Clinical Practice Guideline for the Treatment of Depression Across Three Age Cohorts

American Psychological Association

Guideline Development Panel for the Treatment of Depressive Disorders

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Author Notes

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Please refer to pp. 99–101 of this guideline for a statement on conflicts of interest as well as p. 108 for acknowledgments.

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Abstract

The American Psychological Association (APA) developed this clinical practice guideline to provide recommendations for the treatment of depressive disorders (including major depression, subsyndromal depression, and persistent depressive disorder). It addresses three developmental cohorts: children and adolescents; general adults; and older adults (ages 60 and over). Ten systematic reviews and meta-analyses, along with other literature and observations from practitioners and patients, served as the basis for the guideline. The guideline development panel consisted of health professionals from psychology, psychiatry, and primary care as well as community members who self-identified as having had depression. The panel examined the efficacy of psychological treatments and of complementary and alternative medicine treatments. It also examined comparative effectiveness among psychological treatments (by themselves and in combination with pharmacotherapy) and comparative effectiveness of psychological treatments in relation to pharmacotherapy and to complementary and alternative treatments. The panel made no treatment recommendations specific to children but did make recommendations for treatment of depression in adolescents, adults, and older adults. These recommendations are detailed in the guideline.

Keywords: Depression, clinical practice guideline, best practices

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Intended Use of Guideline

This guideline is intended to be aspirational and is not intended to create a requirement for practice. It is not intended to limit scope of practice in licensing laws for psychologists or for other independently licensed professionals, nor limit coverage for reimbursement by third party payers. Nor is the guideline intended to be used within a legal or judicial context to imply that psychologists or other independently licensed professionals are required to comply with any of its recommendations.

The term *guideline* refers to statements that suggest or recommend specific professional behavior, endeavor, or conduct for psychologists and may be useful for other clinicians. Guidelines differ from standards in that standards are mandatory and may be accompanied by an enforcement mechanism. Thus, guidelines are aspirational in intent. They are intended to facilitate the continued systematic development of the profession and to help assure a high level of professional practice by psychologists. Guidelines are not intended to be mandatory or exhaustive and may not be applicable to every professional and clinical situation. They are not definitive, and they are not intended to take precedence over the judgment of psychologists. Please refer to the APA's (2015a) *Professional Practice Guidelines: Guidance for Developers and Users* for a discussion of the several types of guidelines produced by APA. Clinical practice guidelines are an important tool for determining intervention options but are not the only resource.

Clinicians are encouraged to consider the report from the APA Presidential Task Force on Evidence-Based Practice (APA, 2006), *Evidence-Based Practice in Psychology*, which emphasizes the integration of best available research; patient characteristics, culture, and preferences; and clinical expertise for making treatment decisions.

In reviewing the recommendation statements, the panel reminds the reader that a lack of evidence about a treatment does not imply that that treatment is not efficacious. Rather, there are several gaps in the literature about treatments as well as limitations in the specific literature

reviewed by the panel due to methodological constraints, as discussed later in the guideline document. Clinicians are encouraged to provide informed consent to patients.

Individualizing Treatment

Clinicians strive to individualize treatments. So how might one follow evidence-based clinical practice guidelines, yet honor the individuality of patients? A comprehensive assessment can help identify factors that might require modifications to a treatment recommended by clinical practice guidelines. These include patient factors such as race; ethnicity; socioeconomic status; culture and/or heritage; or other features of their identities, values, or preferences. In addition, the patient's comorbidities, social support, and ability to obtain childcare when needed, as well as the clinician's accessibility, location, hours of operation, available appointments, proximity to public transportation, and other resources that can affect treatment, must be considered. Further, provider and setting factors like constraints tied to duration of treatment, provider availability, or other factors will impact the application of a treatment recommended by a clinical practice guideline. Combining an individual assessment with the research summarized in the clinical practice guideline can help develop a conceptualization of the change processes that underpin the effective treatment to guide individualization decisions. This can promote "flexibility within fidelity" (Kendall, Gosch, Furr, & Sood, 2008) to facilitate the use of research-supported change processes to achieve the patient's goals while individualizing the specific strategies. Especially when a recommended treatment is modified, providing full informed consent about possible treatments is necessary. It is also important across models to set individualized treatment goals collaboratively with the patient and clearly monitor progress on those goals. All these steps can help providers use the guidelines in a way that respects the enormous variability in patients' needs and backgrounds. For more information about individualizing treatments, see p. 63 of this guideline.

Executive Summary

Scope

This guideline is intended to provide recommendations for the treatment of depressive disorders (including major depression, subsyndromal depression, and persistent depressive disorder[1]) based on systematic reviews of the evidence. It addresses three developmental cohorts: children and adolescents, general adults, and older adults (ages 60 and over[2]). Ten systematic reviews and meta-analyses (Cipriani et al., 2016; Cuijpers, Driessen, et al., 2012a; Cuijpers, Karyotaki, Pot, Park, & Reynolds, 2014a; Cuijpers, Koole, van Dijke, Roca, & Reynolds, 2014b; Cuijpers, Donker, Weissman, Ravitz, & Cristea, 2016; Driessen et al., 2015; ECRI Institute, 2015; Gartlehner et al., 2015; Wilkinson & Izmeth, 2012; Zhou et al., 2015) served as the basis for this guideline. This guideline addresses the efficacy of psychological and complementary and alternative medicine treatments, the comparative effectiveness of psychotherapy in combination with pharmacotherapy as well as compared to pharmacotherapy and complementary and alternative treatments.[3] For child and adolescent populations only, the guideline also examines the efficacy of medications, but because other existing guidelines adequately address this for adults, the panel chose not to review this body of evidence. The guideline then addresses harms and burdens of treatment and patient[4] values and preferences. The reviews on which this guideline is based did not specifically address screening for

[1] Note that psychotic depression is not covered by this guideline. The panel recognizes this as an important subset of depression. However, the scope of the guideline is currently extensive, and the incorporation of psychotic depression would have required additional reviews focusing on antipsychotic medications.
[2] Although the panel defined older adults as ages 60 and over, at least one study included in the older adult reviews included individuals as young as 50. This resulted in some overlap between the general adult and older adult populations that the panel was not able to separate out due to the way the data was analyzed. However, a majority of studies defined older adults as ages 60 and up and individual studies that defined older adults as 50 and up will be noted. This overlap may be considered by clinicians when making recommendations for individual patients that fall within this age range.
[3] The panel initially intended to include somatic treatments, but due to limitations in the available reviews the current guideline does not address these areas.
[4] To be consistent with discussions of evidence-based practice in other areas of health care, we use the term *patient* to refer to the child, adolescent, adult, older adult, couple, family, group, organization, community, or other populations receiving psychological services. However, we recognize that in many situations there are important and valid reasons for using such terms as *client, consumer* or *person* in place of *patient* to describe the recipients of services.

depression, assessment of associated comorbid conditions (e.g., suicidality, medical problems), monitoring response to treatment, locus of care, prevention of depression, dose, timing or duration of treatments for depression, costs of treatment, long-term benefits of treatment, mechanisms of change, bipolar disorder, or efficacy of treatments for disorders other than depression. These topics are important to patient care and discussed as appropriate, but the guideline does not contain specific recommendations in these domains. The Process and Method section details the panel's decision-making throughout guideline development. It is important to note that the phrase "insufficient evidence" indicates that there were not enough data to provide for definitive recommendations. However, this lack of data can be due to the situation where (a) no relevant studies existed within the time frame of this review, (b) a very small number of relevant studies existed, or (c) multiple relevant studies existed but only provided equivocal findings. In addition, the lack of relevant studies can exist even if multiple studies did compare certain interventions but did not provide robust findings, as well as no studies were conducted that included comparisons between various interventions.

Background

Major depression is the second leading cause of disability as of 2013 both worldwide (Vos et al., 2015) as well as in the United States (U.S. Burden of Disease Collaborators, 2013). Major depressive disorder is characterized by a depressed mood (or irritability in children) or loss of pleasure or interest for at least 2 weeks (American Psychiatric Association, 2013). It is also accompanied by at least three (for a total of at least five) of the following symptoms present most days: weight loss or change in appetite, insomnia or hypersomnia, psychomotor retardation or agitation, fatigue or loss of energy, excessive/inappropriate guilt or feelings of worthlessness, indecisiveness or diminished ability to concentrate or think, and recurrent thoughts of death or suicidal ideation or suicide plan or attempt (American Psychiatric Association, 2013). Another depressive disorder, persistent depressive disorder (formerly called *dysthymia*) in the *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.; *DSM-5*;

American Psychiatric Association, 2013), is characterized by a depressed mood most of the time for at least 2 years, along with at least two of the following symptoms: feeling hopeless, insomnia or hypersomnia, overeating or poor appetite, fatigue or low energy, low self-esteem, and indecisiveness or poor concentration (American Psychiatric Association, 2013). In children and adolescents, the mood can be irritable, and the duration of persistent depressive disorder is at least 1 year. Moreover, there cannot be a gap in these symptoms for more than 2 months, a hypomanic or manic episode during this time period, nor criteria met for cyclothymic disorder, and symptoms are not better explained by another disorder, cause significant impairment in functioning or distress, and are not due to a different medical condition or a substance use disorder (American Psychiatric Association, 2013). For patients that do not meet full criteria for the aforementioned depressive disorders (depressive episode with insufficient symptoms) but either experience recurrent episodes of depressed mood and at least four other symptoms of depression for 2–13 days (recurrent brief depression) or experience a depressive episode for 4–13 days (short-duration depressive episode), the *DSM-5* presents this as Other Specified Depressive Disorder (American Psychiatric Association, 2013).[5]

The current guideline is designed to complement the existing knowledge base in several ways. It covers a broad range of the population (children through older adults) and includes psychotherapeutic interventions. Earlier guidelines have either been completed 5 or more years prior, provided limited guidance on psychotherapies, or focused on recommendations for a specific population. The current guideline follows the Institute of Medicine (IOM, 2011a; IOM, 2011b)[6] standards to the extent possible for rigorous guideline development. This guideline is also intended for a broad international audience, not only for individuals in the United States.

[5] However, the systematic reviews and studies that are discussed in this guideline use the broader definitions "subclinical" or "subsyndromal" depression (i.e., Cuijpers, Koole, van Dijke et al., 2014).
[6] Of note, as of March 2016, the division of the National Academies of Sciences, Engineering, and Medicine (the National Academies) formerly known as Institute of Medicine (IOM) was renamed the National Academy of Medicine (NAM). Despite the recent name change, the guideline will use IOM when referring to the IOM standards for guideline development and systematic reviews.

Process and Method

Undertaking the creation of a guideline requires several key decisions. APA's Advisory Steering Committee issued a call for nominations (including self-nominations) for individuals to serve as panel members from a variety of backgrounds (patient, psychology, psychiatry, general medicine) with content knowledge or methodological expertise. Conflicts of interest (financial and nonfinancial) were considered and managed both during panel member selection and throughout the guideline development process. Research Triangle International–University of North Carolina (RTI-UNC) Evidence-Based Practice Center and American Psychological Association (APA) staff used the Population, Interventions, Comparators, Outcomes, Timing, and Settings (PICOTS) framework (a systematic approach to conducting a comprehensive literature review of a clinical subject matter) to guide the panel during its initial question-formulation stage.

In selecting which outcomes were most critical for deciding on the level or strength of a recommendation, the panel decided that response to treatment (reduction in depressive symptoms) and serious associated harms/adverse events were critical. The panel further decided that the following additional outcomes were important: remission (no longer having symptoms), quality of life, functional capacity, patient satisfaction, relapse, recurrence, and suicidality.

The guideline was developed in a series of phases, based on the three developmental cohorts. Briefly, with the support of the RTI-UNC Evidence-Based Practice Center scientists, the older adult literature was reviewed based on the results of an umbrella review they conducted to determine existing systematic reviews in the literature. RTI-UNC Evidence-Based Practice Center scientists developed evidence profiles for the panel compiling data from reviews by Wilkinson and Izmeth (2012) and Cuijpers, Karyotaki, Pot, et al. (2014a). For the general adult section, the panel used data from an existing systematic review by RTI-UNC Evidence-Based Practice Center scientists (Gartlehner et al., 2015). The panel supplemented this to fill in

gaps of information with data from several others reviews that met quality criteria based on either an AMSTAR (A Measurement Tool to Assess Systematic Reviews; an instrument used to evaluate systematic reviews and meta-analyses for quality; Shea et al., 2007) review (Cuijpers, Driessen, et al., 2012a; Cuijpers, Koole, et al., 2014b; Cuijpers et al., 2016; Driessen et al., 2015) or having followed IOM systematic review standards (ECRI Institute, 2015). Specifically, this AMSTAR instrument consists of a checklist assessing 11 items and was used by scientists who were not panel members to evaluate systematic reviews for quality. For the child and adolescent literature, the panel used two systematic reviews/meta-analyses that met quality criteria based on an AMSTAR review: Cipriani et al. (2016) and Zhou et al. (2015). Based on the results of the umbrella review as well as follow-up AMSTAR quality reviews, it was determined that existing systematic reviews and meta-analyses were of sufficient breadth and quality such that it was not necessary to commission a de novo review. The panel utilized systematic reviews/meta-analyses that were current within the past 5 years at the time the panel made its recommendation decisions that met IOM (2011b) development and AMSTAR quality standards. While this is consistent with rigorous guideline development, the panel noted this approach can be limiting in that studies exploring the efficacy of psychotherapy are not conducted equally across modalities and are not regularly updated every 5 years due, in part, to psychotherapy research receiving support from government funds (rather than private companies). Altogether, systematic reviews and meta-analyses conducted more than 5 years ago were not explicitly examined by the panel.

The panel considered four factors as it drafted recommendations based on IOM standards: (1) overall strength of the evidence, (2) balance of benefits versus harms/burdens, (3) patient values and preferences, and (4) applicability. Based on the combination of these factors, the panel made a recommendation or conditional recommendation for or against each particular treatment or made a statement that there was insufficient evidence to be able to make a recommendation for or against. The panel used a tool called a *decision table* (created by APA

staff) to document its decision-making process for each recommendation for older adults. Copies of the decision tables are available in Appendix C of the supplemental materials. The panel later streamlined the decision table to a "grid" to document decision- making, which can also be found in the supplemental materials (linked separately).

Discussion

Throughout the panel's discussions, it was emphasized that patient values and preferences should be taken into consideration through shared decision-making with the clinician. Clinicians using this guideline are encouraged to consider challenges faced by patients such as barriers to treatment (i.e., structural and perceptual).

While the panel followed a rigorous methodological process for guideline development, the panel identified challenges and limitations to consider for future efforts. The panel tried to be as broad as possible and used the PICOTS outline, but the scope could not be all-encompassing and thus excluded many important populations (i.e., reviews focused exclusively on individuals with comorbid medical disorders), and settings (i.e., inpatient, collaborative care) were not included in the reviews. Another challenge was balancing adherence to the IOM (2011a) standards for rigorous guideline development while also including adequate coverage of the research literature. We discuss these limitations in full on p. 80 of the guideline. Further, the panel noted a wide range of research concerns, including that many of the studies included in reviews were of low quality. In particular, the panel noted the need to expand the research literature to specifically include underrepresented and underserved populations, including people of diverse racial/ethnic and cultural heritage backgrounds, gender and sexual minority populations, and socioeconomically diverse groups. In addition to the multifocal call for inclusivity in research design and funding to better address the needs of diverse populations, including those that experience lower SES, we encourage clinicians to refer to APA's (2017b) *Multicultural Guidelines: An Ecological Approach to Context, Identity, and Intersectionality* to assist in implementation of recommendations. The labeling of psychotherapies is a challenge as

well, given the large variability in how a systematic review team clusters particular forms of psychotherapies (i.e., “cognitive-behavioral approaches” includes a number of specific treatments such as problem-solving therapy and dialectical behavior therapy; see Table 2 in Appendix G for details).

Additional limitations the panel noted across cohorts include that much research is highly dependent on federal research funding, particularly psychotherapy research. Also, there are differences in the amount of research evidence available for different therapeutic approaches (e.g., there is more evidence available for cognitive-behavioral therapy than for psychodynamic therapy and hardly any for humanistic therapies). Each of these factors limits the broad applicability of research findings. Further, while much research focused on symptomatic change, more research is needed on additional important outcomes such as patient-centered outcomes (i.e., quality of life and interpersonal relationships, social engagement, occupational functioning). Research is also needed on the moderators of treatment and outcomes, matching of patients with treatments, and innovative approaches to dissemination (e.g., collaborative care and integrated care). Finally, the panel agreed that the body of the depression treatment research literature needs far more attention on patient populations that have comorbid conditions; long-term outcomes of psychotherapy; treatment for racially, ethnically, or socioeconomically diverse populations as well as marginalized communities and gender diverse populations; as well as a personalized medicine approach to treatment.

Recommendations

In reviewing the recommendations from the panel, it is important for the reader to be familiar with the definition of several terms as follows:

Treatment as usual. Refers to the care that is customarily provided in a particular situation. The panel notes the challenge of a consistent definition of treatment as usual, given that the exact definition can vary by study.

No treatment. No active treatment was provided (i.e., waitlist).

Efficacy. The impact of an intervention compared to an inactive control.

Comparative effectiveness. Compares at least two different active treatments to each other to assess for the benefits of one (or combination) versus the other (or combination).

The tables below list the recommendations from the APA guideline development panel for treating depression in children and adolescents, the general adult population, and older adults. Note that the recommendations pertaining to efficacy do not imply that these treatments are superior to other active treatments. Further note that the recommendations made by the panel are based on the literature that was included in the guideline (i.e., that met inclusion criteria) and not all the literature on depression treatment. Whenever possible, the tables list which treatments work best for which patients and under what conditions (i.e., treatment for a particular diagnosis for an older adult population with a particular condition). But when not noted, this information was not available. Please see Appendix I for details about the interventions (i.e., dosing, timing) and Appendix J for a list of interventions that were part of the search but for which there was not enough high-quality evidence to make a determination. The ultimate decision about treatment should be based on shared decision-making with the patient and, in the case of youth patients, the parents/guardians or family members actively involved in their care.

The panel used the following as guidance for its decision making:

1) The panel *recommended* treatments that were consistently superior to nonactive control conditions or for which there was evidence of equivalency or superiority to other treatments.
2) The panel *conditionally recommended* treatments that were consistently superior to nonactive control conditions but there were either:
    a. Other active treatments that were superior to the treatment being conditionally recommended.

b. Insufficient evidence that the treatment was equivalent to other effective treatments.

c. Greater harms/burdens than with other treatments.

3) The panel *did not recommend* treatments or *recommended against* treatments if there was insufficient evidence of efficacy or if the harms were considered to outweigh any benefits.

The panel's recommendations are as follows[7]:

[7] Please refer to the section on scoping (p. 23) for the list of topics that the guideline does and does not address. For the list of descriptions of treatments derived from research included in the reviews, please refer to Appendix A of the supplement.

Table 1

Recommendations for the Child Population from the APA Guideline Development Panel for the Treatment of Depression[8]

Recommendation	Strength of Recommendation	Justification
Initial Treatment		
For initial treatment of child patients with depressive disorders[9] there was insufficient evidence to make a recommendation regarding any of the following psychotherapies/interventions[10]: • Behavioral therapy • Cognitive therapy • Cognitive-behavioral therapy (CBT) • Family therapy • Play therapy • Problem-solving therapy • Psychodynamic therapy • Supportive therapy There was insufficient evidence to make a recommendation regarding pharmacotherapy for child patients with depressive disorders.	Insufficient evidence for a recommendation	Based on the literature reviewed that met the AMSTAR requirements, there was insufficient evidence to either recommend or not recommend use of the listed psychotherapies/interventions in children with depressive disorders. Based on the literature reviewed that met the AMSTAR requirements there was insufficient evidence to either recommend or not recommend pharmacotherapy for child patients with depressive disorders. The panel noted safety concerns with using pharmacotherapy with children and recommends shared decision-making regarding medication options with a child psychiatrist in addition to the clinician, patient, and their parents/guardians or family members actively involved in their care.

[8] For further details about the evidence underlying each guideline statement please refer to the child/adolescent grid accompanying the supplemental materials. In this grid, the information on effect sizes incorporated from Figure 3 on p. 216 of Zou et al.'s (2015) review is presented first across the top row followed by information for the Cipriani et al. (2016). Each column in the grid reflects a particular treatment or treatment comparison from the reviews while each row reflects a particular outcome (i.e., reduction in depressive symptoms). The effect size along with relevant information (i.e., confidence interval) is presented at the intersection of rows and columns. This is followed by information on the panel's ratings of the benefits, harms, balance of benefits vs. harms, patient values and preferences, applicability, and overall recommendation statement for each intervention or comparison of treatments.
[9] Types included: minor depression, major depression, persistent depressive disorder (formerly called "dysthymia"), intermittent depression, or having depression symptoms at or above a prespecified level based on a validated measure of depression severity. The Zhou et al. (2015) review excluded patients with psychotic depression.
[10] Throughout the table, interventions are listed alphabetically.

Table 2

Recommendations for the Adolescent Population from the APA Guideline Development Panel for the Treatment of Depression[11]

Recommendation	Strength of Recommendation	Justification
Initial Treatment		
For initial treatment of adolescent patients with depressive disorders[12] the panel recommends that clinicians offer one of the following psychotherapies/interventions[13]: • Cognitive-behavioral therapy (CBT) • Interpersonal psychotherapy for adolescents (IPT-A) The panel recommends fluoxetine as a first-line medication compared to other medications for adolescent patients with major depressive disorder, specifically when considering medication options. There was insufficient evidence to recommend either treatment (psychotherapy or fluoxetine) over the other for major depressive disorder.	Recommendation for use	Based on the literature reviewed that met the AMSTAR requirements, cognitive-behavioral therapy (CBT) and interpersonal psychotherapy for adolescents (IPT-A) were the only psychotherapy interventions with evidence of efficacy.

[11] For further details about the evidence underlying each guideline statement please refer to the child/adolescent grid accompanying the supplemental materials. In this grid, the information on effect sizes incorporated from Figure 3 on p. 216 of Zou et al's (2015) review is presented first across the top row followed by information for the Cipriani et al (2016). Each column in the grid reflects a particular treatment or treatment comparison from the reviews while each row reflects a particular outcome (i.e., reduction in depressive symptoms). The effect size along with relevant information (i.e., confidence interval) is presented at the intersection of rows and columns. This is followed by information on the panel's ratings of the benefits, harms, balance of benefits vs. harms, patient values and preferences, applicability, and overall recommendation statement for each intervention or comparison of treatments.
[12] Types included: minor depression, major depression, persistent depressive disorder (formerly called "dysthymia"), intermittent depression, or having depression symptoms at or above a prespecified level based on a validated measure of depression severity. The Zhou et al. (2015) review excluded patients with psychotic depression.
[13] Throughout the table, interventions are listed alphabetically.

