that last at least up to 2 years.[23]

Synthesis of Findings:

- Most studies are small; studies with larger sample sizes and improved reporting of design are needed.
- There is a dearth of evidence-based studies on pharmacological management of psychotic depression with a combination of antidepressants and antipsychotics versus either alone.
- The evidence about third-wave cognitive and behavioral therapies versus other psychological therapies for depression is limited in quantity, quality, and breadth.
- The evidence is especially weak for the frail and physically ill, for patients with incurable cancer, and for children and adolescent populations.

5. Ongoing Research

A search on clinicaltrials.gov showed 1,701 studies being conducted for MDD in various phases. Of the approximately 200 active trials, 24 are planning to enroll 500 or more patients. The majority of these active trials are drug versus drug (n=7), or drug versus placebo (n=7). None compare pharmacologic treatment versus psychological interventions.

6. Likelihood of Implementation in Practice

Several professional societies have developed guidelines for the care and management of MDD, and there is agreement about the core components of these recommendations; however, there is a need to give providers specific guidance on when each management strategy may be appropriate.[24]

7. Durability of Information

CER priority areas that seek to identify which interventions, combinations of interventions, or sequence of interventions work best for which patients are needed. These types of findings are not likely to become obsolete quickly.

8. Potential Research Questions

1. *Nonpharmacological Treatment [psychotherapy, behavioral interventions, cognitive behavior therapy (CBT), interpersonal therapy (IPT)]*

    a) How effective are the traditional psychotherapies?
        - Many randomized controlled trials have evaluated the efficacy of newer interpersonal or CBT treatments, yet little is known about the efficacy of more traditional dynamic or experiential-humanistic approaches (e.g., Gestalt therapy) in which illness is the result of of the alienation, lack of genuine meaning, and loneliness of the modern world. Even for well-studied modalities, more CER that directly compares two treatment strategies is needed. Past studies often allowed co-treatments to vary, which make conclusions difficult to draw about the direct benefits of one treatment versus another.

b) What is the comparative effectiveness of brief psychotherapies that lend themselves to implementation in primary care? Could these brief psychotherapies be delivered by primary care providers or other trained providers with the same comparative effectiveness as those delivered by mental health professionals?
c) How do the effects of psychotherapy delivered in the real world compare with effects seen in carefully controlled trials?
d) What are the best nonpharmacological approaches for patients with difficult-to-treat MDD? What is the optimal sequence of treatments when a patient does not respond to initial treatments?
    - Comparative research on nonpharmacologic interventions for treatment-resistant depression is relatively new. In a recent Agency for Health Care Research and Quality (AHRQ) review, no identified trials assessed the comparative effectiveness of psychotherapy compared with pharmacotherapy, procedures such as electroconvulsive therapy, or other psychotherapies. Many clinical questions about efficacy and effectiveness remain unanswered.
e) What are the comparative risks and impact on health, or adverse effects, for psychological treatments?
    - Few studies expressly assess adverse outcomes of nonpharmacologic approaches alone.
f) Comparative clinical research on nonpharmacologic interventions in a treatment-resistant depression population.
    - Nonpharmocologic interventions include: electroconvulsive therapy, repetitive transcranial magnetic stimulation, vagus nerve stimulation, or demonstrated effective psychotherapy (e.g., cognitive therapy [CBT or IPT])
g) No evidence exists on how the relative effectiveness of nonpharmacologic treatments differs (or not) as a function of symptom subtypes or for subgroups defined by sociodemographic characteristics (such as age) or coexisting medical conditions (e.g., post-stroke or postmyocardial infarction depression, perinatal depression).
h) When designing for wide implementation, what common factors and elements of healthcare delivery systems, providers, patients, and treatment strategies produce positive outcomes or help sustain change? For example, many psychotherapies include common elements that could contribute to effectiveness, such as psychoeducation, patient and family engagement, goal setting, communication skills, activity scheduling, self-monitoring, or relapse prevention. What are these key elements, and how do they interact in producing outcomes?

2. *Combination Treatment (pharmacological and nonpharmacological treatment)*

a) What is the comparative effectiveness of other nonpharmacological approaches (e.g., self-help, exercise, mind-body interventions) in conjunction with psychotherapy and pharmacotherapy?
b) For patients with treatment-resistant depression, no trials have assessed the comparative effectiveness of psychotherapy compared with pharmacotherapy, somatic therapies (e.g., electroconvulsive therapy), or other psychotherapies.
c) For patients with treatment-resistant depression, there is a need for research on alternative or novel classes of medications, such as ketamine.

d) What are the comparative risk of harms and patient-relevant outcomes, such as functional capacity and quality of life, for nonpharmacological and pharmacological interventions in adults with major depressive disorder?
e) What is the comparative effectiveness of second-line treatment options (e.g. second-generation antidepressants versus complementary and alternative medicine, or exercise treatments) in adults with major depressive disorder?
f) What are the comparative effectiveness of pharmacotherapy, cognitive therapy, and modified therapeutic community interventions in female offenders and in those with primary mood disorders?
i) Do treatments differ in effectiveness for specific subpopulations?
    - Few studies explore how effects differ by key subgroups (e.g., sex, age, baseline depression severity, chronicity of depression). Do certain patient characteristics increase the chances of responding to specific treatments?
j) How do different treatments differ in the durability of effects after stopping treatment? What is the comparative effectiveness of different durations or number of treatments needed to achieve meaningful outcomes for patients? Do these differ by key patient characteristics?

9. Conclusions

Given the high prevalence of MDD and its impact on functional status, productivity, quality of life, and mortality, research to compare the effects of treatments on symptoms, functioning, and quality of life should have a high priority. Given the many gaps in the current body of evidence, new CER could contribute to better patient-centered outcomes.

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