Additional psychotherapy recommendations for initial treatment		
If neither recommended psychotherapy is available or neither is acceptable to the patient and their parent/guardian, the panel suggests considering an alternative model. However, at this time, while the following interventions have been evaluated in adolescents, there is insufficient evidence to recommend for or against clinicians offering any one of the following psychotherapies/interventions over the others: • Behavioral therapy • Cognitive therapy • Family therapy • Problem-solving therapy • Psychodynamic therapy • Supportive therapy	Insufficient evidence for a recommendation	Based on the literature reviewed that met the AMSTAR requirements, for all interventions except for cognitive- behavioral therapy and interpersonal psychotherapy, evidence was not strong enough to determine that any one therapy was superior to another. Decision should be based on shared decision-making with youth patients, their parents/guardians, or family members actively involved in their care.
Additional pharmacotherapy guidance for initial treatment		
Information is lacking regarding other medication options for adolescents. Thus, if fluoxetine is not a treatment option or is not acceptable, the panel recommends shared decision-making regarding medication options with a child psychiatrist in addition to the clinician, patient, and their parents/guardians or family members actively involved in their care.	Conditional recommendation for use	Recommendation is due to safety concerns such as increased suicide risk for adolescents when using other medications.
In general, the panel recommends against using the following medications for adolescent patients with major depressive disorder. However, when other options are not available, effective, and or acceptable to the patient, the panel recommends shared decision-making between the patient and clinician. • clomipramine • imipramine • mirtazapine • paroxetine • venlafaxine	Recommend against use	Based on the literature reviewed that met the AMSTAR requirements the panel recommends against the medications as noted due to safety concerns with using these medications on adolescents.

If these medications are being considered, the panel recommends: • paroxetine over clomipramine when both are being considered. • paroxetine over imipramine when both are being considered. • There was no information available for other comparisons between the listed medications.		Further, the panel recommends only choosing between the medications as noted when other options have been exhausted or are unavailable. This is due to safety concerns with using these medications on children.

Table 3

Recommendations for the General Adult Population from the APA Guideline Development Panel for the Treatment of Depression[14]

Recommendation[15]	Strength of Recommendation	Justification
INITIAL TREATMENT		
Psychotherapy and Pharmacotherapy For initial treatment of adult patients with depression,[16] the panel recommends the following in the context of sharing decision-making with the patient when considering options: 1) That clinicians offer either psychotherapy or second-generation antidepressant.[17] • When selecting between treatments, the panel recommends considering the following options: o Second-generation antidepressants o The panel found that effectiveness studies demonstrated similar effects across psychotherapy. Thus, the panel is not able to recommend specific monotherapies for initial treatment. General models that appear to have comparable effects include:	Recommendation for use	Based on the literature reviewed that met the IOM or AMSTAR requirements, comparative effectiveness research finds either similar effects between treatments or insufficient evidence to determine that one treatment can be offered over another.

[14] The recommendations made by the panel are based on the literature that was included in the guideline (i.e., that met inclusion criteria), and not on all the literature on depression treatment.

[15] For further details about the evidence underlying each guideline statement please refer to the general adult grid accompanying the supplemental materials. In this grid, the information for the Gartlehner et al. (2015) is present first across the top row followed by the additional reviews, Cuijpers et al. (2014), Driessen et al. (2015), Cuijpers et al. (2012), VA/DoD evidence synthesis report (ECRI Institute, 2015), and Cuijpers et al. (2016). Each column in the grid reflects a particular treatment or treatment comparison from the reviews while each row reflects a particular outcome (i.e., reduction in depressive symptoms). The effect size along with relevant information (i.e., confidence interval) is presented at the intersection of rows and columns. This is followed by information on the panel's ratings of the benefits, harms, balance of benefits vs. harms, patient values and preferences, applicability, and overall recommendation statement for each intervention or comparison of treatments.

[16] The depression recommendations refer to the full range of depression diagnoses identified by the panel for inclusion unless a recommendation specifies otherwise. Note that recommendations do not pertain to psychotic depression.

[17] Throughout the recommendations, both the terms "antidepressant medication" and "second-generation antidepressant" are used. Note that "second-generation antidepressants" refers specifically to selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) while the term "antidepressant medication" could include second-generation antidepressants as well as other antidepressants.

▪ Behavioral therapy ▪ Cognitive, cognitive-behavioral (CBT), and mindfulness-based cognitive-therapy (MBCT) ▪ Interpersonal psychotherapy (IPT) ▪ Psychodynamic therapies ▪ Supportive therapy 2) If considering combined treatment, the panel recommends cognitive-behavioral therapy (CBT) or interpersonal psychotherapy (IPT) plus a second-generation antidepressant.		
For adult patients with depression who are also experiencing relationship distress, if a recommended treatment is not acceptable or available, the panel suggests that clinicians offer problem-focused couples' therapy. When selecting between treatments the panel suggests considering the following options: • Suggest behavioral therapy rather than antidepressant medication alone. • If considering combined treatment, the panel suggests cognitive therapy plus antidepressant medication to improve likelihood of full recovery in treatment.	Conditional recommendation for use	Based on the literature reviewed that met the IOM or AMSTAR requirements, if a recommended treatment is not available or acceptable, the panel suggests the listed interventions, which demonstrated efficacy when compared with no treatment (i.e., waitlist) or control.
For adult patients with depression, there is insufficient evidence to recommend for or against clinicians offering • Cognitive-behavioral analysis system of psychotherapy (CBASP) • Brief problem-solving therapy (10 or fewer sessions) vs. treatment as usual.	Insufficient evidence for a recommendation	Based on the literature reviewed that met the IOM or AMSTAR requirements the evidence was insufficient to be able to recommend for or against the listed interventions or treatment comparisons. Decision should be based on shared decision-making with the patient.
Complementary and Alternative Treatments[18] For adults with depression for whom psychotherapy or pharmacotherapy is either ineffective or unacceptable the panel suggests the following options:	Conditional recommendation for use	Based on the literature reviewed that met the IOM or AMSTAR requirements, evidence indicates no difference in effects between St. John's Wort and second-generation antidepressants and

[18] The panel urges caution when using over-the-counter agents to prevent unintended drug-drug interactions particularly given variable manufacturing practices.

• Exercise Monotherapy[19] • St. John's Wort Monotherapy[20] If neither is acceptable or available, the panel suggests consideration of • Bright light therapy[21] • Yoga[22] • If considering adjunctive treatments, the panel suggests adding acupuncture to antidepressant medication.[23] There is insufficient evidence to recommend • Tai Chi • Acupuncture Monotherapy • Combination of second-generation antidepressant and acupuncture • Omega-3 Fatty Acids Monotherapy • Combination of second-generation antidepressant and Omega-3 Fatty Acids • S-Adenosyl Methionine Monotherapy • Combination of second-generation antidepressant and exercise	Conditional recommendation for use Insufficient evidence for a recommendation	indicates some small to medium benefits of the other suggested complementary and alternative treatments. Evidence is insufficient to recommend the last list of complementary and alternative treatments as noted.
For adult patients with subclinical depression, the panel suggests that clinicians offer psychotherapy[24] (psychotherapy in general including both cognitive-behavioral therapy and noncognitive-behavioral therapy psychotherapies [e.g., interpersonal counseling, problem-solving therapy, life-review therapy]).	Conditional recommendation for use	When subclinical depression is the focus of treatment, based on the literature reviewed that met the IOM or AMSTAR requirements, the panel suggests the listed interventions, which demonstrated efficacy when compared with control.

[19] Patients in these trials had moderate to severe depression, according to the HAM-D Scale (Babyak et al., 2000; Blumenthal et al., 1999, 2007; Hoffman et al., 2008). The panel gave a conditional recommendation because it had only efficacy data and not comparative effectiveness data.
[20] The trials included patients with moderate to severe depression.
[21] Included patients aged 60 years and older with a diagnosis of MDD.
[22] Based on a trial with female patients between 18 to 40 years of age.
[23] Trials included patients with a diagnosis of MDD or poststroke depression and were between 33 to 60 years of age.
[24] Recommendation also includes separate examination of non-cognitive behavioral therapy approaches. Psychotherapy in general also found to reduce future episodes of major depressive disorder.

PARTIAL or NONRESPONDERS to INITIAL ANTIDEPRESSANT TREATMENT		
For adult patients with depression who have either not responded or only partially responded to initial antidepressant medication treatment the panel recommends the following options: 1) Switch from antidepressant medication alone to cognitive therapy alone or, 2) Switch from antidepressant medication alone to another antidepressant medication	Recommendation for use	Based on the literature reviewed that met the IOM or AMSTAR requirements, the panel equally recommends the listed interventions, there is evidence demonstrating no difference in effect.
For adult patients with depression who have either not responded or only partially responded to initial antidepressant medication treatment the panel suggests that clinicians offer one of the following psychotherapies/interventions and select between treatments as follows: 1) Add psychotherapy (interpersonal psychotherapy, cognitive-behavioral therapy, or psychodynamic therapy)[25] to the antidepressant medication treatment 2) Augment with another antidepressant medication	Conditional recommendation for use	Based on the literature reviewed that met the IOM or AMSTAR requirements, the panel suggests adding one of the psychotherapies listed or augmenting with another antidepressant medication the treatment of adult patients who have not responded or only partially responded to initial antidepressant medication treatment. However, the panel does not suggest adding CBASP (cognitive-behavioral analysis system of psychotherapy) or brief supportive therapy to antidepressant medication treatment.
For adult patients with major depressive disorder who have either not responded or only partially responded to initial adequate second-generation antidepressant treatment attempt there is insufficient evidence to determine differences in treatment effect for the following:	Insufficient evidence for a recommendation	Based on the literature reviewed that met the IOM or AMSTAR requirements the evidence was insufficient to be able to recommend for or against adding guided cognitive-behavioral therapy self-

[25] The general group of psychotherapies included in the review (ECRI Institute, 2015) were interpersonal psychotherapy, cognitive-behavioral therapy, and CBASP (cognitive behavioral analysis system of psychotherapy). However, based on additional information, CBASP is not recommended due to the increased burden with limited evidence of additional benefit.

• Switching to another second-generation antidepressant[26] • Switching to a nonpharmacologic (i.e., cognitive therapy) monotherapy • Augmenting with guided cognitive-behavioral therapy self-help		help to antidepressant medication treatment or switching or augmenting among other second-generation antidepressants or nonpharmacologic (i.e., cognitive therapy) modalities.
RELAPSE PREVENTION		
For adult patients with depression who have achieved remission the panel suggests clinicians offer psychotherapy (cognitive-behavioral therapy, mindfulness-based cognitive therapy, or interpersonal psychotherapy) rather than antidepressant medication or treatment as usual to prevent relapse. There is insufficient evidence to recommend one form of the three psychotherapies listed.	Conditional recommendation for use	Based on the literature reviewed that met the IOM or AMSTAR requirements, the panel suggests psychotherapy in general (cognitive- behavioral therapy, mindfulness-based cognitive therapy, or interpersonal psychotherapy), which demonstrated comparative effectiveness when compared with treatment as usual and antidepressant medication to prevent relapse. However, there was insufficient evidence to be able to recommend a specific form of psychotherapy to prevent relapse.

[26] Switches included various medications such as bupropion, sertraline, venlafaxine, etc. Please see Table E22, pages E35–E37 of Gartlehner et al. (2015) for specific switch details.

Table 4

Recommendations for the Older Adult Population from the APA Guideline Development Panel for the Treatment of Depression

Recommendation	Strength of Recommendation	Justification
INITIAL TREATMENT—Major Depressive Disorder		
For initial treatment of older[27] adult patients with depression, the panel recommends the following in the context of shared decision-making with the patient: 1) Either group life-review treatment or group cognitive-behavioral therapy (Group-CBT) (either alone or added to usual care) over no treatment 2) Combined pharmacotherapy and interpersonal psychotherapy (IPT) over IPT alone. Of note, while the study upon which this is based used nortriptyline, the panel recommends a second-generation antidepressant due to the reduced risk of side effects.	Recommendation for use	Based on the literature reviewed that met the IOM or AMSTAR requirements, cognitive-behavioral therapy (group) and life review (group) based interventions were the only interventions with adequate efficacy evidence. However, comparative effectiveness research either finds sufficient evidence to recommend between some treatment comparisons or finds similar effects between treatments. While nortriptyline was used in the past due to its efficacy and safety, practices have changed significantly, and nortriptyline is now viewed as a second- or third-line pharmacotherapy strategy for major depression. It is generally reserved for patients who have not done well with a selective serotonin reuptake inhibitor or a serotonin-norepinephrine reuptake inhibitor, which are generally considered to be safer for older adults than nortriptyline. There is some efficacy data from systematic reviews/meta-analyses showing efficacy of second-generation antidepressants over placebo. [Refer to Decision Tables 14, 18, 28 in Appendix C of the supplement.][28]

[27] While the panel defined older adults as ages 60 and over, there was at least one study included in the older adult reviews that included some individuals as young as 50. However, the majority were ages 60 and over.
[28] Decision tables were used in developing the recommendations. These tables begin in Appendix C of the supplement.

For older adult patients with depression, if a recommended treatment is not acceptable or available, the panel suggests that clinicians offer one of the following psychotherapies/interventions[29]: • Cognitive-behavioral therapy (CBT; individual) (either standalone or in combination with usual care), which was found to be superior to: o no treatment o a nonspecific talk therapy control o usual care o desipramine • Combination cognitive-behavioral therapy and nonspecific therapeutic techniques (individual) with pharmacotherapy, which was superior to pharmacotherapy alone. Of note, while a specific study upon which this is based used desipramine, the panel recommends a second-generation antidepressant due to the reduced risk of side effects. • Interpersonal psychotherapy and pharmacotherapy, which was conditionally superior for preventing recurrence to either: o Supportive care o IPT and supportive care o Of note, while the study on which this is based used nortriptyline, the panel recommends a second-generation antidepressant due to	Conditional recommendation for use	Based on the literature reviewed that met the IOM or AMSTAR requirements, if a recommended treatment is not available or acceptable, the panel suggests the use of interventions that demonstrated efficacy when compared with no treatment (i.e., waitlist) or treatment as usual. Further, comparative effectiveness research finds evidence to suggest certain treatments or combinations of treatments over others. While nortriptyline and other tricyclic antidepressants were used in the past due to its efficacy and safety, practices have changed significantly, and nortriptyline is now viewed as a second- or third-line pharmacotherapy strategy for major depression. It is generally reserved for patients who have not done well with a selective serotonin reuptake inhibitor or a serotonin-norepinephrine reuptake inhibitor, which are generally considered to be safer for older adults than nortriptyline. There is some efficacy data from systematic reviews/meta-analyses showing efficacy of second-generation antidepressants over placebo. [Refer to Decision Tables 6, 8, 10, 11, 15, 16, 23, 35, 36 in Appendix C of the supplement.]

[29] Throughout the table, interventions are listed alphabetically.

the reduced risk of side effects • Problem-solving therapy (group), which was superior to reminiscence therapy (group) • Interpersonal psychotherapy (individual), which was superior to supportive care		
For older adult patients with depression, there is insufficient evidence to recommend for or against clinicians offering • Problem-solving therapy (in-person) vs. attention control (phone call) for major depressive disorder • Problem-solving therapy (video call) vs. attention control (phone call) for major depressive disorder	Insufficient evidence for a recommendation	Based on the literature reviewed that met the IOM or AMSTAR requirements there is insufficient evidence available to determine differences in treatment effect for the listed treatment comparisons for older adult patients with depression. Thus, the panel makes no recommendations of one treatment over the other for the treatments in each pair comparison. Decision should be based on shared decision-making with the patient. [Refer to Decision Tables 33, 34 in Appendix C of the supplement.]
INITIAL TREATMENT—Subthreshold/minor depression		
The panel suggests considering one of the following options for subthreshold or minor depression • Cognitive-behavioral therapy (internet) for subthreshold depression • Cognitive-behavioral therapy (individual) and usual care for minor depressive disorder • Cognitive-behavioral therapy (group) and usual care for treating minor depressive disorder • Combination cognitive-behavioral therapy and treatment as usual rather than combination of talking	Conditional recommendation for use	Based on the literature reviewed that met the IOM or AMSTAR requirements for subthreshold depression, there was no efficacy data sufficient to recommend treatment. Thus, the panel makes the listed suggestions. While paroxetine was used in the past, currently many geriatric psychiatrists would prefer another SSRI (like escitalopram or sertraline) to paroxetine due to the anticholinergic side effects of paroxetine. [Refer to Decision Tables 3, 13, 24, 24B, 29, 30, 31, 39, 42 in Appendix C of the supplement.]

control[30] (individual) and usual care for older adults with minor or major depressive disorder • Life review course (group) rather than an educational video for older adults with subclinical depression • Problem-solving therapy (individual) • paroxetine ○ Of note, while the study on which this is based used paroxetine, some argue that paroxetine is contraindicated in older adults due to its anticholinergic side effects and many geriatric psychiatrists would prefer another SSRI (i.e., escitalopram or sertraline). The panel encourages shared decision-making with patients of benefits versus harms of treatment.		
The panel had insufficient evidence to recommend the following treatments: • Behavioral bibliotherapy (self-guided) vs. treatment as usual for subthreshold depression. • Life review therapy (individual) vs. treatment as usual for subclinical depression.	Insufficient evidence for a recommendation	Based on the literature reviewed that met the IOM or AMSTAR requirements there is insufficient evidence available to determine differences in treatment effect for the listed treatment comparisons for older adult patients with subthreshold or minor depression. Thus, the panel makes no recommendations of one treatment over the other for the treatments in each pair comparison. Decision should be based on shared decision-

[30] Participants in this condition received attention and warm interactions from therapists during discussion of neutral topics.

		making with the patient. [Refer to Decision Tables 38, 46 in Appendix C of the supplement.]
MDD or minor depression + cognitive impairment/dementia		
The panel suggests considering one of the following options for MDD or minor depression in the context of cognitive impairment or dementia: • Problem-solving therapy (individual) for older adult patients with major depressive disorder and executive dysfunction[31] • Problem-solving behavioral therapy (individual) or pleasant events behavioral therapy (individual) for minor or major depressive disorder in older adults with dementia	Conditional recommendation for use	Based on the literature reviewed that met the IOM or AMSTAR requirements for MDD or minor depression plus cognitive impairment/dementia, there was no efficacy data sufficient to recommend treatment. Thus, the panel makes the listed suggestions. [Refer to Decision Tables 2, 26 in Appendix C of the supplement.]
The panel had insufficient evidence to recommend the combination of behavioral activation therapy (individual) and treatment as usual over treatment as usual for depressive symptoms in older adults with mild to moderate cognitive impairment.	Insufficient evidence for a recommendation	Based on the literature reviewed that met the IOM or AMSTAR requirements there is insufficient evidence available to determine differences in treatment effect for the listed treatment comparisons for older adult patients with MDD or minor depression plus cognitive impairment/dementia. Thus, the panel makes no recommendations of one treatment over the other for the treatments in each pair comparison. Decision should be based on shared decision-making with the patient. [Refer to Decision Table 27 in Appendix C of the supplement.]
Persistent depressive disorder		
The panel suggests considering one of the following options for MDD or minor depression in the context of cognitive impairment or dementia: • Problem-solving therapy (individual) or paroxetine for	Conditional recommendation for use	Based on the literature reviewed that met the IOM or AMSTAR requirements for persistent depressive disorder in older adults, there was no efficacy data sufficient to recommend treatment. Thus, the panel

[31] Disruption to cognitive processes generally housed in the frontal lobes of the brain.

persistent depressive disorder Of note, while the study on which this is based used paroxetine, some argue that paroxetine is contraindicated in older adults due to its anticholinergic side effects, and many geriatric psychiatrists would prefer another SSRI (i.e., escitalopram or sertraline).		makes the listed suggestions. Of note, while some evidence supported problem-solving therapy, it was not significantly superior to attentional control conditions using either phone or video contact. While paroxetine was used in the past, currently many geriatric psychiatrists would prefer another SSRI (like escitalopram or sertraline) to paroxetine due to the anticholinergic side effects of paroxetine. [Refer to Decision Table 12 in Appendix C of the supplement.]
MDD with medical or other complications		
The panel suggests considering the following options for patients with both depression and the indicated complicating factors: • Combination of cognitive-behavioral therapy (individual) and usual care for minor or major depressive disorder with type II diabetes mellitus or chronic obstructive pulmonary disease • Multicomponent intervention (individual) for treating symptoms of depression in temporarily homebound African American adults • Coping improvement (group) rather than psychotherapy[32] on request (individual) for older adults with mild to severe depressive symptoms and HIV	Conditional recommendation for use	Based on the literature reviewed that met the IOM or AMSTAR requirements for MDD with medical or other complications, there was no efficacy data sufficient to recommend treatment. Thus, the panel makes the listed suggestions. [Refer to Decision Tables 25, 37, 51 in Appendix C of the supplement.]

[32] Participants in this condition were able to access typical psychosocial services from the community (e.g., 12-step programs, support groups for AIDS, individual therapy). They also were given three brief phone calls to assess for any clinical concerns that may have arisen.

PREVENTION OF RECURRENCE-MDD		

For older adult patients with a history of depression, the panel recommends clinicians offer any of the following options:
 	
• Either:
  ○ Combination interpersonal psychotherapy and pharmacotherapy
 	
  ○ Combination supportive care and pharmacotherapy
 	
Of note, while the study on which this is based used nortriptyline, the panel recommends a second-generation antidepressant due to the reduced risk of side effects.
	Recommendation for use	Based on the literature reviewed that met the IOM or AMSTAR requirements, comparative effectiveness research demonstrated sufficient evidence for the panel to recommend some combinations of treatments over others due to differences in treatment effect for prevention of recurrence.
		
		Other treatment/combinations of treatments were equally recommended by the panel based on comparative effectiveness research evidence demonstrating no difference in effect for prevention of recurrence.

The panel suggests considering the following option if the prior options are not acceptable or available • Interpersonal psychotherapy (individual) alone	Conditional recommendation for use	While nortriptyline was used in the past due to its efficacy and safety, practices have changed significantly, and nortriptyline is now viewed as a second- or third-line pharmacotherapy strategy for major depression. It is generally reserved for patients who have not done well with a selective serotonin reuptake inhibitor or a serotonin-norepinephrine reuptake inhibitor, which are generally considered to be safer for older adults than nortriptyline. There is some efficacy data from systematic reviews/meta-analyses showing efficacy of second-generation antidepressants over placebo. [Refer to Decision Tables 19, 20, 20 (pg. A-378), 21, 22 in Appendix C of the supplement.]

For older adult patients with a history of depression there is insufficient evidence to recommend between clinicians offering cognitive-behavioral therapy (group) plus pharmacotherapy and pharmacotherapy alone for preventing recurrence. Thus, the panel makes no recommendations of one treatment over the other.	Insufficient evidence for a recommendation	Based on the literature reviewed that met the IOM or AMSTAR requirements, there is insufficient evidence. available to determine differences in treatment effect. Thus, the panel makes no recommendations of one treatment over the other. Decision should be based on shared decision-making with the patient. [Refer to Decision Table 17 in Appendix C of the supplement.]

Clinical Practice Guideline for the Treatment of Depression Across Three Age Cohorts

Scope of the Problem

Definition of the problem. Depressive disorders (e.g., major depressive disorder, persistent depressive disorder) are some of the most prevalent, impairing, and costly disorders of any kind. The Global Burden of Disease Study reported that major depression was the third leading cause of worldwide disability in 1990 and had risen to the second leading cause by 2013 both worldwide (Vos et al., 2015) and in the United States (U.S. Burden of Disease Collaborators, 2013). Major depression leads to lost work productivity and increased morbidity and mortality due to direct effects associated with increased risk of suicide, reduced functional behaviors, and interpersonal functioning. It also leads to added consequences due to indirect effects on health through the exacerbation of other major causes of morbidity and mortality (Cuijpers, Vogelzangs, Twisk, Kleiboer, & Penninx, 2014c; Elderon & Whooley, 2013; Katon, 2003; Liu et al., 2017) and increasing prevalence of diabetes—especially among youth and middle-aged adults in the United States and worldwide (Lin et al., 2009).

Major depressive disorder is characterized by a depressed mood (or irritability in children) and/or loss of pleasure or interest for at least 2 weeks (American Psychiatric Association, 2013). It is accompanied by at least three (for a total of at least five) of the following symptoms present most days: weight loss and/or change in appetite, insomnia or hypersomnia, psychomotor retardation or agitation, fatigue or loss of energy, excessive/inappropriate guilt or feelings of worthlessness, indecisiveness or diminished ability to concentrate or think, and recurrent thoughts of death or suicidal ideation or suicide plan or attempt (American Psychiatric Association, 2013). Another depressive disorder, persistent depressive disorder, is characterized by a depressed mood most of the time for at least 2 years, along with at least two of the following symptoms: feeling hopeless, insomnia or hypersomnia, overeating or poor appetite, fatigue or low energy, low self-esteem, and indecisiveness or poor concentration (American Psychiatric Association, 2013). In children and adolescents, the duration is at least

one year, and the mood can be irritable. Moreover, there cannot be a gap in these symptoms for more than 2 months, a hypomanic or manic episode during this time period, nor criteria met for cyclothymic disorder. Further, symptoms are not better explained by another disorder, cause significant impairment in functioning or distress, and are not due to a different medical condition or a substance (American Psychiatric Association, 2013).

The level of population disability associated with depressive disorders (major depressive disorder, persistent depressive disorder, subsyndromal depression, and other manifestations) is a function of the severity and chronic or recurrent nature of the symptoms, and the high frequency of the disorder. Unlike other chronic illnesses, first onset of major depressive disorder often occurs in late teens or early adulthood. In the United States, approximately 6.7% to 7.6% of adults report an episode of major depression in a 12-month period, with women having approximately 1.7 times the risk as men (Substance Abuse and Mental Health Service Administration, 2015; Kessler, McGonagle, Swartz, Blazer, & Nelson, 1993). In marginalized populations and those of lower SES, rates are likely to be significantly higher (Weinberger et al., 2017). Lifetime prevalence is estimated at 17.9%. Major depression is frequently comorbid with other mental health disorders, particularly anxiety disorders and substance use disorders. The extensive burden on individuals, families, health care systems, and society makes it imperative to develop and implement effective tools and strategies to assess and treat major depressive disorder and other depressive disorders.

Children and Adolescents

Prevalence among children and adolescents. Depression is one of the most common psychiatric disorders in adolescents (Costello, Erkanli, & Angold, 2006). There are reports of a 11.7% lifetime prevalence rate for major depressive disorder or dysthymic disorder in adolescents based on data from the National Comorbidity Study—Adolescent Supplement (Merikangas et al., 2010). Moreover, there was a 2.6% increase between 2005 to 2014 in adolescents experiencing a major depressive episode (Mojtabai, Olfson, & Han, 2016). Rates

among same-aged youth of low SES, or who are members of marginalized populations, are believed to be significantly higher (Hasin, Goodwin, Stinson, & Grant, 2005). Adolescence is a unique period given the dramatic increase in risk for depression during this period. The impairments associated with adolescent depression also have been found to persist into adulthood and reflect the significant morbidity and lifelong impairment associated with the disorder (Glied & Pine, 2002; Lewinsohn et al., 1994; Lewinsohn, Rohde, Klein, & Seeley, 1999). The National Comorbidity Study—Adolescent Supplement found that rates of depression markedly increased among youth ages 13 through 18 years (Avenevoli, Swendsen, He, Burstein, & Merikangas. 2015) and that prevalence of major depressive disorder (MDD) is two times higher in older than younger adolescents as well as higher in female than male adolescents (Avenevoli et al., 2015). Furthermore, adolescents with anxiety disorders, attention-deficit/hyperactivity disorder, substance use disorders, and behavior disorders (i.e., oppositional defiant disorder, conduct disorder) have significant rates of comorbid MDD and higher risks of developing MDD, particularly severe MDD (Avenevoli et al., 2015).

In contrast, prevalence rates for depression are lower in children and preadolescents ranging from 0.4% to 2.5% of preadolescent children (Birmaher & Rozel, 2003). These rates are for those children meeting full diagnostic criteria for major depressive disorder. Therefore, rates likely underestimate the impact of depression on youth, as preadolescent children who present with clinically significant symptoms and impaired functioning, but not full clinical diagnosis are not always considered. These data may also not include significant representation of children of color or other minorities less likely to receive evaluation and treatment. These children with subsyndromal depression are at risk for developing depression diagnoses later in childhood and adolescence. Early longitudinal studies of children with depression suggested that early onset depression in children was associated with a more protracted course of illness and was a marker for more severe psychiatric outcomes in adolescence and adulthood (Kovacs et al., 1984; Kovacs, Feinberg, Crouse-Novak, Paulauskas, & Finkelstein, 1984). Specifically, it was

also associated with adult depression based in part on family psychiatric history (Wickramaratne, Greenwald, & Weissman, 2000). The Oregon Adolescent Depression Study findings suggested that childhood depression doubled the risk of experiencing depression in adolescence, and adolescent depression strongly predicted depression in early adulthood (Lewinsohn, Rohde, Seeley, Klein, & Gotlib, 2000; Rohde, Lewinsohn, Klein, Seeley, & Gau, 2013).

Despite the prevalence of symptoms, less than 1% of community-dwelling children and adolescents in the United States receive outpatient treatment for depression each year (Avenevoli et al., 2015). In particular, racially and ethnically diverse youth consistently demonstrate the greatest unmet need for mental health treatment (Alegría, Vallas, & Pumariega, 2010; Caldwell, Assari, & Breland-Noble, 2016). Children and youth living in rural, remote, and other underserved locations are least likely to receive needed mental health treatment (Blackstock, Chae, Mauk, & McDonald, 2018). Depressed children and adolescents are much less likely to receive mental health treatment than adults (Olfson, Gameroff, Marcus, & Waslick, 2003). Most youth who do use mental health services receive them in the school setting (Slade, 2003). Of those who reported receiving treatment for major depressive disorder in any setting (60.4%) in the National Comorbidity Study—Adolescent Supplement, only 33.9% stated that they received treatment specific to their depressive disorder or in a mental health service setting (Avenevoli et al., 2015). Accordingly, it is important to identify effective treatment strategies for childhood and adolescent depression to decrease current functional impairments and potentially disrupt the negative developmental trajectories that can continue into adulthood.

Characteristics of depression in children and adolescents. With the introduction of the *DSM-5*, what were formerly known as “Mood Disorders” are now referred to as “Depressive Disorders” and include Disruptive Mood Dysregulation Disorder, Major Depressive Disorder—Single and Recurrent Episodes, Persistent Depressive Disorder, Premenstrual Dysphoric Disorder, Substance/Medication-Induced Depressive Disorder, Depressive Disorder Due to

Another Medical Condition, Other Specified Depressive Disorder, and Unspecified Depressive Disorder (American Psychiatric Association, 2013). As indicated earlier, Major Depressive Disorder—Single and Recurrent Episodes and Persistent Depressive Disorder are the disorders with the highest prevalence in adolescents.

Depressive disorders are generally characterized by a cluster of symptoms including sadness or low mood, crying, loss of interest in once-enjoyed activities, decreased energy, and sleeping and eating changes. While these symptoms can be present in youth and adults, in adolescence, depression may manifest in slightly diverse ways. For example, over 60% of depressed teens reported severe impairment in functioning related to school/work, family, chores, and social roles (Avenevoli et al., 2015). Recent research has shown that typical presentations of youth depressive illness may include fatigue, irritability, and anger with behavioral correlates including poor school performance, negative acting out, and poor interpersonal and peer relationships (Jaycox et al., 2009). Typically, individual behavior changes must occur for at least 2 weeks and must represent a notable change in functioning from earlier levels considered normal for that individual to be considered impaired. Although episodes of major depressive disorder are less frequent in children than adolescents, the length of the episode was significantly longer in duration in children than adolescents (median of 16 weeks versus 8 weeks, respectively; Rohde et al., 2013). Regardless of the length of the episode, clinicians are encouraged to intervene as opposed to watchful waiting to alleviate suffering, particularly given the sensitive developmental periods and tasks of childhood and adolescence.

The *DSM-5* diagnostic criteria for characteristics of depressive disorders note some exceptions for children or adolescents, such as an exception specific to children for major depressive disorder that failure to gain expected weight rather than just significant weight loss or gain should be considered during diagnosis (American Psychiatric Association, 2013). Regarding the manifestations of major depressive disorder in youth, the American Academy of

Child and Adolescent Psychiatry (2013) indicated that children and adolescents with depression exhibit symptoms including social isolation, extreme sensitivity to rejection or failure, and increased irritability. While these symptoms can also occur in adults, these are symptoms that may be of great import for recognizing depression in youth, particularly because there are important developmental differences in verbal expression and emotional maturity between youth and adults. Overall, much of the literature does not treat children and adolescents as separate developmental cohorts, thereby limiting our understanding of unique symptom presentations among children and adolescents, respectively. This is a concern because distinct differences in development may have implications for treatment (e.g., the appropriateness of some cognitive strategies or forms of play therapy).

Sex differences in children and adolescents. Rates of depression differ among the sexes across the age span of childhood to adolescence. Prior to puberty, rates for depressive disorders are equivalent between the sexes. After puberty, this shifts to a 2:1 ratio of females to males, which continues throughout adulthood (Hatcher-Kay & King, 2003). The emergence of the sex difference in adolescence is consistent across samples from different countries and irrespective of the measure used to assess depressive symptomatology (Wade, Cairney, & Pevalin, 2002). Studies are consistent in finding that the increase in rates for females begins to emerge around the age of 13 (Nolen-Hoeksema & Girgus, 1994; Thapar, Collishaw, Pine, & Thapar, 2012). The reasons for the post-pubertal onset of rate differences among the sexes are not fully understood, but factors thought to play an influence include the hormonal and social changes that occur during puberty (Hatcher-Kay & King, 2003; Nolen-Hoeksema, 2001; Thapar et al., 2012).

Child/adolescent depression and race/ethnicity. Researchers have posited many explanations for the disengagement of African Americans and other people of color in clinical treatment, mostly focusing on access to care barriers (Alegría et al., 2002; Snowden & Yamada, 2005). For example, many African Americans view psychiatric illness as a proscribed subject

unattributable to genetic and dysfunctional familial precursors, favoring instead attributes toward lack of resoluteness, spirituality, and stress (Cauce et al., 2002; Kendrick, Anderson, & Moore, 2007; Schnittker, Freese, & Powell, 2000). Further, there are barriers to care related to other people of color focused on lack of multilingual, multicultural providers; differing conceptualizations of mental illness; and stigma. Other literature has suggested reasons including lack of nonracially diverse professionals in leadership roles, questioning of motives of nondiverse clinicians/researchers, fears of exploitation, and lack of knowledge about the process of medical research and clinical care as the rationale for people of color not participating in clinical research/treatment (Connell, Shaw, Holmes, & Foster, 2001; Corbie-Smith, Thomas, Williams, & Moody-Ayers, 1999; Murray, 1998). As it relates to youth, the literature indicates that African American parents specifically are fearful of the negative consequences typically prescribed for emotionally or behaviorally disturbed children, as well as mislabeling of their children with disruptive behavior problems instead of depressive illness (McMiller & Weisz, 1996; Pastore, Juszczak, Fisher, & Friedman, 1998; Wu et al., 2001). These concerns are also relevant for other groups of people of color.

Research has suggested heterogeneity in the development and expression of depressive symptoms, as evidenced by diverse trajectories for different racial/ethnic groups (Costello, Swendsen, Rose, & Dierker, 2008). Some studies reported higher rates of depression among non-White youth than White youth (Moon & Rao, 2010; van Voorhees et al., 2008), while others show a greater percentage of White youth with depressive symptoms than African American youth (Saluja et al., 2004). Additionally, data from several large studies suggested that, after controlling for socioeconomic status, there are no differences in the prevalence of depressive symptoms or affective disorders among Black, Hispanic/Latino, Asian, and White youth (Doi, Roberts, Takeuchi, & Suzuki, 2001; Garrison, Addy, Jackson, McKeown, & Waller, 1992; Rushton, Forcier, & Schectman, 2002). Other studies indicated that Latino and Native American youth have the highest rates of depression among youth of color (Centers for Disease

Control [CDC], 2012; Kann et al., 2014; Saluja et al., 2004). Given the profound impact of SES on the developmental trajectory and the strong association between poor mental health outcomes and the sequelae of poverty (Matthew & Brodersen, 2018), further research that better depicts rates and presentation of depression among marginalized populations is necessary.

While treatment of depression in children and adolescents with cognitive treatments is promising, little research exists about the treatment of depressive illnesses in exclusive samples of youth of color. Specifically, only a small handful of studies on exclusive samples of youth of color were identified through APA staff review of studies included in the underlying reviews. For example, a randomized controlled trial examined the use of interpersonal psychotherapy (IPT) for the treatment of depression in Latino youth (Mufson et al., 2004). In this study, IPT was found to be superior to treatment as usual[33] for a sample of under resourced Latino youth regarding symptom reduction and behavioral functioning compared with youth receiving treatment as usual. Two additional studies examined the use of both cognitive-behavioral therapy and interpersonal psychotherapy for the treatment of Latino youth (Rosselló & Bernal, 1999; Rosselló, Bernal, & Rivera-Medina, 2012). These findings are promising, but considerably more research on youth of color from varied socioeconomic backgrounds is needed to support these findings and to expand the knowledge base regarding the treatment of depression in racially diverse youth. Finally, given greater underutilization of clinical depression care by youth of color, more research is needed to examine the impacts of engaging this population in depression treatment. Currently, a growing body of research exists in treatment engagement (Breland-Noble & AAKOMA Project Adult Advisory Board, 2012; Breland-Noble, Bell, Burriss, & AAKOMA Project Adult Advisory Board, 2011), with promising findings. However, considerably more research is needed to replicate current findings and establish the

[33] Treatment as usual refers to the treatment that a patient would ordinarily receive. The panel noted the challenge of a consistent definition for treatment as usual given that the definition varies by study.

effectiveness of engagement methods (Lindsey et al., 2014). And, research with youth of color must be based on an understanding of multicultural concerns as well as practical barriers that limit access to care.

Child/adolescent depression and suicide. While adolescents who experience an episode of depression have a 30-fold increased risk of deaths by suicide (Brent, 1993; Brent et al., 1988), the suicide rates for children and adolescents have generally stabilized or declined over the past 20 years (McLoughlin, Gould, & Malone, 2015). According to Shain and colleagues' (2016) analysis, the suicide rate in teens decreased by 28% from 1990 to 2013.

Even though there is stability in rates of suicide among youth, suicide is the third leading cause of death for youth between the ages of 10 and 24 (CDC, 2017) as well as for Hispanic males ages 15 to 34 (Suicide Prevention Resource Center, 2013) and Black youth ages 15 to 24 (Al-Mateen & Rogers, 2018). Depressive disorders are linked with increased risk for suicidal ideation, suicide attempts, and completed suicides (Hatcher-Kay & King, 2003). The prevalence of seriously attempting suicide was higher among gay, lesbian, and bisexual youth than their heterosexual counterparts (42.8% and 14.8%, respectively; Frieden, Jaffe, Cono, Richards, & Iademarco, 2016). Depression is a major risk factor for suicide with more than half of adolescent suicide victims reported to have a depressive disorder at time of death (Thapar et al., 2012). Rates of suicide among Native American youth are the highest across all populations and are at epidemic levels (Herne, Bertholomew, & Weahkee, 2014). According to the National Comorbidity Study—Adolescent Supplement, nearly 30% of adolescents with major depressive disorder reported some form of suicidality in the past year, with 10.8% reporting a suicide attempt (Avenevoli et al., 2015). Thus, providing effective treatment for depression in youth and reduction of access to lethal means might have a significant impact on preventing suicidal behavior and attempts in this age group.

Child/adolescent depression and co-morbidity. A large proportion of children and adolescents with depression also meet criteria for comorbid psychiatric disorders, with the most

common disorders including anxiety and behavioral (conduct and oppositional defiant) disorders (Avenevoli et al., 2015). Research has indicated that youth with primary depression, compared with youth with primary anxiety, are more likely to have other comorbidities (such as anxiety). For example, research over the past 10 years suggests that almost half of community youth with primary depression also meet criteria for anxiety disorders while just under 20% of community youth with primary anxiety also meet criteria for a depressive disorder (Garber & Weersing, 2010). Aside from anxiety, other common psychiatric comorbidities present in youth with primary depression include substance use and abuse (Curry & Hersch, 2016), sleep problems and attention-deficit/hyperactivity disorder (Becker, Langberg, & Evans, 2015).

There are also some reported sex differences in patterns of concurrent comorbidity, with some studies showing depression comorbid with conduct disorder in girls but not boys, and depression comorbid with substance use disorders in boys but not girls (Costello, Mustillo, Erkanli, Keeler, & Angold, 2003). However, recent research points to fewer sex differences and greater depressive illness severity associated with likelihood of co-morbidity equally between boys and girls (i.e., more severe major depressive disorder is associated with presence of conduct and anxiety problems than less severe major depressive disorder in both sexes; Avenevoli et al., 2015). As shown earlier, depression was often studied as a secondary co-occurring disorder to other behavior and mental health problems (i.e., conduct disorder and oppositional defiant disorder) in youth of color. However, it is unlikely that high representation of this research area shows greater likelihood of externalizing behavior problems in depressed youth of color. Therefore, future research is needed with large samples of youth of color to determine actual correlation between disruptive behavior problems and the presence of major depressive disorder in racially diverse youth.

Finally, physical health conditions, such as smoking, obesity, and drug use (Conway, Swendsen, Husky, He, & Merikangas, 2016; Merikangas, Mendola, Pastor, Reuben, & Cleary,

2012) are also associated with depression that differs across racial groups. Overall, the current body of research has suggested that youth across race and sex experience depression in consort with other mental illnesses and that clinical interventions for depression may need to account for the presence of symptoms reflecting multiple mental illnesses in children and teens.

General Adult Population

Prevalence among adults. Major depression is one of the most common mood disorders among young and middle-aged adults. According to a 2014 report by the Substance Abuse and Mental Health Services Administration (SAMHSA), an estimated 15.7 million adults in the United States aged 18 and older had at least one major depressive episode during the past year. This represented 6.7% of all U.S. adults (SAMHSA, 2015).

In addition, 4.3% of adults (10.2 million individuals) reported experiencing a major depressive episode with “severe impairment” (SAMHSA, 2015). Severe impairment occurred if their depression resulted in severe problems in their ability “to manage at home, manage well at work, have relationships with others, or have a social life” (SAMHSA, 2015, p. 30). Among the U.S. adult population, the highest percentage of individuals with a previous-year major depressive episode occurred for young adults aged 18 to 25 (9.3%). This was followed by adults aged 26 to 49 (7.2%) and then by individuals older than 50 (5.2%). Regarding the experience of a major depressive episode leading to severe impairment, the age group with the highest percentage of adults involved those aged 18 to 25 (6.0%), followed by people aged 26 to 49 (4.6%) and persons older than 50 (3.5%; SAMHSA, 2015).

Not only is depression pervasive, it also carries the heaviest burden of disability among psychological disorders. Specifically, major depression accounts for 3.7% of all U.S. disability-adjusted life years and 8.3% of all U.S. years lived with disability (National Institute of Mental Health, 2015). Worldwide, it is estimated that on average 1 in 20 people experienced a depressive episode in the previous year, affecting 350 million people (Marcus et al., 2012).

Characteristics of depression in the general adult population: *Sex differences in adults.* Across the world, women are approximately twice as likely to experience depression as men (Albert, 2015). For example, women have a lifetime prevalence for major depression of approximately 21%, compared with 12% among men (Kessler et al., 1993). This sex difference appears early during adolescence. Explanations for this difference include a variety of developmental, biological, cultural, and social causes (Albert, 2015).

Regardless of the reasons, the World Health Organization (WHO) estimated that the burden of depression is approximately 50% higher for women than men (WHO, 2008). Moreover, it is the leading cause of functional impairment for women regardless of the socioeconomic status of a given country. Of related concern is the notion that maternal depression, especially in developing countries, may be a risk factor for impoverished growth in young children (Rahman, Patel, Maselko, & Kirkwood, 2008), underscoring the cross-generational impact of depression.

There are also sex differences in the presentation of adult depression. For example, according to the National Institute of Mental Health (NIMH), women tend to have symptoms of sadness, worthlessness, and guilt, whereas men are more likely to report experiencing tiredness, irritability, sleep problems, and loss of interest in previously pleasurable activities (NIMH, 2015).

Adult depression and race/ethnicity. Different depression prevalence rates as a function of race and ethnicity have been identified. This relationship, however, can be somewhat complex. For example, while large-scale studies tend to find that Blacks (e.g., African Americans, Caribbean Blacks) have lower lifetime rates of major depressive disorder compared with non-Hispanic Whites, the chronicity and burden of depression appears the opposite for these groups. Specifically, one study found that while lifetime major depressive disorder prevalence estimates were the highest for Whites, the chronicity of major depressive disorder

for the Caribbean Black and African American samples was substantially higher than for Whites (Williams et al., 2007). Moreover, both Black groups, in comparison to Whites, were less likely to receive any form of psychotherapy or pharmacotherapy for depression and were more likely to rate their major depressive disorder as more severe and disabling.

One concern involved in estimating difference in prevalence rates as a function of race and ethnicity is to avoid "lumping" various subgroups together. For example, 27% of a group of over 16,000 individuals of Hispanic/Latino origin reported elevated levels of depressive symptoms, but rates varied between 22.3% among individuals of Mexican background to 38% among those of Puerto Rican background (Wassertheil-Smoller et al., 2014). Also, despite similarities in ethnic background/heritage, an individual's location of birth may play a role in influencing differences in depression prevalence rates. One study found that prevalence rates of depression among U.S. born Chinese Americans was much higher (21.5%) than that of non-U.S. born Chinese Americans (7.7%; Jackson et al., 2011). Further, the prevalence rates of depression among Asian Americans were higher than among Asians in Asia (Yang & WonPat-Borja, 2007). An added concern in estimating differences in prevalence rates is that socioeconomic status and poverty are not only independent predictors of depression, they are also strongly associated with race/ethnicity and depression (Riolo, Nguyen, Greden, & King, 2005). Notably, in many places around the world, people of color (compared with Whites) are overrepresented in groups with less access to socioeconomic resources. Research that fully explores rates of depression among multicultural and diverse populations inclusive of SES, gender identity, sexual orientation, cultural heritage, and geography is needed.

Adult depression and suicide. It is estimated that approximately two thirds of those in the United States who die by suicide suffer from depression at the time of the suicide act (CDC, 2012). Moreover, the likelihood for a lifetime suicide attempt has been estimated to be approximately five times greater for individuals with major depressive disorder or persistent

depressive disorder compared with an individual without a diagnosis (Nock, Hwang, Sampson, & Kessler, 2010). Such statistics strongly underscore the need for adequate assessment of the presence and degree of suicidality when working with depressed adults, the reduction of access to lethal means, and the need for effective depression treatment to reduce suicide.

Adult depression and comorbidity. Depressive symptoms and disorders are commonly associated with a wide range of other psychiatric and medical disorders and diseases. These include anxiety, posttraumatic stress disorder, substance use, personality disorders, heart disease, cancer, multiple sclerosis, pain, dementia, and diabetes (e.g., Katon et al., 2010; Richards & O'Hara, 2014; Simon et al., 2005). Such comorbidity can have significant impact on people's health outcome beyond the disease itself. For example, depression among patients with diabetes is associated with higher risk of significant complications such as amputation, blindness, and dementia (Katon et al., 2010; Simon et al., 2005). Moreover, depression itself has been found to predict comorbid medical diseases such as diabetes (Katon et al., 2010). Research has shown that among people without cardiovascular disease but depression at baseline, there is an approximately 200% increase in relative risk (or probability) of developing heart disease compared with nondepressed persons (Wulson & Singal, 2003). Additionally, depression is commonly reported in patients with HIV/AIDS (Rabkin, 2008). The literature on the assessment and treatment of diseases comorbid with depression is large and growing.

Older Adult Population

Prevalence of depression in older adults. The prevalence rate of depression in the overall older adult population is estimated to be 2.6% (Haigh, Bogucki, Sigmon, & Blazer, 2016; Kessler et al., 2003). The estimate point prevalence of major depression among older patients ranges between 5%–10% in primary care settings and is higher still (10%–42%) among older patients in inpatient settings, including long-term care (Blazer, 2003; Djernes, 2006; Schulberg,

Katon, Simon, & Rush, 1998). Epidemiological studies of late-life depression show that the prevalence of depression and of clinically significant depressive symptoms increases with greater medical burden/comorbidity and disability. Subthreshold depression is 2–3 times more common than major depression in older adults, and 8%–10% of those with subthreshold symptoms develop major depression each year (Meeks, Vahia, Lavretsky, Kulkarni, & Jeste, 2011). Cognitive decline, age-associated neurobiological changes, stressful events, and sleep disturbance are also risk factors for late-life depression (Fiske, Wetherell, & Gatz, 2010; Sözeri-Varma, 2012). It is also important to consider cohort differences in the prevalence, presentation, and treatment of depression among older adults. For example, the issues of a typical young–old person in their 60s may be quite different than that of an older–old person in their 90s.

Characteristics of depression in older adults. The clinical presentation of depression in older adults is also distinctive and, to an important extent, differs from early periods in the life cycle by following a relapsing and recurrent course. Depression in older adults is often treatment resistant, that is, patients may improve partially but do not remit symptomatically nor regain full functional status (Ng & Schweitzer, 2002). Partial response, as marked by the presence of residual symptoms, is associated both with continuing disability, caregiver burden, and elevated risk for early relapse and recurrence. The literature on treatment resistance in older adults is still rather sparse, but recent leads in the pharmacotherapy of treatment-resistant depression are promising (Lenze et al., 2015).

Subsyndromal depression in old age is an important opportunity for early interventions to preempt the development of full-blown clinical depression. Learning-based interventions and those that are behaviorally activating (e.g., behavioral activation, cognitive-behavioral therapy, problem-solving therapy) are a promising method of depression prevention (with a focus on mildly symptomatic people; Reynolds et al., 2014). These interventions are also amenable for outreach to, and effective in, low-income older African Americans (Reynolds et al., 2014).

Older adult depression and race/ethnicity. The growth in the nation's older population is characterized also by increasing racial and ethnic diversity and the need for preventive and treatment interventions that are culturally appropriate. Models employing lay health counselors of similar ethnic and racial backgrounds to the patient increasingly seem to be a rational and cost-effective use of resources to reach diverse racial and ethnic groups in underserved and disadvantaged older adults (Patel et al., 2010).

Treatment accessibility and use can vary among older adults of differing ethnic backgrounds. Such disparities in treatment accessibility and/or use have been attributed to financial hardship, unique presentations of depressive symptoms, culturally based mistrust of providers, negative attitudes about seeking mental health care (e.g., feelings of shame/guilt), anticipated or previously experienced racism or discrimination in treatment settings, language barriers, and the limited accessibility of ethnically diverse mental health professionals (Conner et al., 2010; Unützer et al., 2003). However, more research is needed to understand other groups of people of color and people of color across socioeconomic strata.

Older adult depression and suicide. Another and particularly important aspect of depression in older adults is the risk for suicide, particularly in older White males who typically use handguns to end their lives (Bruce et al., 2004). Increasing the accessibility and utilization of care for depression in older adults as well as all age populations and reducing access to highly lethal means (e.g., firearms) are key strategies for reducing proximal risk factors for suicide.

Older adult depression and comorbidity. Although core symptoms are the same as in the general adult population (e.g., low mood and anhedonia), depression in older adults typically co-occurs with often chronic medical disorders, amplifying disability (Lin et al., 2003). For example, Lin and colleagues (2003) found that enhancing care for depression was related to lower levels of pain as well as higher quality of life and functional status among a diverse

sample of older adults with comorbid depression and arthritis. Further, depression in older adults either coexists with or foreshadows the development of cognitive impairment and dementia (Butters et al., 2004; Diniz, Butters, Albert, Dew, & Reynolds, 2013). For example, in a meta-analysis, Diniz and colleagues (2013) found a link between depression in older adults and risk of dementia, including both Alzheimer's disease and vascular dementia. This risk was particularly high for vascular dementia compared with Alzheimer's disease. These signature comorbidities of late-life depression complicate its management and need to be addressed in treatment planning.

Treatment issues in older adults. Many older adults prefer psychosocial treatments to pharmacotherapy for depression (Hanson & Scogin, 2008; Raue, Schulberg, Heo, Klimstra, & Bruce, 2009). Multiple factors influence these preferences including insurance coverage, availability of specific treatments, transportation, and reduced patient mobility and make input from patients and families important. In depression treatments, older adults with depression, as well as their family caregivers, define treatment goals in terms of well-being and return of functional status and engagement in key social and familial roles (Lebowitz et al., 1997). It is often difficult, however, to provide psychosocial treatment, given the paucity of specialty-trained providers to treat depression in older adults, especially in primary care settings. Primary care settings remain the principal locus where treatment of late-life depression takes place. At any one point in time, it is estimated that 6%–10% of older patients in primary care settings qualify for a diagnosis of current major depressive episode and another 10%–20% have subsyndromal symptoms that are disabling and that pose risk for conversion to major depression. To some extent the locus of care reflects patient and family preferences, as well as stigma against mental health specialty referral. The challenge here is to identify models of evidence-based depression care management that are transferrable to and practical within primary care settings (e.g., Improving Mood-Promoting Access to Collaborative Treatment [IMPACT] intervention; Unützer

et al., 2002); and Prevention of Suicide in Primary Care Elderly: Collaborative Trial [PROSPECT]; Bruce et al., 2004). There is considerable progress in the development and implementation of collaborative care models for both treatment and prevention. In low resource countries, such as India, progress is also evident in the development of models that use lay health counsellors for the implementation of depression treatment and prevention programs (e.g., the MANAS trial in Goa; Patel et al., 2010). Many frail, homebound older adults who have symptoms of depression and cognitive impairment have difficulties in obtaining appropriate care. Programs for reaching out to this particularly vulnerable population have been developed, together with pathways to implementation of appropriate treatment (Scogin, Moss, Harris, & Presnell, 2014; Sirey, Hannon, D'Angelo, & Knies, 2012). Family and psychoeducational interventions may be particularly useful in reaching diverse older adults. As such, a public health and clinical priority in optimizing care for older adults is identifying psychosocial treatments that are effective across diverse racial, ethnic, and socioeconomic groups; can be carried out in general medical settings (such as problem-solving therapy; Unützer et al., 2002); and are sensitive to culturally specific experiences and beliefs of diverse racial, ethnic, and socioeconomic groups.

The Need for a Clinical Practice Guideline and Decisions about Scope and Goals of the Clinical Practice Guideline

Available treatment guidelines for the problem. Given the evidence that depression is a disorder whose cost and burden justify extensive efforts at intervention, providers need access to information that will help guide intervention. While there is now a substantial body of research literature examining a broad range of approaches to assessment and treatment (including psychotherapeutic, pharmacologic, and other interventional approaches), studies have indicated that of those who receive treatment, between 30% (Teh et al., 2010) and 59% (Kessler et al., 2003) do not receive a minimally adequate dose of treatment (as defined by Kessler et al., 2003 on p. 3098). Some subpopulations are at even higher risk for failure to

receive adequate treatment (i.e., African Americans and individuals who begin their depression treatment with an inpatient hospitalization for depression; Teh et al., 2010). These findings strongly demonstrate the need for providers, consumers, and health care systems to have access to guidelines that provide information about effective treatment options as well as a focused application of dissemination and implementation science.

Fortunately, there have been several guideline development efforts addressing major depression, including the National Institute for Health and Care Excellence (NICE) guideline in the United Kingdom (NICE, 2009), the Department of Veterans Affairs/Department of Defense (VA/DoD, 2016) guideline, and the American Psychiatric Association (2010). How the current guideline complements these prior efforts is discussed on p. 72.

The APA Clinical Practice Guideline for the Treatment of the Problem

In considering how the current guideline development could complement the existing knowledge base, the guideline development panel had several overarching goals. The panel intended to develop a guideline that would be applicable to a broad range of the population, including adolescents through older adult populations. Of note, in reviewing the literature, the panel found that it was unable to separate child research from adolescent research consistently and, therefore, expanded the domain reviewed to include children. In addition, the panel identified the need to include psychotherapeutic interventions. In considering prior guidelines, they either provided limited guidance on psychotherapies or had been completed 5 years or more prior and there was a need for an updated review of the literature (following IOM [2011b] standards). One exception is the VA/DoD guideline focused on veteran and military populations, which was completed while this guideline was in development and whose underlying systematic review has been drawn on to support this current effort.

What the current guideline provides beyond existing ones. This clinical practice guideline differs in substantive ways from others that are currently available. This guideline is

predicated on the three dimensions mentioned in the American Psychological Association Presidential Task Force on Evidence-Based Practice (2006): (1) grounding in the best available science; (2) practitioner expertise in application decisions; and (3) patient expertise regarding their preferences, culture, and values. These three areas were consistent with earlier work by the Institute of Medicine (IOM) and are areas that are universally accepted in medicine. In addition, the steering committee and panel made every effort to fully apply the standards set forth by the Institute of Medicine of the National Academies of Sciences, Engineering, and Medicine for developing independent, reliable, and high-quality clinical practice guidelines (IOM, 2011a; IOM, 2011b).[34] This document goes beyond previous treatment of depression guidelines and literature in the following important ways: (a) involvement of consumer (patient) stakeholders as panel members in addition to professionals from multiple disciplines involved in the delivery of the treatment of depression; (b) use of procedures for identifying and managing real and potential conflicts of interest (COIs) throughout the guideline development process that required all panel members to routinely disclose all conflicts of interest; (c) identification of patient values and preferences through review of published research literature and input from consumer members of the panel; (d) identification of harms and burdens of treatments through review of published research literature and input of consumers and clinician members of the panel in evaluating those harms and burdens; (e) the use of decision-table (for older adults) and grid (for general adults and children/adolescents) templates to systematically guide panel members in the development of recommendations that take into account the strength of the research evidence for benefits and harms, the relative balance of treatment benefit versus treatment harm, the values and preferences of patients, and applicability.

[34] Of note, as of March 2016, the division of the National Academies of Sciences, Engineering, and Medicine (the National Academies) formerly known as Institute of Medicine (IOM) was renamed the National Academy of Medicine (NAM). Despite the recent name change, the guideline will use IOM when referring to the IOM standards for guideline development and systematic reviews.

For the general adult population, the panel used an independent, newly released, systematic review of the depression treatment literature that provided clearly specified inclusion and exclusion criteria, a standard method for grading risk of bias of individual studies and strength of evidence for bodies of evidence. The systematic review was supplemented by a review of existing reviews as well as meta-analyses to provide more comprehensive coverage of the literature. The panel used existing meta-analyses of the child and adolescent literature that were identified by panel members, and all existing meta-analyses and reviews were evaluated using the same AMSTAR (a measurement tool to assess systematic reviews; Shea et al., 2007) quality criteria.

Institute of Medicine (IOM) standards as the basis for this clinical practice guideline. Another goal of the panel was to take a methodologically rigorous approach to guideline development, following the current IOM recommendations (IOM, 2011a). This, however, led to one of the more significant challenges in the guideline development process. The systematic reviews conducted by the evidence-based practice centers met IOM criteria but excluded bodies of literature because of inadequate quality, yet such exclusions meant some of the panel's key questions were not addressed. Rather than not address those questions, the panel chose to modify its criteria for systematic reviews and include manuscripts that had used a single rather than dual review process to evaluate articles for inclusion in the review (i.e., one reviewer vs. two for article inclusion) but otherwise met all IOM requirements. The consequence is a less methodologically rigorous systematic review because there is an increased risk of bias in the choice of journal articles (Edwards et al., 2002; IOM, 2011b). However, key questions could not have been answered otherwise. The single reviewer in each of the three meta-analyses utilizing single review was panel member and lead author of these published meta-analyses, Dr. Pim Cuijpers. To reduce potential COI, as noted each of these reviews was independently analyzed with AMSTAR prior to use by the panel. The panel is therefore able to

address these questions but does so with proper precautions about the literature on which the recommendations are based.

Shared versus unique contributions of different psychotherapy models. A fourth goal was to attempt to address the issue of shared versus unique contributions of different psychotherapy models. Most of the psychotherapy treatment literature examines specifically defined models. However, there is a growing body of literature suggesting that shared aspects (common factors [e.g., hope, expectancy, therapeutic alliance]) of interventions (Norcross, 2011) relative to model-specific components are germane to optimal treatment outcomes (regardless of the therapeutic orientation implemented). An analysis of treatments for major depression found evidence consistent with this (Cuijpers, Driessen, Hollon et al., 2012a). In addition, the definitions of treatments in articles and reviews varied greatly. Further, in some reviews, treatments were grouped that were arguably not part of the shared family of interventions, reducing panel confidence in consistency across treatment comparisons and judgments about specific contributions of distinct psychotherapies. Thus, the panel was not able to realize this goal but makes recommendations for future research that explicitly addresses the shared components of effective psychotherapy, the necessity of appropriately defining treatments, and newer models of the treatment of depression. Further discussion of this topic is provided in the Discussion section.

Guideline recommendations for underserved populations. Similarly, a fifth goal was to provide appropriate guideline recommendations for underserved populations. However, it was immediately apparent that randomized controlled trials (RCTs) included in the reviews had limited information available to inform recommendations for such populations. While the panel made extensive efforts to draw guidance from the literature available, the limitations of that literature made clear to the panel the need for a vigorous call for increased dedication to RCTs specifically studying diverse samples. Of note, the limitations of the literature highlighted the

need for funding agencies and investigators to explicitly address differences, in particular, culture, ethnicity, sex, sexual minority, gender identity, disability, nationality of origin, generation status, race, socioeconomic status, and others, as well as the intersection of these variables, which can further influence treatment. These are areas that could contribute to the experience and treatment of depression but for which the panel did not have an adequate literature to address.

Finally, arising from these last two goals, the panel was determined to develop a series of recommendations for future research to address the gaps and limitations in the literature that were observed. The panel's goal is that this guideline serves as a current and functional tool to guide providers, health care systems, and consumers in decision-making regarding treatment and provides investigators guidance on key clinical research questions that are necessary to address so that all can meaningfully improve the ability to treat this pervasive and debilitating disorder.

Guideline Purpose and Scope: What the Guideline Does and Does Not Address

The purpose of this guideline is to provide recommendations on the treatment of depression in three developmental cohorts: children and adolescents; general population of adults; and older adults. This guideline is based on several systematic reviews and meta-analyses of the evidence on treatment of depression, two of which were sponsored by the Agency for Health Care Research and Quality (AHRQ)[35] and conducted by the Research Triangle Institute–University of North Carolina (RTI-UNC) Evidence-Based Practice Center (Gartlehner et al., 2015) and the ECRI Institute (2015). The other reviews were independently conducted by teams of researchers (Cipriani et al., 2016; Cuijpers, Driessen, et al., 2012a; Cuijpers, Karyotaki, Pot, et al., 2014a; Cuijpers, Koole, et al., 2014b; Cuijpers et al., 2016, Driessen et al., 2015; Wilkinson & Izmeth, 2012; Zhou et al., 2015).

[35] The AHRQ (an agency that works within the U.S. Department of Health and Human Services) strives to improve health care by enhancing access to the relevant evidence bases in collaboration with partners.

This guideline attempted to address the following four key questions[36]:

1. For individuals in each of the three age cohorts with major depressive disorder, persistent depressive disorder,[37] or subsyndromal depression,[38] what is the efficacy and risk of harms of psychotherapy or complementary and alternative medicine treatments?[39]
2. For individuals in each of the three age cohorts with major depressive disorder, persistent depressive disorder, or subsyndromal depression, what is the effectiveness and risk of harms of psychotherapy or complementary and alternative medicine treatments in comparison either with one another or with pharmacotherapy?
3. For individuals in each of the three age cohorts with major depressive disorder, persistent depressive disorder, or subsyndromal depression, what is the effectiveness and risk of harms of combinations of pharmacotherapy, psychotherapy, or complementary and alternative medicine treatments compared with inactive or active single or combined treatments?
4. Are the benefits and risks of these treatment options moderated by subgroup characteristics, including suicidal ideation, treatment-resistant depression, co-occurring anxiety disorders, or co-occurring personality disorders?[40]

The reviews underlying this guideline *did not* explicitly search for or include the following items:

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[36] The exact wording of the key questions evolved from the original commissioned review in order to best capture the full scope of the work of the panel. The original key questions can be found in the RTI-UNC Evidence-Based Practice Center Team paper (2015).
[37] Formerly "dysthymia," changed to be consistent with *DSM-5* though some studies were conducted prior to the release of the *DSM-5*.
[38] Also known as "Other Specified Depressive Disorder" (*DSM-5*, APA, 2013).
[39] Note that while the panel initially decided not to look at efficacy of medication treatments alone, rather to only examine medications in combination with or in comparison to (comparative effectiveness) psychotherapy, it later decided to examine efficacy of medication treatment alone (using medication only studies) for children/adolescents due to potential safety concerns about medications in this population.
[40] Note that while the panel was also interested in differential effectiveness based on race/ethnicity, the included reviews did not have sufficient information to inform such recommendations.

1. Screening for depression, assessment of associated or comorbid conditions (e.g., suicidality,[41] medical problems), monitoring response to treatment, or follow-up after treatment.
2. Prevention of depression.
3. Dose (differential beyond current recommended), timing, or duration of treatments for depression.
4. Costs of treatments.
5. Model or locus of care.
6. The long-term benefits of treatment for maintenance of recovery and prevention of relapse.[42]
7. Mechanisms of change.
8. Efficacy of treatments for disorders other than depression.
9. Bipolar disorder.

The panel had originally proposed to include somatic treatments in the review, but the nature of the search criteria did not adequately capture the literature, and the panel was unable to make recommendations about those interventions. The panel utilized systematic reviews/ meta-analyses that were current (within the past 5 years) at the time the panel made its recommendation decisions that met IOM (2011b) development and AMSTAR quality standards (Shea et al., 2007).[43]

[41] In particular, there is need for expanded guidance on the assessment and management of suicidal behavior. While beyond the scope of this guideline, recent evidence of increasing rates of suicide across a number of cohorts indicates this is a high-priority domain.
[42] There were not enough studies in the reviews to address this independently. The panel stresses the importance of this area of practice and the need for more research to contribute to systematic reviews of long-term depression treatment.
[43] By the time of finalization of the current guideline document several of the underlying reviews will have crossed the 5-year mark for being considered a current review. However, it should be noted that the panel completed its decision-making about the recommendations during the 5-year window in which each review was considered current.

Process and Method

Vetting and Appointment of Members to the Depression Guideline Development Panel

The Advisory Steering Committee (ASC) put out a call for the nomination (including self-nomination) of both researchers and clinicians across various professional disciplines (psychology, social work, psychiatry, general medicine) who had content expertise in the topic area of depression treatment as well as in biostatistics or methodology. The ASC sought those with knowledge of depression across age groups, gender identity, populations (veterans, ethnic minorities), and treatment settings to seat a diverse panel with a variety of perspectives on depression and its treatment that could discuss the research data and its applicability to those seeking treatment. Additionally, the ASC sought community members who self-identified as having had depression (currently or in the past) or were a close family member of someone with depression and who were active in the leadership of groups that looked to enhance public awareness and access to services.

In constituting the panel, there was an effort to incorporate members who represented a broad range of experiences and expertise in the treatment of depression, including variation in terms of psychotherapy models, populations (e.g., adolescent, adult, older adult, underserved populations), settings (academic, community, primary care), roles (clinician providers, researchers, health care administrator, health care consumer), and discipline (psychology, psychiatry, family medicine). While it would not be possible in a panel of this size to represent all constituencies and interests in a truly equitable fashion, the mandate to the panel was to include as broad a perspective as possible when reviewing the literature.

Conflicts of Interest

As noted above, before final appointment to the guideline development panel, nominees gave information about possible conflicts of interest (COIs), a significant issue in the IOM standards and current best practices in guideline development. COIs are defined as:

> a divergence between an individual's private interests and his or her professional obligations such that an independent observer might reasonably question whether the individual's professional actions or decisions are motivated by personal gain, such as financial, academic advancement, clinical revenue streams, or community standing. (Institute of Medicine [IOM], 2011a, p. 78; the definition is drawn from Schünemann et al., 2009, p. 565)

The IOM report additionally discusses intellectual COIs relevant to clinical practice guidelines, defined as "academic activities that create the potential for an attachment to a specific point of view that could unduly affect an individual's judgment about a specific recommendation" (IOM, 2011a, p. 78; the definition is drawn from Guyatt et al., 2010, p. 739).

Candidates to the guideline development panel each completed an APA Conflicts of Interest disclosure form. Emphasis was placed on disclosing all potential conflicts for the APA staff and ASC members to review and decide on. While intellectual affiliations were expected, no panel members were to be singularly identified with particular interventions, nor were they to have significant known financial conflicts that would compromise their ability (or appearance thereof) to weigh evidence fairly. The ASC understood, however, that some "adversarial collaboration" (Mellers, Hertwig, & Kahneman, 2001) or standing for different points of view was expected and encouraged as part of the process. On successful completion of the reviews, the ASC made the final membership recommendations to the APA Board of Directors for confirmation.

Once the panel was formed, all members completed an educational module on conflicts of interest that underscored the importance of identifying and managing any that had either been identified or that might come to light. At request, members verbalized any actual or potential conflicts in their face-to-face meetings, so all members of the guideline development panel would be familiar with the diversity of perspectives and range of possible influences and

biases. Conflicts of interest forms were updated annually, and panel members and staff were asked to give more prompt updates if there were any changes in their disclosures that could be relevant to the development of an unbiased guideline.

Multiple strategies were used to identify and manage COI. Panel members (and ASC members and associated staff) all completed a disclosure form on an annual basis that was reviewed by the panel and ASC chairs. Panel members were expected to disclose potential COI at all face-to-face meetings and on phone calls whenever new COI emerged. This was structured in the agendas for the meetings. Several strategies were used to manage COI and typically these involved some combination of recusing from the discussion of a particular topic, recusing from voting on certain issues, or a combination of the two. The APA conflicts of interest policy and disclosure form is in Appendix E.

Scoping

At its first in-person meeting, the panel began discussion of topic scoping and continued to discuss scope over several subsequent conference calls. The panel followed a PICOTS (Population, Intervention, Comparator, Outcomes, Timing, and Setting) approach to scoping. Using this approach, each PICOTS element served to frame decision-making about scope. The panel also used the Delphi method to complete an outcomes prioritization survey. On this survey panel members rated outcomes from 1 “not important” to 9 “critical” for deciding about what treatment to recommend. Based on the results of this survey, the panel found “response to treatment” (reduction in depressive symptoms) and “serious adverse events” as its two most critical outcomes. Scoping decisions about which populations, interventions, comparators, outcomes, timing, and settings to include as well as the key questions are noted in the Scoping section at the beginning of this document.

Comprehensive Search of the Professional Literature: Systematic Reviews and Meta-Analyses

A *systematic review* involves a methodical and organized search for studies and evidence of efficacy and effectiveness of the treatment under consideration (IOM, 2011b). A *meta-analysis* is the use of quantitative statistical methods in a systematic review to integrate the results of included studies. Briefly, a systematic review or meta-analysis involves searching a variety of scientific databases using selective search terms to find relevant studies. The individual studies identified by the panel are then assessed to decide whether they meet inclusion criteria as well as assessed for the risk of bias using predefined criteria. Results are then compiled and analyzed.

Institute of Medicine (IOM) guidelines require the use of one or more systematic reviews for guideline development. APA, initially, commissioned an “umbrella review” of relevant systematic reviews and meta-analyses by the RTI-UNC Evidence-Based Practice Center, which helped to identify already existing bases of evidence and areas that might be missing. For the current guideline, the panel used a systematic review of the literature focused on comparisons of mainly second-generation antidepressant medication and psychotherapy with focus on primary treatment goals (e.g., achieving response and remission) rather than those of longer term treatment (e.g., preventing relapse and recurrence), although the panel recognizes the latter is essential for individual well-being. However, due to gaps in the types of treatment comparisons and approaches included in the first review, more reviews were identified and used to address the limitations of the initial review. Gaps found by the panel included an examination of supportive therapy, psychodynamic therapy, subclinical depression, and efficacy of psychological treatments. The panel followed best practices of using reviews current within the past 5 years, and an independent search was not conducted outside of these reviews for additional studies that may not have met inclusion criteria for the reviews. The panel used 10 systematic reviews or meta-analyses, each either independently conducted via IOM standards

or evaluated using AMSTAR quality standards and went ahead to draft recommendations in three phases based on population age: first older adults, next the general adult population, and finally adolescents and children. Systematic reviews and meta-analyses used were as follows (see Table 5 on p. 34 for a summary) and refer to Appendix H for results of the AMSTAR evaluation of these reviews. By the time of finalization of the current guideline document, several of the underlying reviews will have crossed the 5-year mark for being considered a current review according to best practices. However, it should be noted that the panel completed its decision-making about the recommendations during the 5-year window in which each review was considered current.

Children and adolescents. The panel used two meta-analyses after determining they were of sufficient quality. One meta-analysis focused on psychotherapies for depression in children and adolescents (Zhou et al., 2015). In this review, the study authors defined depression in youth ages 6 to 18 years having either received a diagnosis of depression (minor, intermittent, or major) or dysthymia or had an elevated score on the depression rating scale. The other meta-analysis focused on antidepressants for major depressive disorder in children and adolescents (Cipriani et al., 2016). Cipriani and colleagues defined depression in youth ages 9 to 18 years having received a diagnosis of major depressive disorder according to the *DSM-III-TR, DSM-IV,* or *DSM-IV-TR*. For more information on the inclusion/exclusion criteria implemented in these reviews, please refer to sections in Zhou et al.'s (2015) *Study selection* (pp. 208–209) and Cipriani et al.'s (2016) *Methods: Search strategy and selection criteria* (p. 2). For the list of keywords used in searches for articles for these reviews, please refer to sections in Cipriani et al.'s (2016) *Appendix 2: Search strategy and results* (pp. 4–5) and Zhou et al.'s (2015) *Study protocol and search strategy* (p. 208).

General adult population. The panel used data from several reviews and meta-analyses that met quality criteria. The panel used two systematic reviews conducted by

Evidence-Based Practice Centers, which follow quality standards for conducting systematic reviews set forth by the former Institute of Medicine (2011b) report. The first of these focused on comparisons of pharmacological treatments with nonpharmacological treatments (Gartlehner et al., 2015) while the second covered a broad range of treatment comparisons (ECRI Institute, 2015). The Veterans Administration/Department of Defense (VA/DoD) utilized the latter in their creation of a clinical practice guideline, and the review was used by this panel with permission. This systematic review for the VA/DoD included as data previously published systematic reviews as well as clinical studies. Gartlehner and colleagues (2015) defined depression in adults ages 18 and older who received diagnoses of major depressive disorder from a standardized diagnostic manual or from elevated scores on validated instruments. For more information on the inclusion/exclusion criteria used in this review, please refer to Gartlehner et al.'s (2015) *Table A. Inclusion/exclusion criteria* (pp. ES-3 to ES-5). The VA/DoD guideline developers defined depression in adults age 18 or older having received a first diagnosis of major depression, currently receiving treatment for depression, and adults with chronic depression in a VA/DoD setting (ECRI Institute, 2015). For more information on the inclusion/exclusion criteria used for this review, please refer to the VA/DoD's section *Methods of Systematic Review: Study Selection Criteria* (p. 5).

The panel then used four additional AMSTAR evaluated meta-analyses to supplement the reviews. The first focused on nondirective supportive psychotherapy (Cuijpers, Driessen, et al., 2012a), and the second focused on subclinical depression (Cuijpers, Koole, et al., 2014b). Cuijpers, Driessen, and colleagues (2012a) defined depression as adults who received a diagnosis of major depressive disorder from either a diagnostic interview or a validated self-report measure. For the inclusion/exclusion criteria of selecting the studies for this review, please refer to Cuijpers, Reynolds, et al.'s (2012b) section *2.1 Identification and selection of studies* (pp. 281–282). The authors of the second review defined depression as either having

scores above the threshold on a validated questionnaire or meeting the standardized diagnostic criteria for minor depression (Cuijpers, Koole, et al., 2014b). To review the authors' inclusion/exclusion criteria for selecting studies in this review, please refer to Cuijpers, Koole, et al.'s (2014b) Method section (pp. 268–269). The third review focused on short-term psychodynamic psychotherapy (Driessen et al., 2015), and the fourth focused on interpersonal psychotherapy (Cuijpers et al., 2016). The authors of the third review defined depression in adults ages 18 and older that either met the diagnostic criteria for a mood disorder, specifically major depressive disorder, or had elevated scores on a validated instrument (Driessen et al., 2015). For the inclusion/exclusion criteria utilized in this review, please refer to Driessen et al.'s (2015) section *2.3 Selection of studies* (p. 3). The authors of the final review defined depression as elevated scores on a validated instrument pre- and posttreatment (Cuijpers et al., 2016). For more information on the inclusion/exclusion criteria utilized, please refer to Cuijpers et al.'s (2016) section *Method: Identification and Selection of Studies* (p. 681). To view the list of keywords used in searches for articles in the four reviews, please refer to the following references' sections:

- *Section 2.1: Identification and selection of studies* (Cuijpers, Driessen, et al., 2012a, p. 281).
- *Table 1: Searches in bibliographical databases: Searchstrings and hits* (Cuijpers et al., 2008).
- *Identification and selection of studies* (Cuijpers et al., 2016, p. 681).
- *Section 2.2: Search strategy* (Driessen et al., 2015).
- *Appendix A: Literature search methods* (ECRI Institute, 2015, pp. 492–517)
- *Appendix A: Search strategy* (pp. A1–A20) and *Appendix B: Cochrane depression, anxiety, and neurosis (CCDAN) topic list: Intervention-psychological therapies* (pp. B1–B3) (Gartlehner et al., 2015).

Older adults. The panel used two reviews identified via the umbrella review. One review (Cuijpers, Karyotaki, Pot, et al., 2014a) served as the basis for developing evidence profiles on active interventions. The other review (Wilkinson & Izmeth, 2012) served as the basis for developing evidence profiles on maintenance treatments. Authors of the first review defined depression in older adults ages 50 and older who either met the diagnostic criteria for depression at assessment or had ratings beyond the threshold in a validated self-report measure (Cuijpers, Karyotaki, Pot, et al., 2014a). For more information on the inclusion/exclusion criteria utilized in this review, please refer to Cuijpers Karyotaki, Pot, et al.'s (2014a) section *2.1 Identification and selection of studies* (p. 2). Wilkinson and Izmeth (2012) defined depression in older adults aged 60 and older who met diagnostic criteria for a depressive disorder (in remission) or have experienced a depressive episode. Please refer to Wilkinson and Izmeth's (2012) *Methods: Criteria for considering studies for this review* section for more information on their inclusion/exclusion criteria. For the list of keywords used in searches for articles for these reviews, please refer to Cuijper et al.'s (2008) *Table 1: Searches in bibliographical databases: Searchstrings and hits* and Wilkinson and Izmeth's (2012) *Search methods for identification of studies* (pp. 5–6).

Generally, the identified reviews and meta-analyses covered cognitive-behavioral therapy, interpersonal psychotherapy, problem-solving therapy, and psychodynamic treatment of depression. No acceptable meta-analyses or reviews included humanistic therapies or emotion-focused therapy. Also, while the panel wished to review different treatment modalities, including self-help, Internet, and group compared with individual, appropriate studies were not included in the identified reviews to be able to examine this question. The panel did not evaluate evidence reviews of long-term intervention to target relapse and recurrence and evidence reviews of prevention intervention, consistent with its scoping decision.

Table 5

Summary of Systematic Reviews and Meta-Analyses Used for Each Age Group

Age Group	Systematic Reviews and Meta-Analyses Used
Children and Adolescents	• "Comparative efficacy and acceptability of psychotherapies for depression in children and adolescents: A systematic review and network meta-analysis" (Zhou et al., 2015) • "Comparative efficacy and tolerability of antidepressants for major depressive disorder in children and adolescents: A network meta-analysis" (Cipriani et al., 2016)
General Adult Population	• "Nonpharmacological versus pharmacological treatments for adult patients with major depressive disorder" (Gartlehner et al., 2015) • "Management of major depressive disorder, Evidence synthesis report, Clinical practice guideline" (ECRI Institute, 2015) • "The efficacy of non-directive supportive psychotherapy for adult depression: A meta-analysis" (Cuijpers, Driessen, et al., 2012a) • "Psychotherapy for subclinical depression: Meta-analysis" (Cuijpers, Koole, et al., 2014b) • "The efficacy of short-term psychodynamic psychotherapy for depression: A meta-analysis update" (Driessen et al., 2015) • "Interpersonal Psychotherapy for Mental Health Problems: A Comprehensive Meta-Analysis" (Cuijpers et al., 2016)
Older Adults	• "Managing depression in older age: Psychological interventions" (Cuijpers Karyotaki, Pot, et al., 2014a) • "Continuation and maintenance treatments for depression in older people" (Wilkinson & Izmeth, 2012)

Strengths and Limitations of the Systematic Reviews and Meta-Analyses

There are a number of strengths as well as some limitations of the systematic reviews and meta-analyses underlying the panel's recommendations. The two systematic reviews conducted by evidence-based practice centers (ECRI Institute, 2015; Gartlehner et al., 2015) (two of five used for the general adult population) had important strengths as well as limitations. First, they were conducted in accordance with the IOM's (2011b) systematic review standards by designated Agency for Healthcare Research and Quality (AHRQ) evidence-based practice centers. Further, both reviews are transparent in including background data as well as strength of evidence and risk of bias information. However, some limitations of these reviews included that there were some areas not covered (as noted above) on which the panel would have liked information and the focus of both was only on major depressive disorder, thus the panel had to look elsewhere for information on additional diagnoses.

The reviews for older adults (Cuijpers Karyotaki, Pot, et al., 2014a; Wilkinson & Izmeth, 2012) were examined by RTI-UNC Evidence Based Practice Center scientists who then extracted data from these reviews into evidence profiles for the panel to use. Strengths of the Wilkinson and Izmeth (2012) review include that it focused on a population that is understudied and focused on longer term continuation and maintenance treatment as opposed to the shorter term acute focus of most older adult reviews (Wilkinson & Izmeth, 2012). The authors of the review noted that there was a significant amount of clinical heterogeneity between trials. Further, it is possible that there was selection bias (i.e., given challenges of recruiting older adults, it is possible that those recruited do not fully represent older adults in the general population) as well as possible funding bias (the authors were not able to analyze data on this possibility as data were not collected) in the included studies (Wilkinson & Izmeth, 2012). However, the authors concluded that altogether the studies had low risk of bias (Wilkinson & Izmeth, 2012). Strengths of the Cuijpers, Karyotaki, Pot, et al. (2014a) review include that it

focuses on an understudied population and provides an update of the literature in an area that is quickly changing. Some limitations of this review are that many included studies that were not of ideal quality, and few included studies used control groups that were placebos (most used treatment as usual or waiting list comparisons; Cuijpers, Karyotaki, Pot, et al., 2014a).

Among the reviews that were not provided or assessed by an evidence-based practice center (Cipriani et al., 2016; Cuijpers, Driessen, et al., 2012a; Cuijpers, Koole, et al., 2014b; Cuijpers et al., 2016; Driessen et al., 2015; and Zhou et al., 2015) (two for the child/adolescent population, the remainder for the general adult population) there were a number of strengths as well as some limitations. Based on an AMSTAR review, strengths of all these reviews were that they included a comprehensive literature search; provided characteristics of the included studies; an assessment of quality was conducted, documented, and used in conclusions; and finally, the methods used to combine findings were appropriate. Further strengths are that five of the six did not base inclusion on publication status and also assessed for likelihood of publication bias. A limitation of all but one of these reviews is that they did not provide a list of studies that were included and excluded. Beyond these, limitations varied based on the particular review and included such things as not duplicating the selection of studies and extraction of data, not having study design a priori, and not stating conflicts of interest (see Appendix H for details of AMSTAR ratings by review).

In summary, each review used by the panel has strengths as well as limitations. Importantly, a review is not a final statement and has its own limits, but it allows the field to obtain a better handle on what information is lacking and what needs to be done in the future (e.g., more funding, better quality research, more focus on diverse populations, etc.). Information from these reviews was considered together with information on strength of the evidence base, balance of the benefits vs. harms/burdens of a treatment, patient values and preferences, and applicability to form the panel’s recommendations. In light of these limitations,

it needs to be recognized that any recommendations made are based on evidence derived by a method with some drawbacks for psychotherapy research. Psychotherapy research differs in nature from medical research both in the number of variables effecting outcomes and the amount of research that met IOM standards. Results should therefore be read as best evidence according to method used and viewed as a guideline not a prescription for treatment funding and decision-making.

Characterizing the Study Samples Included in the Reviews

Decisions regarding assessment and inclusion/exclusion of studies. Decisions on the assessment and inclusion/exclusion of studies varied based on the particular systematic review/meta-analysis. Please refer to the systematic reviews/meta-analyses for specific details. However, broadly, the reviews included only randomized controlled trial (RCT) studies (Driessen et al.'s, 2015 review was an exception to this because it included non-RCT data in addition to RCT data; however, the APA panel used only the RCT data to examine efficacy of interventions) as those studies met the quality criteria for questions regarding efficacy. Some reviews excluded certain diagnoses such as psychotic depression and required that the included studies be published in particular languages. Several reviews included studies that had patients with comorbidities such as other psychiatric disorders. Please refer to the section on comorbidities for further detail.

Diversity of samples included in reviews. The reviews used to explore the effectiveness of treatments for depression in children and adolescents are comprised of 51 studies examining psychotherapies (Zhou et al., 2015) and 27 studies examining antidepressants (Cipriani et al., 2016). These studies included ages ranging from 6 to 18 years of age and, out of the studies with available data, 75 studies for children and adolescents had approximately 50% female. Also, studies included international samples with approximately 85% of samples from United States. The non-U.S.-based samples included Mexico, Finland,

France, Germany, Russia, Slovakia, Estonia, Ukraine, South Africa, Belgium, Italy, United Kingdom, Spain, The Netherlands, Canada, South Africa, United Arab Emirates, Argentina, Japan, China, Costa Rica, India, Uganda, Turkey, Norway, New Zealand, Australia, and Greece. Overall, of the studies with available data, 63 studies for children and adolescents had a range of 10% to 100% of non-White participants. Regarding study exclusions in each of the respective child/adolescent reviews, the Zhou et al. (2015) excluded clinical trials where children and adolescents had a diagnosis of treatment-resistant depression or psychotic depression in order to eliminate extraneous noise in their results.

The reviews used for general adult population included 482 studies exploring psychotherapies and medication in this population (Cuijpers, Driessen, et al., 2012a; Cuijpers, Koole, et al., 2014b; Driessen et al., 2015; ECRI Institute, 2015; Gartlehner et al., 2015) and 84 studies for medication. These studies included individuals between 18 to greater than 65 years of age and are 70.7% female. Also, studies included international samples with approximately 38% of samples from United States. The non-U.S.-based samples include Canada, Iran, Switzerland, Italy, United Kingdom, Germany, The Netherlands, Australia, Sweden, Finland, Denmark, Chile, Mexico, Spain, Brazil, China, and Romania. The review that assessed efficacy of short-term psychodynamic psychotherapy for depression included 35 RCTs (Driessen et al., 2015). Overall, in the studies with available data, general adult population had approximately 50% of non-White participants.

Finally, the combined reviews for older adults included 53 studies for psychotherapies and medication (Cuijpers, Karyotaki, Pot, et al., 2014a; Wilkinson & Izmeth, 2012). The samples within the reviews included adults ages 50 and older with approximately 83% females across all studies. Reviews had limited international representation compared with the other age groups with samples from the following countries: Singapore, The Netherlands, Germany, Switzerland, Spain, Canada, Australia, United Kingdom, United States, Denmark, and various European

countries. Of the studies in the reviews with reported data, the sample included only a range of 6.7% to 100% of non-White participants.[44]

Comorbidity of samples included in the reviews: *Children and adolescents.* The reviews for depression in children and adolescents did not exclude comorbid psychiatric disorders. However, there were a few limitations noted in these reviews. Regarding the review that assessed the efficacy of interpersonal psychotherapy versus cognitive-behavioral therapy in the treatment of child/adolescent depression, Zhou and colleagues (2015) found that the studies that recruited patients with comorbid psychiatric disorders had lower effect sizes.[45] The authors emphasized the need for more research on the efficacy of interpersonal psychotherapy and cognitive-behavioral therapy in patients with comorbid psychiatric disorders due to the small samples sizes that may have contributed to this finding (Zhou et al., 2015). While Cipriani and colleagues (2016) included pharmacological studies that recruited children and adolescents with comorbid psychiatric disorders, they excluded studies that recruited "participants with treatment-resistant depression, with treatment duration of less than 4 weeks, or with an overall sample size of fewer than ten patients" (p. 2).

General adult population. Four out of the six reviews of depression in the general adult population did not exclude comorbid psychiatric and medical disorders (Cuijpers, Driessen, et al., 2012a; Cuijpers, Koole, et al., 2014b; ECRI Institute, 2015; Gartlehner et al., 2015).[46] Reviewers from the ECRI Institute (2015) included the following comorbid psychiatric and medical disorders in one of their key questions: cardiovascular disease, dementia, arrythmias, seizure disorders, lower back pain, Alzheimer's, and stroke. Regarding the review of short-term psychodynamic psychotherapy (Driessen et al., 2015), the reviewers did not consider comorbid

[44] Please see Appendix K of the supplement which summarizes the demographics from each of the 10 reviews.
[45] To view the forest plot presentation of the effect sizes for both child/adolescent reviews, the interested reader is referred to Appendix 11, pp. 36-40 of Cipriani et al. (2016) and p. 218 of Zhou et al. (2015).
[46] To view the forest plot presentation of the effect sizes for the adult reviews, please refer to p. 287 of Cuijpers, Driessen, et al. (2012a), pp. 271-272 of Cuijpers, Koole, et al. (2014b), pp. 7-11 of Driessen et al. (2015), and pp. ES-7-ES-8, 26-27, 33-35, 53-54, 77-84, 89-91, 94, and 97 of Gartlehner et al. (2015).

somatic disorders. While Gartlehner and colleagues (2015) searched for studies that had comorbidity as an inclusion criterion, they noted the paucity of high-quality studies that included patients with comorbid psychiatric and medical disorders in most of the studies.

Older adult population. The reviews for depression in older adults did not exclude comorbidity. However, Cuijpers, Karyotaki, Pot, and colleagues (2014a) as well as Wilkinson and Izmeth (2012)[47] were unable to find studies that included older adults with depression as well as comorbid medical and psychiatric disorders in clinical trials. Both reviews emphasized the need for future research to include comorbid disorders in assessing treatment efficacy for depression in older adults.

Defining Efficacy and Comparative Effectiveness

In this guideline, the term *efficacy* refers to the impact of a treatment compared with an inactive control (i.e., waitlist). The term *comparative effectiveness* refers to the benefit of one active treatment compared with another.

Types of comparison (control) groups used by studies. The type of comparison (control) group used by studies varied across the systematic reviews/meta-analyses. Please refer directly to the reviews for specific details. Broadly, however, control groups used by studies included both active and nonactive controls. An example of an often-used active control was treatment as usual (whose exact definition varies by study). Examples of nonactive controls included such things as waitlist and no treatment.

Evaluating the Evidence

The development of evidence profiles. *Evidence profiles* (summaries of data in available studies) were created by the RTI-UNC Evidence-Based Practice Center team from data reported in the systematic reviews on the efficacy of psychological treatments and the comparative effectiveness of psychological treatments to pharmacological treatments in head-

[47] To view the forest plot presentation of the two older adult reviews, please refer to p. 165 of Cuijpers, Karyotaki, Pot, et al. (2014a) and p. 14, pp. 16-17, and pp. 19-20 of Wilkinson & Izmeth (2012).

to-head trials for older adults. The evidence profiles were summaries of data included in the systematic reviews and include, for each outcome, the number of studies, absolute effect sizes, confidence intervals (when available), and strength of evidence ratings. For adults, evidence profiles were provided in the report "Nonpharmacological Versus Pharmacological Treatments for Adult Patients With Major Depressive Disorder," (Gartlehner et al., 2015). The panel worked with data directly from the report for the remainder of the systematic reviews and meta-analyses. Thus, the panel had evidence profiles for some but not all of the data. Evidence profiles (in the format provided by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Consortium Working Group in particular) typically have information beyond effect size, such as information about the quality of included aggregated studies for a particular outcome, which is not always the case for data taken directly from other systematic reviews or meta-analyses. So, in some cases the panel had additional quality information for particular outcomes included in the evidence profiles but did not have that data for all interventions and outcomes.

The development and use of decision tables and the grid. *Decision tables* and *grids* are documents developed and then used by panel members to summarize and evaluate the evidence generated in the systematic review or meta-analyses, along with any supplemental information. Panel ratings and judgments were documented on the decision tables and grids to aid in the formulation of recommendations (Treweek et al., 2013). These tables allow panel members to document decisions, compare consistency across decisions, and give transparency to reviewers and users of the guideline document. The four main domains of decision-making are documented as follows: (1) strength of evidence; (2) treatment outcomes and the balance of benefits vs. harms and burdens of interventions; (3) patient values and preferences; and (4) applicability of the evidence to various treatment populations.

Strength of evidence was rated as either insufficient/very low, low, moderate, or high based on the combined results of analyses of risk of bias, inconsistency, indirectness, and imprecision. Only for interventions that had at least low strength of evidence for one of the outcomes were decision tables or grids completed. The panel generated evidence that met the criteria for the completion of 38 decision tables and three grids on which to base the APA Depression Guideline. While APA staff prepared the decision tables and grids for the panel based on information extracted from the reviews and studies, the panel made all the decisions regarding the evidence and recommendations. Specifically, APA staff inserted information from the reviews and studies on quality ratings, outcomes examined and associated effect sizes, harms and burdens of interventions (as described in more detail below), study results on patient values and preferences, and study participant descriptions the panel might want to reference for discussions on applicability. As the panel discussed each decision table or grid, APA staff transcribed the panel's decisions into each decision table or grid.

As the panel progressed with its work, they decided that the creation and review of evidence in decision tables resulted in redundancy as the same information concerning possible harms and burdens or patient values and preferences was considered repeatedly for different bodies of outcome evidence. To facilitate decision making yet maintain consistency and transparency, a revised "grid" process was created that included distinct columns for separate questions and outcomes and individual decision-making regarding efficacy but allowed consideration of the same data for harms and burdens across those columns. This greatly increased the efficiency of the evidence review while keeping consistency and transparency.

Although some have questioned the applicability of some randomized trials due to potential differences between sample characteristics or treatment settings and the "real world" application (Shean, 2016), the panel decided to not supplement the randomized trials included in the reviews with observational (i.e., nonrandomized and less methodologically rigorous) or

other treatment studies, due to the potential for confounding bias in observational studies (Fewell, Smith, & Sterne, 2007; Rothman, Greenland, & Lash, 2008). This decision is consistent with the position of all major organizations that evaluate research and conduct systematic reviews, including GRADE, Cochrane, The National Institute for Health and Care Excellence (NICE), The Agency for Healthcare Research and Quality (AHRQ) Evidence-Based Practice Centers (Guyatt et al., 2011; NICE, 2012; Reeves, Deeks, Higgins, & Wells on behalf of the Cochrane Non-Randomised Studies Methods Group, 2011; Viswanathan et al., 2012).

Panel members made two significant exceptions to this decision when it became clear that data were lacking in randomized trials findings on two outcomes: (1) harms and burdens of psychological treatments and (2) patient values and preferences regarding particular treatments. In response, the panel decided there was a need to gather and review more information on these topics. Concerning harms, panel members decided to review those observational studies that gave attention to the assessment of harms that were identified in the reviews. It also authorized APA staff assigned to the guideline development panel to compile information on possible harms and burdens of interventions as well as patient values and preferences from an additional search of the literature. Details of the search process methodology for both of these supplemental sources of information are described below. The findings of these additional reviews along with input from clinicians and consumers on the panel were used to make the treatment recommendations more comprehensive with regard to the risk of harm or adverse events associated with various interventions for depression (determined to be a *critical outcome)* and patient values and preferences.

Each panel member received an explicit opportunity to raise any questions or concerns about the process of completing each decision table or the grid. The panel as a group reviewed each decision table and grid to identify any questions or concerns that users of the guideline (including patients, clinicians, scientists, and administrators) might raise. After completing all the

decision tables and grids, the panel globally reviewed all tables and grids to assess any inconsistency and assure consistency in decision-making across tables. For purposes of consistency across all clinical practice guidelines, the Advisory Steering Committee established voting procedures that can be found in Appendix F.

Completion of decision tables and grid. The four domains below formed the basis on which each treatment recommendation and its strength were decided. For each recommendation, text description and a justification for the recommendation were included on the decision table and grid (see Appendix C as well as additional appendices links).

Rating of aggregate/global strength of evidence. For each of the decision tables and grids, *aggregate/global strength of evidence* was based on the strength of evidence from the review for the two critical outcomes, namely, response to treatment (reduction in depressive symptoms) and serious adverse events. The panel adopted the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) consortium standard that the aggregate strength of evidence could be no higher than the lowest individual strength of evidence for each of the critical outcomes (Guyatt et al., 2013). For example, if one critical outcome had “high” strength of evidence but the other critical outcome had “low” strength of evidence, the global quality of evidence for that particular decision table or column in the grid would be low, because that is the lowest strength of evidence for an individual critical outcome. The strength of evidence for serious harms, one of the panel’s critical outcomes, was insufficient/very low, for all interventions for which decision tables and grid columns were completed. This explains why the global strength of evidence was insufficient/very low for all interventions, despite low, moderate, or high strength of evidence for the critical outcome of response to treatment.

Assessing magnitude of benefits. One of the key components of the decision-making process for the guideline developmental panel was assessment of the balance between benefits and harms. This required the quantification of both benefits and harms.

Quantification of benefits was based on data from the quantitative meta-analyses for each of the important and critical outcomes that the panel had selected at the start of the guideline development panel process for those interventions that had at least low quality of evidence for the critical outcome, response to treatment. For each of the outcomes on the decision tables, magnitude of benefits and harms/burdens was rated on a five-point scale: (1) large/modest[48] benefit; (2) small benefit; (3) no effect; (4) small harm; and (5) modest[49]/large harm.[50] On the grids, the panel rated the magnitude of benefits as large, modest,[51] or small benefit of Treatment 1 relative to Treatment 2 and the reverse or No difference in effect or Unable to rate. The same was done for harms/burdens.

Assessing magnitude of harm/burdens. Because "serious adverse events" was one of the two critical outcomes of treatment decided on by the panel, these needed more precise specification and definition. Ultimately, panel members considered events such as the need for hospitalization secondary to suicidality as a serious adverse event and then identified additional harms such as medication side effects. Harms were differentiated from burdens that were identified as disruptions associated with treatment (i.e., time spent, homework/need to practice, cost, convenience) rather than as injury. As discussed earlier, the review of the treatment literature did not generate sufficient data on harms and burdens of interventions because, unfortunately, this information is not routinely reported in studies of psychosocial interventions and not reported in detail in many studies of psychopharmacological interventions. In light of this deficit, the APA Task Force to Revise the Journal Article Reporting Standards (JARS) for

[48] However, the panel later decided that it preferred the term "moderate" instead of "modest."
[49] Same as footnote #48.
[50] The following served as an approximate rule of thumb: a small effect size is 0.20, medium is 0.50 and large is 0.90.
[51] Same as footnote #48.

quantitative research included in the new standards the suggestion that randomized controlled trial researchers report data regarding harms and burdens including indicating “none” if there were none (Appelbaum et al., 2018).

In response to this deficit, the panel requested that APA staff examine each article in the reviews to extract data regarding harms and burdens, such as dropout/attrition, symptom worsening, homework, etc. For the older adult review, the same data extraction was also conducted on those studies identified but excluded from the systematic review because of high risk of bias to expand the available pool of information. In addition, a focused literature search of the PsycINFO® database was conducted for older adults. Some of the search terms used included: “depression,” “treatment,” and “older adults.” Recognizing time constraints and expecting only limited incremental additional evidence, the adult and child/adolescent data on harms and burdens was derived from only an examination of the articles included within the reviews and not additional searches or examination of any excluded articles. It was from these studies that the panel had additional information on possible harms or burdens associated with the interventions under consideration. Further, as described in more detail below, physician members of the panel provided information on potential harms/burdens of medications. Moreover, panel members consulted with a prominent expert in child psychiatry regarding the panel’s recommendations pertaining to medication in children/adolescents to review and assess for any potential concerns.

The panel also addressed the issue of attrition as a possible harm. Because attrition in a randomized trial can signify different things (e.g., stopping because treatment is not acceptable or tolerable versus discontinuing due to early symptom relief) the panel did not consider it to be a harm unless information regarding the reasons for attrition were specified or unless there were differential attrition rates across treatment groups (Zandberg, Rosenfield, Alpert, McLean, & Foa, 2016).

Finally, in order to supplement the limited information on harms and burdens gleaned from published research, clinicians on the panel reported their experiences in delivering, supervising, or training in particular interventions and the concerns noted by colleagues. Consumer members reported on both their own and peer experiences with various interventions. In general, many of the identified harms and burdens pertaining to psychosocial interventions were more general and common to most psychosocial treatments, for example, the potential for short-term exacerbation of symptoms (harm) or the time necessary for multiple psychotherapy sessions (burden). Further, clinicians and consumer members reported various side effects as potential harms of medication treatment. Though it was important to obtain all available sources of information on patient values and preferences, due to the inclusion of both anecdotal (i.e., clinician and consumer report) and peer-reviewed article information, the strength of evidence on these topics was rated as insufficient/very low.

Once possible harms and burdens were identified, panel members then compared these with the benefits of the interventions. On the decision table for each intervention, the panel rated whether the benefits “clearly outweigh” or “slightly outweigh” the harms and burdens or the reverse. On the grids the panel rated whether the balance of benefits to harms/burdens strongly or slightly favors Treatment 1 over Treatment 2 or the reverse, the balance of benefits to harms/burdens was the same, or it was unable to determine the balance of benefits to harms/burdens between Treatment 1 and Treatment 2.

Assessing patient values and preferences. In addition to assessing the benefits and the harms/burdens associated with specific interventions, the panel attempted to ascertain patient values and preferences. As described above, in order to ascertain this information, the panel relied on a search of the literature as well as clinicians and consumers on the panel who voiced their perspectives about preferences for different interventions as well as the value that patients might place on different outcomes or harms/burdens associated with particular treatments. The

strength of evidence (SOE) for all this information was very low because it included observational studies and “expert” (i.e., panel member) opinion.

Applicability of evidence. The final determinant that panel members considered, before making recommendations, was the *applicability (generalizability*) of the evidence to various populations and settings. To organize information on applicability, panel members applied the PICOTS framework (referring to Populations, Interventions, Comparators, Outcomes, Time and Settings; Samson & Schoelles, 2012) to review specific information from the studies to determine if there were any concerns pertinent to applicability pertaining to population, interventions, comparators, outcomes, timing, or settings to be noted in each decision table or on the grid.

Decision-making regarding treatment recommendations. On the basis of the ratings of these four factors (strength of evidence, balance of benefits versus harms/burdens, patient values and preferences, and applicability), the panel then made a decision regarding its recommendation for a particular treatment or comparison of treatments. The options ranged from a strong (“the panel recommends”) or conditional (“the panel suggests”) recommendation either in support of or against a particular treatment based on the combination of these factors. The panel could also choose to decide that there was insufficient evidence to make a recommendation about a particular treatment. Panel members were able to reach consensus regarding the strength of recommendation given to each treatment in most cases via discussion but, for several, a vote was required. Please refer to Appendix F in the supplemental appendices for voting procedures established by the Advisory Steering Committee (ASC).

External Review Process

A draft document was submitted to the APA Advisory Steering Committee for Development of Clinical Practice Guidelines for feedback and modified based on that feedback. This draft document was posted on the APA website and public feedback was solicited for 60

days. That draft document was revised based on that feedback. Detailed responses to public comments will be made available on the APA website.

The final document will be reviewed within 5 years following adoption as policy. A decision to sunset, update, or revise the guideline will be made at that time.

Discussion of Clinical Recommendations

Children and Adolescents

The treatment of depression in children and adolescents is recognized as an issue of public health significance given the detrimental impacts of depression on development and interpersonal interactions, as well as functioning at school and work, impairments that continue to have deleterious effects into adulthood (Avenevoli et al., 2015; Glied & Pine, 2002; Lewinsohn et al., 1994; Lewinsohn et al., 1999; Merikangas et al., 2010). The panel originally drafted recommendation statements for the combined populations of children and adolescents given that the underlying reviews on children and adolescents combined the age groups together and it was not possible to review the data separately. However, on further consideration the panel decided to separate the recommendations for children and adolescents, not only for reasons of development but also due to underlying methodological reasons in the included reviews. Specifically, the child and adolescent reviews (Cipriani et al., 2016; Zhou et al., 2015) both included only a relatively small pool of studies that focused on children only as opposed to a combined or adolescent population and the Zhou et al. (2015) review specifically noted less robust findings for children specific to CBT and IPT. Thus, the panel retained the recommendation statements for adolescents only and then separately noted that evidence was insufficient to be able to make specific recommendations for type of psychotherapy or pharmacotherapy for children.

The generalizability of the evidence reviewed and presented here has some important limitations, which must be noted at the outset. Very few of the studies included in the reviews

included a wide range of racially diverse youth and focused instead primarily on socioeconomically diverse White youth and lower socioeconomic status youth of color (when they were included). This reflects both that relatively few studies met the inclusion criteria (thereby potentially excluding studies that included more diverse samples) and the limited diversity in treatment samples in the published literature in general. Therefore, these recommendations must be viewed as limited in applicability to a diverse community of mental health consumers.

With this caveat, the panel's comprehensive review leads to the recommendation for the use of psychotherapy to treat adolescent depression. The best evidence is for interpersonal psychotherapy (adapted for adolescents, IPT-A) and cognitive-behavioral therapy (CBT), enabling a recommendation for both of these psychosocial interventions versus no treatment or waitlist, and versus treatment as usual or psychological placebo conditions. The evidence base for behavioral therapy, cognitive therapy, family therapy, play therapy, problem-solving therapy, and psychodynamic therapy and supportive therapy is insufficient for recommendation of any of these treatments versus no treatment or waitlist, and versus treatment as usual or psychological placebo conditions. When the aforementioned treatments (CBT, IPT-A, behavioral therapy, cognitive therapy, family therapy, play therapy, problem-solving therapy, psychodynamic therapy and supportive therapy) were compared with each other, there was insufficient evidence for the panel to recommend for or against clinicians offering any of the psychotherapies over any of the other psychotherapies listed. CBT and IPT are two psychotherapies which have multiple RCTs demonstrating their efficacy in decreasing depression symptoms in adolescents. The comparison conditions in these studies include waitlist control group and supportive therapy/treatment as usual; however, they do not include behavior therapy, play therapy, problem-solving therapy, psychodynamic therapy, or manualized supportive therapy. Thus,

there is insufficient information regarding their comparative effectiveness to a greater number of therapeutic approaches.

Addressing diverse child/adolescent populations. Interestingly, IPT-A has an evidence base focused on a more racially diverse (African American and Latino) sample of youth than CBT (Zhou et al., 2015). However, studies of each of these therapies contain areas of insufficient data and information to allow the panel to judge them in more depth or to make more nuanced recommendations. Specifically, most of the studies on IPT-A did not include information on long-term outcomes of treated participants. Moreover, for many of the studies of CBT reviewed by the panel, the CBT condition was compared with a waitlist condition rather than other active treatments. Thus, the effect sizes of the outcomes in the CBT arm might be overstated given evidence that waitlist control conditions show greater effect sizes in favor of the active treatment than no treatment or usual treatment comparisons (Steinert, Stadter, Stark, & Leichsenring, 2017). Despite these concerns, IPT-A and CBT still present the best evidence that the field has to date on positive outcomes for the treatment of depression in youth.

Efficacy of child/adolescent psychopharmacological interventions. The panel also reviewed the evidence for psychopharmacologic interventions for depression in children and adolescents. In this regard, while the panel found a review that met AMSTAR criteria (Cipriani et al., 2016), many other reviews did not. The review included studies of medications that are not currently widely used in the treatment of youth depression due to safety concerns. So, while there is clear evidence from multiple randomized controlled trials for the use of fluoxetine (Prozac) in children and adolescents, there is limited evidence meeting the IOM or AMSTAR criteria for other antidepressants, including the other Food and Drug Administration (FDA) approved antidepressant for youth, escitalopram (Lexapro). In this regard, we note that although the FDA approved the medication escitalopram, in the panel's review of the evidence, we were unable to recommend for or against this medication. Finally, although Nefazodone (Serzone)

was included in our review, the panel has elected not to provide recommendation on the use of this medication as an antidepressant given its lack of clinical relevance for current practice (i.e., expert psychiatrist indication that this medication is almost never used for child or adolescent care due to significant side effects). Thus, the panel concludes that the strongest evidence for a pharmacologic treatment for adolescent depression is fluoxetine (Prozac). If fluoxetine is not a treatment option or is not acceptable, the panel recommends shared decision-making regarding medication options with a child psychiatrist in addition to the clinician, patient, and their parents/guardians or family members actively involved in their care. However, more research is needed comparing the efficacy of active medications with diverse populations and in combination with psychotherapy.

General Adult Population

The panel found that various types of interventions are available for the treatment of depression in the general adult population. For the initial treatment of adult patients with depression, the panel recommends that clinicians offer either psychotherapy or second-generation antidepressants and use a shared decision-making approach to consider options. Comparative effectiveness studies indicated similar effects across different models of psychotherapy. Thus, the panel does not make a recommendation for a specific therapy for initial treatment among the following models, presented in alphabetical order: behavioral therapy, cognitive therapy, cognitive-behavioral therapy (CBT), interpersonal psychotherapy (IPT), mindfulness-based cognitive therapy (MBCT), psychodynamic therapy, and supportive therapy. If considering combined treatment, the panel recommends cognitive-behavioral therapy or interpersonal psychotherapy plus a second-generation antidepressant. Note that there are some differences in how the panel chose to structure recommendations for children/adolescents versus those for adults because there was insufficient evidence for treatments other than CBT and IPT-A in the adolescent literature, while evidence of no difference between multiple

treatments in the adult literature. The panel chose to emphasize comparative effectiveness data in the adult literature.

Beyond these recommendations the panel conditionally suggests several treatments based on particular nuanced situations (i.e., for an individual with depression who is also experiencing relationship distress; please refer to Table 3 for details based on specific situations) and notes several treatments for which there is insufficient evidence to be able to make a recommendation. Regarding complementary and alternative treatments, the panel gave no higher than a conditional recommendation for use. Specifically, the panel suggested starting with exercise and St. John's Wort and then suggested several alternatives if these were not available or acceptable. The panel also noted a variety of complementary and alternative treatments for which the evidence is insufficient to be able to make a recommendation. However, the panel urges caution when using over-the-counter agents to prevent unintended drug-drug interactions particularly given variable manufacturing practices.

Partial- or non-responders to initial antidepressant treatment and relapse prevention. The panel then considered partial or non-responders to initial antidepressant treatment and recommended that these individuals switch from antidepressant medication alone to cognitive therapy alone or switch from antidepressant medication alone to another antidepressant medication. The panel then made no higher than a conditional suggestion and noted several instances in which there was insufficient information to make a recommendation for nuanced situations with this population. Finally, the panel considered relapse prevention and made a conditional suggestion that clinicians offer psychotherapy rather than antidepressant medication or treatment as usual to prevent relapse.

Overall, the effect sizes of these therapies are comparable and direct comparisons among therapies do not indicate major differences between the therapies. There were many instances in which the panel determined there was insufficient evidence to be able to determine

whether there was a difference in effect between two potential treatment options. The panel encourages shared decision-making with the patient.

Subgroup effects. Unfortunately, there are no clear indications regarding which patient with which characteristics will benefit from which treatment, although there has been some recent work developing algorithms that are promising (Cohen & DeRubeis, 2018; DeRubeis et al., 2014). It is therefore up to the therapist to discuss with each patient which treatment he or she prefers, with consideration of expected outcomes, side effects, possible negative effects, costs, and time investment of patients. The majority of patients prefer psychotherapy over pharmacotherapy (McHugh, Whitton, Peckham, Welge, & Otto, 2013), although an important minority (about 25%) prefer pharmacotherapy. Patient preferences for specific psychotherapies were not available in the reviewed systematic reviews/meta-analyses.

In addition, combined treatments of psychotherapy and pharmacotherapy are more effective than either of the treatments alone in some subpopulations, but the costs, risk of side effects, and demands on patients are greater. In addition, some research suggests combined treatment may interfere with enduring effects for psychotherapy (Hollon et al., 2014). As such it is up to the provider and patient to decide whether a combined treatment is preferable. For patients with chronic and treatment-resistant depression, combined treatment is usually recommended (Cuijpers et al., 2010; Jobst et al., 2016).

Delivery of treatments. Although the recommendations focus on types of interventions, the way in which treatments are delivered is also important. However, the current review provided limited information in this area. For example, collaborative care approaches have been well established, and a considerable number of trials have shown that collaborative care is an evidence-based and well-established system for delivering treatments of depression. The collaborative care model for depression involves depression care managers with special training in evidence-based interventions and regular mental health specialty consultation and can

provide efficacious care for primary care patients across the life span—adolescents, young, middle-aged, and older adults (IMPACT; Unützer et al., 2002; Richardson, McCarty, Radovic, & Suleiman, 2017). However, the current review did not address this or other considerations of treatment delivery.

The panel found insufficient evidence about the effectiveness of psychotherapies in specific target groups, such as students, and people with general medical conditions, such as diabetes, heart disease, and cancer. There was also very limited data on which to determine whether treatment format (e.g., individual, group, phone-based, computer delivered, bibliotherapy, etc.) influenced efficacy. What little evidence was available regarding format was primarily for CBT and did not find differences. However, the limitations of the literature reflect the need for more research comparing modalities.

Overall, treatments for depression have a modest impact on alleviating symptoms of depression (with numbers-needed-to-treat of about six to eight [meaning about six to eight need to be treated for each one that is successfully treated]). This reflects both the high rate of spontaneous recovery, placebo effects of treatment, and the modest effect of treatment (either psychotherapy or pharmacotherapy). It should also be noted that there is an important group of patients who do not recover, neither through spontaneous recovery nor treatments.

Enduring effects of treatment. Overall psychotherapies seem to have longer term effects that can be seen 6 to 12 months after treatment ends, while the relapse rates after discontinuation of antidepressants are very high, and direct comparisons between psychotherapies and antidepressants suggest that the effects of psychotherapies may be better in the longer term (Cuijpers et al., 2013; Karyotaki, Smit, de Beurs, et al., 2016; Karyotaki, Smit, Henningsen, et al., 2016). There is clear evidence that CBT has an enduring effect, and other types of psychotherapies may as well, that is not found for antidepressant medications (Cuijpers, 2013). The enduring effect is large (odds ratio greater than two), and it is robust (six

out of eight studies reviewed by Cuijpers with a seventh just under two) and it is at least as large in magnitude as keeping patients on continuation antidepressant medication. Behavioral activation also showed a similar effect in the one study in which it was tested (Dobson et al., 2008) and long-term dynamic psychotherapy relative to treatment as usual (which could include antidepressant medication) may have a similar effect as well (Fonagy, 2015). Further, the possibility remains that any psychosocial intervention that teaches skills or changes underlying diatheses will have an enduring effect that would not be expected for antidepressant. The possibility of enduring effects of different treatments is a topic that may be discussed between clinicians and patients as part of shared decision-making about treatment.

Older Adults

The panel's recommendations and suggestions for CBT, problem-solving therapy, and life-review therapy rather than no treatment or treatment as usual are largely consistent with other reviews of older adult depression treatment research (Cuijpers, Karyotaki, Pot, et al., 2014a; Wilkinson & Izmeth, 2012). These treatments included modifications that made them more appropriate for use with older adults, as noted in the APA (2014) *Guidelines for Psychological Practice with Older Adults*. When considering initial treatment of major depressive disorder in older adults, the panel recommends either group life-review treatment or group CBT (either alone or added to usual care) over no treatment or combined pharmacotherapy and interpersonal psychotherapy over interpersonal psychotherapy alone. If these options are not available or acceptable the panel then conditionally suggests particular treatments based on nuanced situations and also notes situations in which the evidence is insufficient to be able to make a recommendation.

For subthreshold/minor depression the panel conditionally suggests CBT, life-review treatment, and problem-solving therapy and notes situations in which there is not sufficient evidence to make a recommendation. For situations in which there is major depressive disorder

or minor depression and cognitive impairment, the panel suggests problem-solving therapy but notes insufficient evidence to make a recommendation about the combination of behavioral activation and treatment as usual.

For persistent depressive disorder, the panel conditionally suggests problem-solving therapy (individual) or paroxetine though notes that some argue that paroxetine is contraindicated in older adults due to its anticholinergic side effects (see the American Geriatrics Society 2015 Beers Criteria) and many geriatric psychiatrists would prefer another SSRI (i.e., escitalopram or sertraline). When an older adult presents with both major depressive disorder and medical or other complications, the panel makes several conditional suggestions based on the particular nuanced situation.

Relapse prevention in older adults. Finally, for prevention of recurrence the panel recommends combination interpersonal psychotherapy and pharmacotherapy or combination supportive care and pharmacotherapy. If those options are not available, the panel conditionally suggests interpersonal psychotherapy for prevention of recurrence. The panel notes that the evidence is insufficient to be able to recommend between cognitive-behavioral therapy (group) plus pharmacotherapy and pharmacotherapy alone for preventing recurrence.

Relation to other literature. In another effort, Scogin and colleagues (2005), using Society of Clinical Psychology criteria (a less rigorous criteria than that of the IOM for guideline development), also found CBT, problem-solving therapy, and life-review to be beneficial but in addition found behavior therapy, brief psychodynamic therapy, and cognitive bibliotherapy to be evidence-based therapies. Studies of these latter interventions did not meet criteria for inclusion in current systematic reviews due to lack of some methodological features to reduce bias and improve the quality (typical of studies of psychological treatments conducted prior to 2000). Similarly, interpersonal psychotherapy has been identified by some as an effective treatment for older adults (Hinrichsen, 2009).

The panel's recommendations and suggestions that psychological treatments be provided across the severity spectrum (i.e., major depressive disorder, subthreshold) is important because subsyndromal or minor depressive symptom presentations are frequently occurring among older adults. Pharmacotherapy is usually not indicated for subsyndromal depressive symptom cases and thus there is a particular need for psychological treatments and CBT, problem-solving therapy, life-review and possibly other interventions can be recommended. It is also worth noting that older adults and younger adults appear to demonstrate similar improvements in response to psychotherapy (Cuijpers et al, 2009).

Older adults' treatment preference and treatment considerations. Because older adults often express a preference for psychological treatments and provision of such service in primary healthcare settings, it is important that efforts to integrate the two continue. However, specialists in delivering late-life depression treatment, particularly in the fields of psychology, psychiatry, and social work, are scarce and thus create a conundrum for delivering efficacious interventions identified by this panel. Integrated care is one such model that may address the underuse of depression treatment services by older adults (Bruce et al., 2004; Unützer et al., 2002). In addition, given that older adults are more likely to have other health conditions, psychotherapy remains a preferred treatment as medications have potential for adverse interactions with other medications. Integrated care can help address both mental and physical health problems and ensure more seamless treatment (Reiter, Dobmeyer, & Hunter, 2018). Finally, regarding the medication recommendations it should be noted that while nortriptyline was used in the past due to its efficacy and safety, practices have changed significantly, and nortriptyline is now viewed as a second- or third-line pharmacotherapy strategy for major depression. It is generally reserved for patients who have not done well with a selective serotonin reuptake inhibitor or a serotonin-norepinephrine reuptake inhibitor, which are generally considered to be safer for older adults than nortriptyline. Moreover, some argue that

paroxetine is contraindicated in older adults due to its anticholinergic side effects (see American Geriatrics Society 2015 Beers List) and many geriatric psychiatrists would prefer another SSRI (i.e., escitalopram or sertraline). There is some efficacy data from systematic reviews/meta-analyses showing efficacy of second-generation antidepressants over placebo (i.e., see Nelson, Delucchi, & Schneider, 2008). The panel encourages shared decision-making between patients and clinicians (see the following for additional resources: Cipriani et al., 2009; Fournier et al., 2010; & Nelson, Delucchi, & Schneider, 2013).

Considerations for Treatment Implementation

Importance of Informed Consent

The panel encourages all clinicians to provide informed consent to patients. According to the American Psychological Association's Ethical Principles of Psychologists and Code of Conduct (2017a), psychologists should obtain an informed consent from the patient prior to implementing psychological services. An informed consent is where psychologists (or other psychotherapy clinician) "inform clients/patients as early as is feasible in the therapeutic relationship about the nature and anticipated course of therapy, fees, involvement of third parties, and limits of confidentiality and provide sufficient opportunity for the client/patient to ask questions and receive answers" (APA, 2017a, p. 14).

The informed consent process is not only evident in psychotherapy but in other medical fields as well and it ensures that the patients' rights are respected throughout treatment. For example, the American Medical Association's Code of Ethics also mandates that physicians provide informed consent to patients (American Medical Association, 2016). After assessing for the patient's ability to make decisions this code notes that informed consent should include information about any known diagnosis; why particular interventions are recommended and what is involved in these interventions; and benefits, harms, and burdens of possible interventions including those for choosing to receive no treatment (American Medical

Association, 2016). The informed consent process allows the patient to make an informed decision of whether to initiate or continue treatment, and it also satisfies the General Principles of Beneficence and Nonmaleficence common across ethics codes in which clinicians "take care to do no harm" (American Psychological Association, 2017a, p. 3). When working with children and adolescents, the provider should convey this same information to the parent/guardian who must provide consent for treatment along with conveying this information to adolescents who must assent to treatment. For children, it also would be helpful to convey some of the information regarding interventions to be provided and the rationale in an age-appropriate manner (American Academy of Child and Adolescent Psychiatry, 2017).

Incorporation of research not included in the current guidelines. The panel recognizes that there is literature that is relevant to decision-making about treatments that has not been incorporated in this guideline. In considering implementation of an intervention that is not reviewed in the guideline, the panel encourages readers to consider number and quality of studies available. Interventions with both well-controlled studies of efficacy and comparative effectiveness relative to other effective treatments should be prioritized.

Improving Access While Supporting Patient Culture, Values, and Preferences

Panel (including community and clinician members) discussions regarding patient preferences, culture, and values highlighted the challenges patients face in finding adequate mental health treatment and particularly access to evidence-based interventions. Consequently, the panel encourages clinicians to strive to address potential barriers to treatment with the patient. Moreover, clinicians are encouraged to engage in shared decision-making with the patient to ensure that the patient's needs and wants are taken into consideration.

In the search for treatment options, it is important for providers to address the difficulties patients face. The panel identified many such barriers to adequate treatment, some of which were observable in the research literature (when the literature adequately reported information

on harms, burdens, and attrition), and some of which were apparent in feedback from individuals with lived experience. These barriers generally fell into two categories: structural barriers (i.e., all related financial costs, affordable transportation, clinic hours and locations, and childcare) and attitudinal barriers (i.e., experiences of racial, ethnic, and cultural bias) for the purpose of discussion (Sareen et al., 2007). The panel identified practical examples, listed in Table 6.

Table 6

Patients' Values and Preferences

Types of Barriers		Examples of Barriers to Continued Care
Structural		
	Awareness of resources	*"I don't know what to do."*
	Financial needs	*"My insurance won't cover it, and it's too expensive to pay out of pocket."*
	Time needs	*"I can't make it to the session in between my jobs."*
	Transportation needs	*"The Metro doesn't run that far out of the city."*
	Treatment availability	*"I was told to look for interpersonal therapy, but the closest person is 2 hours away."* *"You can't be seen for 45 days if it's not an emergency."*
	Treatment compatibility	*"He's Christian, and I'm an atheist."*
	Treatment harms	*"It gave me chronic headaches."*
Attitudinal		
	Perceived need	*"I'll solve it myself." "I'm not sick enough to need help."*
	Treatment alienation & dissatisfaction	*"That therapist was horrible. He just wanted to prescribe me medications."*
	Negative associations	*"What if I'm hospitalized against my will?"*
	Stigma	*"What if they find out and I'm fired from my job?" "I don't want people to think I'm crazy!"*

Through this framework, the panel asserted that clinicians seeking to optimize the patient's therapeutic journey are faced with a distinct challenge to meet the patient "where s/he stands." The clinician might best help the patient navigate around such barriers while using empirically guided judgment by personalizing treatment approaches, prioritizing shared decision-making, communicating openly and directly (when appropriate), utilizing technologies that improve accessibility (when viable), making a concerted effort to accept more insurance options or provide sliding-scale fee structures, and ultimately by creating a nurturing and strong therapeutic alliance and treatment engagement.

For the patient that successfully navigates the barriers and begins treatment, many factors hold significant influence over the relevance and compatibility of the treatment with his or her needs, culture, values, and beliefs. These factors include demographic characteristics, SES, preferences, values, personality traits, conversational styles, treatment history, trauma history, coping mechanisms, support networks, life circumstances, and resource availability (time, money, and energy), as well as the real and perceived commonalities and differences between patient and provider.

Ultimately, each of these factors along with the intended or unintended effects of the intervention a clinician provides can play a significant role, dramatically influencing the patient's progress. Depending on the individual, any one factor may "tip the scale," helping or hurting a patient's resolve. In effect, any one of these factors can result in treatment adherence or nonadherence and thus in the success or failure of the individual's recovery. When the individual fails to recover, chronic illness, treatment recidivism, and burdening of the crisis intervention systems can result.

When considering treatment compatibility, clinicians could benefit their patients by recognizing these many complex factors, while using empirically guided judgment and remembering that seeking treatment is itself a large hurdle for the majority of individuals. The

challenge to find adequate care, acceptance of diversity, cultural competence, then compounded by the difficulty and exhaustion of the cognitive, behavioral, and emotional work of therapy, strongly necessitates the need for a beneficial therapeutic alliance and treatment engagement.

Further, it also means that a disconnect between patient and provider (e.g., any discord between the patient's ideal clinician and the clinician received, or ideal services and the services rendered [i.e., lapses in communication, discrepancies in treatment goals, momentary discomfort or perceptions of "awkwardness" for the patient]) can disrupt the therapeutic alliance (i.e., alliance rupture; Muran & Barber, 2010) and the individual's commitment to treatment. Stated simply, clinically evidenced best practices are not universally synonymous with the patient's personal idea of treatment success, and as such, any minute incongruities can be the final straw that results in treatment dropout. This dropout has the potential for life-long negative associations and treatment alienation.

The community members and clinicians on the panel emphasized the importance of personalizing each individual's care in accordance with his or her specific needs, within the context of empirically guided judgment. Even the most efficacious, best evidence-based treatments for particular diagnoses may have no therapeutic benefit for a patient if the provider elicits a negative association or if the patient cannot adhere to treatment due to financial or other barriers. In the current context where data do not generally provide support for one treatment over another, supporting patients in educational and decision-making capacities may increase engagement and overall success of treatment.

Adapting Treatment to Fit the Individual

One hallmark of a scientifically sound outcome study is the ability to document that individuals providing a particular treatment, especially with psychotherapy, competently adhered to a treatment protocol. This refers to the notion of *treatment fidelity* or *integrity*. Including

protocols to evaluate treatment fidelity within a given clinical trial makes it easier to assess whether the treatment under evaluation was actually delivered in the manner intended and prescribed (Nezu & Nezu, 2008). However, within "real-world" contexts, it is likely that various exigencies arise such that complete adherence to a treatment protocol becomes difficult. Once again, treatment providers must rely on their sound clinical judgment to know when to "deviate" from the protocol or cease a given treatment if it is not "working."

Applicability of results and clinical significance. The present clinical practice guideline was developed to provide advice and guidance to various stakeholders (e.g., practitioners, patients) based on valid scientific evidence obtained within recent years. Whereas scrutiny of the extant scientific literature to inform such guidelines is critical and considered to be the "gold standard" methodology, the applicability of even an exhaustive and comprehensive review and its subsequent conclusions is also dependent on various contextual factors as noted. As such, when reading the recommendations, the reader should also consider the ability to generalize from aggregate data to the individual.

Ability to generalize from aggregate data to the individual. All research data that were included as evidence (or lack) of the efficacy of a given approach to treat depression is based on group data. In fact, a hallmark of sound outcome research involves including a sufficient number of participants in the study such that meaningful statistical analyses can be conducted. This is referred to as *power*, or the ability of a given study to validly detect a result that truly exists in nature. However, such results can only provide *general* types of information. The more that the sample population of a given investigation deviates from various characteristics of a given patient, the more informed clinical judgment is necessary to validly identify a particular treatment approach for that individual. For example, if a given set of studies that support the efficacy of a given approach included primarily White males as subjects between the ages of 25 to 50 years, it becomes less scientifically rigorous to suggest that this

same intervention would *automatically* be effective for others who are depressed but are outside of the pool of these specific subject demographics. While some of the studies included in the reviews were relatively homogenous, patients in other studies had greater demographic diversity and comorbidity. Unfortunately, subgroup analyses were not available during the current guideline development to draw adequate conclusions regarding treatment efficacy for specific subgroups, so when implementing these guideline recommendations, clinicians will especially need to consider their individual patients' backgrounds and needs.

Considering Patients' Diverse Backgrounds, Identities, and Comorbidities

One aspect of professional competence is cultural and diversity competence. The American Psychological Association's (2017b) *Multicultural Guidelines: An Ecological Approach to Context, Identity, and Intersectionality* encourage the provision of multiculturally competent services. Broadly, this multicultural competence includes "appreciation for, understanding of, and willingness to learn about the multicultural backgrounds of individuals, families, couples, groups, research participants, organizations, and communities" (American Psychological Association, 2017b, pp. 7–8). *Multicultural* refers to a range of factors including culture, immigration status, race, language, ethnicity, race, gender identity, sexual orientation, ability status, religion, socioeconomic status, employment, education, spirituality, and others (APA, 2002; as cited in APA, 2017b). Clinicians are also encouraged to refer to the APA's (2015) *Guidelines for Psychological Practice with Transgender and Gender Nonconforming People* and APA's (2012) *Guidelines for Psychological Practice with Lesbian, Gay, and Bisexual Clients,* as this population experiences increased mental health concerns. Providers are encouraged to provide multiculturally competent services in the context of the current depression guideline recommendations.

Existence of a behavioral health or medical disorder comorbidity. As noted earlier, depression is frequently found to be comorbid with other mental health problems (e.g., anxiety,

posttraumatic stress disorder), as well as in combination with various medical problems (e.g., heart disease, cancer, stroke). Comorbidity was not directly reviewed and is not reflected in the recommendations. However, given the ubiquity of comorbidity, all stakeholders need to take this limitation into consideration when reviewing the present guideline recommendations.

Generalizability of Treatments to Different Settings and Providers

Ability to generalize from a given setting—patient perspective. An aspect of professional competence involves the ability to accurately generalize to a given setting and set of circumstances. Scientifically sound research studies generally require that providers are experienced and trained in the given approach under evaluation. This may differ from typical usual care depending on the setting or place that a treatment is provided. Patients seeking a particular treatment may wish to ask questions, not only about a given treatment, but the extent to which those providing the treatment have been well trained. Within this context, prospective patients seeking treatment for depression should ask related questions to be assured that the treatment they believe they will be receiving will be provided in a quality fashion. This care would ideally be provided by a qualified mental health specialist though the panel acknowledges that accessibility to these specialists can be a barrier to treatment. Similarly, behavioral health professionals seeking to provide those treatments recommended in these guidelines need to receive adequate training and experience in the specific treatment approaches prior to offering such services.

Ability to generalize from a given setting—provider perspective. Just as prospective recipients of psychotherapy should consider the above issues, so should treatment providers (including administrators) consider similar issues. For example, the efficacy of a given approach as found in a research study may only reflect its efficacy based on the specific treatment circumstances. Examples of circumstances might include a treatment being delivered in an outpatient rather than an inpatient setting or whether there were any additional resources made

available to study participants that are unavailable to patient's in the provider's treatment setting (e.g., monetary incentive to minimize attrition, providing treatments for free). Such circumstances may limit the generalizability of treatment efficacy to real-world contexts.

When providers are confronted with implementing treatment in settings that may be atypical from the "standard" outpatient psychotherapy or pharmacotherapy structure often included in research studies, an option for individualizing the treatment might include an emphasis on a collaborative model where patients become more active participants in the treatment process. For example, certain general medical settings have adopted a collaborative care model whereby patients are provided an initial choice of psychotherapy or pharmacotherapy and depending on one's progress, predetermined algorithms help to determine further treatment choices (e.g., Unützer et al., 2002; depression with comorbid medical disease—Katon et al., 2010). Such protocols require involvement of various health care specialists to work together to improve a patient's depression and overall heath quality of life and require additional resources beyond typical outpatient services. Altogether, administrators and therapists need to consider the relevance of the literature to their specific treatment setting/context, options for addressing such gaps in literature when making treatment choices, and the applicability of the collaborative care model for their specific treatment setting or context.

Monitoring Engagement with Treatment

In a related manner, in order to better assess whether a treatment works involves determining the recipient's (i.e., patient's) actual comprehension or application of any suggestions or directions "prescribed" by the therapist. From a pharmacotherapy perspective, this involves identifying whether the patient followed directions regarding medication (e.g., taking the prescribed pills at the appropriate time). In other words, if one is uncertain whether a person actually ingested the medication, it becomes difficult to conclude whether any

improvement (or lack of) in symptoms occurred because of the medication. For directive psychotherapy approaches, this might involve evaluating whether the patient completed a homework assignment, practiced a certain skill, or read a prescribed book. For nondirective approaches, this may be difficult as there may be no instructions or guidance given; however, certain subtle indicators of patient comprehension or application may include a patient's increased curiosity, awareness, or insight into his/her experiences. The panel highlights these treatment integrity concerns to underscore their importance regarding the quality of a given research study (Sharpless & Barber, 2009) and implications for recommendations.

Contributions from Shared and Specific Factors to Treatment Outcome

Future research is needed to address the lack of adequate research examining the effective components of psychotherapy, or studies examining psychotherapeutic process, in the available reviews. This, in part, reflects the IOM's emphasis on quality of research for determination of efficacy of interventions, resulting in a focus on randomized controlled trials. While there is significant discussion of the relative importance of shared versus model-specific aspects of psychotherapy, there is not adequate research examining this question that sufficiently reduces potential risks of bias and other issues in a manner that could inform treatment recommendations. However, there is research suggesting that this may be a promising area for future studies. For example, a study by Cuijpers, Reynolds, et al. (2012b) examined the contributions of nonspecific, extra-therapeutic, and specific factors to patients' improvement. Results indicated that nonspecific factors accounted for 49.6% of the improvement, whereas extra-therapeutic factors accounted for 33.3% and specific factors accounted for 17.1% of the improvement (Cuijpers, Reynolds, et al., 2012b). This correlational study suggests an important role for nonspecific factors in treatment. The panel strongly recommends that researchers (and funding institutions) support studies that can identify key

components for successful treatment of depression across models of psychotherapy and test aspects of therapeutic process that contribute to treatment outcomes.

Enhancing Therapeutic Alliance and Other Principles/Processes of Change

Ideally, depression treatment research needs to provide evidence of efficacy, and also specify the change processes that account for the treatment's effects. Change processes can be defined in terms of: (1) *change principles*, which refer to conditions or characteristics (e.g., participant, relationship, and treatment components) that have been shown to predict treatment outcome (see APA, 2006; Castonguay & Beutler, 2006; see also Goldfried, 1980); (2) *change mechanisms*, which refer to factors that lead to therapeutic change as demonstrated by mediational or related analyses (Kazdin, 2007; Laurenceau, Hayes, & Feldman, 2007; Lorenzo-Luaces, German, & DeRubeis, 2015); and (3) *change events*, which refer to in-session interactions between patients and therapists that are linked to overall treatment outcomes (Greenberg, 1986).

It is important to note that this brief discussion of change processes is descriptive and is *not* based on a systematic review. Rather, the panel is highlighting a few examples of commonly cited change processes because of the value gained by understanding some of the ways that recommended treatments exert their beneficial effects. The panel is not making any formal recommendations in this section, and this is not a comprehensive list of all the change processes in the treatment of depression.

Change Principles

Castonguay and Beutler (2006) reviewed numerous change principles that have been shown in empirical studies to play a role in the treatment of depression (see Beutler, Castonguay, & Follette, 2006, for an integration of these findings). Examples include:

Participant. Patient expectations; readiness to change; and attachment, coping, and personality styles (Beutler et al., 2006; see also Bernecker, 2012).

Technical. Cognitive reappraisals, trying new behaviors, altering behavioral reinforcements, improving interpersonal and social functioning, promoting emotion processing and regulation, and conducting a structured therapy session (Follette & Greenberg, 2006; see also Auszra, Greenberg, & Hermann, 2013; Missirlian, Toukmanian, Warwar, & Greenberg, 2005; Pos, Greenberg, Goldman, & Korman, 2003; Whelton, 2004).

Relationship. Research on psychotherapy per se has underscored the association between having a positive therapeutic relationship or alliance, that is, the means by which a therapist and a patient hope to engage with each other, and positive change (Cuijpers, Driessen, et al., 2012a). Norcross (2011) presents a number of meta-analyses that examined the effect of elements of the therapeutic relationship on treatment outcome. An interdisciplinary task force concluded that evidence supported a *demonstrable effect* of the alliance and empathy, the *probable effect* of consensus and positive regard, and the *promising effect* of rupture repair and management of the therapist emotional reactions (Norcross & Wampold, 2011). The implication of such consensus is that in addition to a given treatment approach for depression, people seeking treatment need to also consider the relationship one has with the potential provider as it has been shown to be correlated with treatment outcome. Similarly, providers should attempt to offer evidenced-based treatment within the context of a positive therapeutic alliance.

Change Mechanisms

Lemmens, Müller, Arntz, and Huibers (2016) conducted a systematic review of 35 studies aimed at identifying mediators in various forms of psychotherapy for depression. They found that change in dysfunctional attitudes, negative “automatic” thoughts, mindfulness and worry skills, and rumination mediated change in outcomes (e.g., depression symptoms) in most studies, and they found mixed evidence supporting mediational roles for attributional style, behavioral components, and therapeutic alliance.

A review by Lorenzo-Luaces et al. (2015) reported some evidence that cognitive change (including both ability to use skills to modify cognitions and changes in cognitions, such as automatic thoughts and beliefs) mediates symptom change in cognitive therapy and mindfulness-based cognitive therapy for depression, as predicted by the theoretical models underpinning those therapies. A review by van der Velden et al. (2015) reported that changes in mindfulness, rumination, worry, compassion, or meta-awareness mediated effects of mindfulness-based cognitive therapy for depression. In addition, S. Cohen, O'Leary, Foran, and Kliem (2014) reported that among women who received brief couple therapy for depression, changes in depressive symptoms were mediated by changes in their own illness-related cognitions and behaviors, and in their perceptions of increased positivity and support from their husbands. There is also some evidence that skills learning and practice during homework assignments contribute to better outcomes for cognitive, behavioral, and cognitive-behavioral therapies for depression (Kazantzis, Whittington, & Dattilio, 2010; Terides et al., 2017).

Research on change mechanisms in psychodynamic therapies (some focused on depression) has provided varying support for the following variables facilitating better outcomes: greater insight, change in defensive style (more mature), less relationship rigidity and maladaptive representations, higher object relations, greater reflective functioning, and better therapeutic alliances (see Barber, Muran, McCarthy, & Keefe, 2013, for a review; see also Minges, Solomonov, & Barber, 2017; Zilcha-Mano, Chiu, et al., 2016a; & Zilcha-Mano, Muran, et al., 2016b). Research on change mechanisms in humanistic-experiential therapies has shown that emotional processing facilitates better outcomes (Auszra et al., 2013; Pos, Greenberg, & Warwar, 2009; Pos et al., 2003). Finally, changes produced by antidepressant treatments are extremely complex and our understanding of those changes is evolving (Dell'Osso, Palazzo, Oldani, & Altamura, 2011).

Change Events

With regard to research on in-session change events, there have been several intensive (small-scale, mixed-method) studies in which patient and therapist interactions have been reliably observed, and these interaction features are found to be related to treatment outcomes for depression (Greenberg, 1986; Greenberg & Newman, 1996). Examples include resolving problematic reactions (i.e., the reexperiencing of a problematic situation to better symbolize it in awareness and understand its personal significance; Watson, 1996), unfinished business (i.e., exploring lingering negative feelings toward a significant other; (Greenberg & Malcolm, 2002), and alliance ruptures (i.e., understanding and overcoming difficulties in the patient–therapist relationship; Safran & Muran, 1996). This is an area of research that requires more investment as it can provide clinicians more detailed information on how to interact with their patients.

Although a full review of the change processes (including principles, mechanisms, and events) that predict or mediate outcomes for depression treatment is beyond the scope of this clinical practice guideline, the panel encourages providers to review this important work because of the critical clues this research provides about how to improve therapeutic outcomes, and how to understand why a treatment may not be working as anticipated. Analogously, the panel encourages researchers to prioritize this critical domain of study so that the field will be able to make stronger statements about the mechanisms underlying efficacious treatments.

How the APA Clinical Practice Guideline Compares to Other Clinical Practice Guidelines for Treatment of Depression

Various other organizations and professional associations have also developed guidelines on treating depression, though the most recent versions of several of these documents are now considered to be outdated. This section will highlight guidelines for depression treatment from the American Psychiatric Association (2010), the American Academy of Child and Adolescent Psychiatry (2007), Kaiser Permanente Care Management Institute

(2012), the Veteran's Affairs/Department of Defense (2016), and the National Institute for Health and Care Excellence (updated in 2015).

The American Psychiatric Association's last guideline on depression (Gelenberg et al., 2010) focused on major depressive disorder in adults and was published in 2010, prior to the association's adoption of the former Institute of Medicine's (2011) standards for guideline development. This guideline is now listed as outdated. However, its main recommendations include overall psychiatric management for the disorder (i.e., therapeutic alliance, assessment, safety evaluation, determining the setting for treatment, consideration of functioning and quality of life, coordination of care, monitoring treatment response, outcome measurement, working on treatment adherence, and psychoeducation). For patients with mild to moderate major depressive disorder, antidepressant medication or psychotherapy were recommended as initial treatments. For moderate to severe major depressive disorder, a combination of antidepressant medication and psychotherapy was recommended. For severe major depressive disorder that was not responding to medication or psychotherapy or for which there was also associated catatonic or psychotic features, electroconvulsive therapy was recommended. The recommendations also included monitoring during the continuation phase of treatment, a maintenance phase of treatment, and tapering of medication during the discontinuation phase. The guideline also included clinical factors to consider during treatment such as psychiatric factors, psychosocial and demographic factors, and other medical conditions that are co-occurring.

Like the American Psychiatric Association's guideline, the present American Psychological Association's guideline also includes recommendations for psychotherapy and for antidepressant medication; however, it more commonly recommends combinations of psychotherapy and antidepressant medication versus antidepressant medication alone. The

American Psychological Association's guideline does not detail recommendations for the various stages of treatment as does the American Psychiatric Association's guideline.

The most recent practice parameter for the American Academy of Child and Adolescent Psychiatry for depressive disorders in children and adolescents (Birmaher et al., 2007) is listed as historical and not considered to be current. Many recommendations were similar in style to the American Psychiatric Association's practice guideline, focusing on general considerations such as confidentiality, screening, evaluation, phases to include in treatment (i.e., acute and continuation, possibly maintenance), and prevention. It also included some specific treatment recommendations. For children with a brief or uncomplicated depression, it recommended case management, support, and psychoeducation. For children with more complicated depression or who do not respond to supportive psychotherapy, further treatment with psychotherapy or antidepressant medication was recommended. Regarding moderate depression, it recommended either interpersonal psychotherapy or cognitive-behavioral psychotherapy. For severe depression, antidepressant medication is also recommended alone until the child can begin psychotherapy or in combination with psychotherapy from the start. A combination of antidepressant medication and psychotherapy was recommended for children that do not respond to monotherapy of either medication or psychotherapy.

The American Academy of Child and Adolescent Psychiatry's guideline recommendation for interpersonal psychotherapy or CBT is similar to the American Psychological Association guideline's recommendation for interpersonal psychotherapy (adapted for adolescents) or CBT treatment. The American Academy of Child and Adolescent Psychiatry guideline also cautiously recommends certain antidepressant medications (selective serotonin reuptake inhibitors) and suggests combination of treatment may be warranted with more severe clinical presentations. The APA guideline recommendations, however, do not address combination treatment of psychotherapy and antidepressant medication for children/adolescents. However, it should be

noted that the Treatment of Adolescent Depression (TADS) study is the largest study to date examining adolescents with persistent and impairing major depression. This study compared CBT as a stand-alone intervention to antidepressant medication (fluoxetine), the combination of CBT and medication, and a placebo sugar pill across 13 sites and included over 400 adolescents (March et al., 2004). The study concluded that combination treatment of fluoxetine and CBT resulted in significantly better outcomes than CBT or fluoxetine alone (March et al., 2004). A more recent evidence-based update examined psychosocial interventions for the treatment of child and adolescent depression (Weersing, Jeffreys, Do, Schwartz, & Bolano, 2016). This study concluded that both CBT and interpersonal psychotherapy are well-established interventions (though they have limited evidence for racially diverse youth), with evidence of efficacy in multiple trials by independent investigative teams. However, the conclusion is tempered by the smaller number of studies for interpersonal psychotherapy adapted for adolescents and the concern that the effects of CBT may be diminished when applied to populations with more comorbidity and diversity of ethnicity and socioeconomic status, and when compared to active treatments (Weersing et al., 2016). While informative, the panel did not find these studies to yet warrant recommendations regarding combined treatment for children and adolescents and desires more comparative effectiveness and combined treatment research.

The guideline for treating depression in adults from the Kaiser Permanente Care Management Institute (2012) recommends either antidepressant medication or psychotherapy (cognitive-behavioral therapy, interpersonal psychotherapy, or problem-solving therapy) as first line treatments for patients whose major depressive disorder is mild to moderate, with consideration given to patient and clinician preferences, medication side effects, and cost. A combination of antidepressant medication and psychotherapy (cognitive-behavioral therapy, interpersonal psychotherapy, or problem-solving therapy) is recommended for patients with

chronic or severe major depressive disorder. According to that guideline, the following medication classes can be used as first line treatment: tricyclics, selective serotonin reuptake inhibitor (SSRI), serotonin–norepinephrine reuptake inhibitor (SNRI), norepinephrine reuptake inhibitor (NRI), or dopamine agonist, based on patient and clinician preferences, medication side effects, and cost. The Kaiser guideline does not recommend for or against St. John's Wort (hypericum) for mild to moderate major depressive disorder but recommends against St. John's Wort for severe major depressive disorder. The Kaiser guideline recommends consulting with specialized behavioral health providers for those patients with suicidal ideation, plans, intent, or previous suicide attempts.

The Kaiser guideline goes on to discuss second line treatments for those patients who continue to have symptoms after first line treatment. These second line treatment recommendations include an examination of adherence to treatment, and options such as combining treatments, increasing antidepressant dosage, and switching treatments. The Kaiser guideline recommends against augmenting with pindolol but does not recommend for or against providing atypical antipsychotics or inositol or folate as second line treatments.

APA's guideline also recommends that certain treatment approaches might be considered or applied first (i.e., psychotherapy or pharmacotherapy for adults) and then suggests other options (i.e., complementary and alternative treatments for adults) if the first options are not available or acceptable. Both the APA and Kaiser guidelines recommend consideration of patient culture, values and preferences, and medication side effects. The APA guideline was frequently unable to recommend a specific antidepressant medication over another treatment due to insufficient evidence, though did recommend a combination of antidepressant medication and psychotherapy versus antidepressant medication alone in some cases.

The focus of the VA/DoD (2016) guideline is on adults with major depressive disorder being treated in the Veteran's Affairs/Department of Defense setting. Recommendations from this guideline include the domains of identification, assessment and triage, treatment setting, and management. The management recommendations for adults are the closest in content scope to APA's guideline. First line psychotherapy treatments recommended by the guideline for mild to moderate major depressive disorder include: acceptance and commitment therapy, behavioral therapy/behavioral activation, cognitive-behavioral therapy, interpersonal psychotherapy, mindfulness-based cognitive therapy, and problem-solving therapy. First line pharmacotherapy treatments recommended by the guideline for mild to moderate major depressive disorder include selective serotonin reuptake inhibitor (except fluvoxamine) (SSRI), serotonin–norepinephrine reuptake inhibitor (SNRI), mirtazapine, and bupropion. The Veterans Affairs/Department of Defense guideline did not find sufficient evidence to be able to recommend one particular psychotherapy or pharmacotherapy versus another. The guideline further recommends that if a patient has not demonstrated sufficient response after 4 to 6 weeks of trying a pharmacotherapy, the patient should switch to another medication or to psychotherapy or augment with another medication or psychotherapy. It recommends that patient preference should be used to determine psychotherapy format (individual or group). Computer-based cognitive-behavioral therapy can be offered as a first-line treatment or as an augmentation to treatment based on patient preferences for patients with mild to moderate major depressive disorder. Further for those with mild to moderate major depressive disorder who decline or are unable to access first line recommended psychotherapies or pharmacotherapies, the guideline suggests offering short-term psychodynamic psychotherapy or nondirective supportive psychotherapy. In treating severe or chronic or recurrent complex major depressive disorder the guideline recommends a combination of pharmacotherapy and psychotherapy. The VA/DoD guideline also goes on to provide recommendations for monitoring,

continuation and maintenance, and additional treatment considerations (i.e., for specific populations, for severe or chronic or recurrent complex major depressive disorder, and complementary and alternative treatments and self-help).

Although the APA guideline used the same review that served as the evidence base for the VA/DoD guideline as one source of information for its guidelines, the reader will note some differences. For example, in some instances the VA/DoD guideline recommends a particular intervention for which the APA guideline does not due to insufficient evidence or other factors. It should be noted that the APA guideline deemed evidence to be insufficient for drafting a recommendation if all the outcomes for that particular intervention were classified as having very low/insufficient evidence and only drafted recommendations for those interventions included in the review in which at least one outcome was of low or higher quality evidence. Moreover, following best practices, the APA panel only used data from a systematic review included in the VA/DoD review if it was considered current from the past 5 years (dating no farther back than 2012). Thus, the reader will note some differences in conclusions drawn from the same data review between the guidelines.

The guideline from the National Institute for Health and Care Excellence (NICE) focuses on children and adolescents ages 5–18 years old. It was published in 2005, and currently another update is in progress with information on antidepressant medication and psychotherapies. This guideline recommends providing good psychoeducation, support and informed consent, consideration of language and culture, assessment and care coordination, organizing and planning of service, considering various factors in treatment across settings (e.g., treat on outpatient basis, assessment of social network and bullying, treatment alliance), and stepped care depending on the focus of treatment. For mild depression and persistent depressive disorder, the guideline recommends watchful waiting for up to 4 weeks, nondirective supportive therapy, group cognitive-behavioral therapy, or guided self-help. The NICE guideline

recommends against using antidepressant medication as an initial treatment for mild depression in children and adolescents. For moderate to severe depression, the guideline recommends brief psychological therapy (individual CBT, interpersonal psychotherapy, family therapy, or psychodynamic psychotherapy) with or without fluoxetine.

For depression that is recurrent, unresponsive to treatment, or psychotic, the NICE guideline recommends intensive psychological therapy of an alternative therapy than what was already tried (individual CBT, interpersonal psychotherapy, or shorter term family therapy, lasting at least 3 months) or systemic family therapy or 30 weekly sessions of individual child psychotherapy. This treatment may be done with or without fluoxetine. If the child is unresponsive to fluoxetine, then sertraline or citalopram may be used. The NICE guideline recommends against using paroxetine, venlafaxine, tricyclic antidepressants, or St. John's Wort. For psychotic depression, the guideline recommends that consideration be given to augmenting treatment with an antipsychotic. The guideline goes on to discuss inpatient care, electroconvulsive therapy, discharge planning, recurrent depression and prevention of relapse, and the transition of the child to adult services, areas not covered for children and adolescents in the APA guideline. The NICE guideline also contains recommendations for future research based on the panel's review of the research evidence.

Similar to APA's guideline, the NICE guideline looks at both children and adolescents. Portions of the NICE guideline focus on contextual factors, similar to the focus of APA's professional practice guidelines. While the NICE guideline recommends various psychotherapies depending on where the patient's diagnosis and response fits in the stepped care model, the APA guideline recommends CBT or interpersonal psychotherapy and notes insufficient evidence to recommend particular treatments over others. The NICE guideline focuses its medication recommendation for moderate or severe depression on fluoxetine, with a few other antidepressants recommended as alternatives if the patient is not responsive to

medication. The APA guideline likewise recommends fluoxetine as a first line medication, given the lower risk for suicidal ideation and behavior, compared with other medications for adolescent patients with major depressive disorder. The APA guideline then notes that if fluoxetine is not a treatment option or is not acceptable, the panel recommends shared decision-making regarding medication options with a child psychiatrist in addition to the clinician, patient, and their parents/guardians or family members actively involved in their care.

Challenges in Developing the Guideline and Recommendations for Future Efforts

In developing this guideline, the panel consistently identified and documented challenges and limitations for the purposes of improving future efforts at both research and guideline development and implementation. The challenges fell broadly into three domains:

1. The limitations of the guideline's scope based on the PICOTS (Population, Interventions, Comparators, Outcomes, Timing, and Settings) chosen.
2. Constraints and applicability of the IOM guideline development standards to mental health and particularly depression.
3. General and cohort-specific limitations of the current research literature.

Considerations Regarding Guideline Scope

The current guideline focused on the PICOTS (Population, Interventions, Comparators, Outcomes, Timing, Settings) described in the introduction. The panel wanted to be as broadly inclusive as possible, but nonetheless had to limit the areas of focus to rigorously evaluate a segment of literature in a realistic time frame. The panel therefore did not systematically review the literature relevant to a number of important populations (e.g., populations with bipolar disorder, psychotic depression, or other medical disorders) and settings (e.g., collaborative care, inpatient treatment). An additional area not captured by the panel was stepped care. Some clinicians, for example, may follow a stepped care approach to treatment based on the patient's history of number of prior episodes of depression. Some of these components not

reviewed by the panel were captured partially within the available reviews, but the presentation of the data prevented systematic recommendations. These decisions reflected the panel's desire to address questions of care relevant to the largest segment of individuals with depression and focus on topics of broadest interest to the membership of APA and related disciplines. The panel expects future efforts will expand on this and other guidelines to address important areas such as populations with comorbid medical disorders, populations with comorbid substance use disorders, collaborative care models, treatment specifically in primary care settings, alternative treatment modalities, and models using longer term or maintenance approaches to treatment. For example, there is emerging research regarding promising Internet-based interventions in general and particularly for children and adolescents (Reyes-Portillo et al., 2014). There is need for a more detailed examination of complementary and alternative interventions for depression than what was included in the current guideline, as well as examination of the role of peer providers (individuals with lived experience of depression) in treatment.

As noted previously, the guideline initially was going to only address treatment for adolescents. However, the available reviews often included both children and adolescents together. The panel incorporated children into the guideline, but because the original search focused solely on adolescents, the sampling of the child literature is likely incomplete. In addition, while the literatures were often combined, there are important developmental and theoretical reasons to consider children and adolescents separately. The panel ultimately decided to separate recommendations for children versus adolescents but was constrained in its ability to make specific recommendations for children due to the limited literature focusing exclusively on children included in the reviews. Future efforts would benefit from a separate systematic review dedicated to childhood depression.

Another domain not included but that is an important priority is universal prevention. The panel focused on treatment of depressive disorders, determining this would be the domain of most interest to the consumers of this report. However, the panel also recognizes that preventive interventions are an important aspect of care, particularly for health care systems, and recommends that future guidelines address prevention approaches (e.g., Horowitz & Garber, 2006; Garber et al., 2009; Horowitz, Garber, Ciesla, Young, & Mufson, 2007).

As noted in the introduction, a number of areas were not addressed in the PICOTS for the guideline, including screening for depression, assessment of associated or comorbid conditions (e.g., suicidality, medical problems), monitoring response to treatment and follow-up after treatment, locus of care, primary prevention of depression, dose (differential beyond current recommended), timing or duration of treatments for depression, costs of treatments, specific populations (e.g., caregivers), and mechanisms of change. These areas are important domains of investigation and comment. The panel has supplemented the guideline mechanisms in some sections with information related to some of these domains when appropriate, but the panel is supportive of future efforts to incorporate these domains formally into guidelines, where there is literature available.

Implications of Alignment with the Institute of Medicine Standards

It is noted throughout this document that the current clinical practice guideline development panel adopted the Institute of Medicine's (2011a) standards for guideline development. What are these standards? To begin with, the definition of a clinical practice guideline according to the IOM (2011a) involves ". . . statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options" (p. 4).

Historically, these standards are the product of a collaboration between the IOM and the Agency for Health Care Research and Quality in 2008. The impetus for this partnership was

initially called for by Congress and the then-Secretary of Health and Human Services as a means of empowering committees to conduct two major studies—one devoted to identifying standards for conducting systematic reviews of clinical effectiveness research, and the second to develop standards for developing clinical practice guidelines.

The first committee report describes the specific means by which systematic reviews and meta-analyses are to be conducted. Elsewhere in the current document, it is noted that in order to follow IOM standards, it was important to generally include reviews that involved more than one individual to screen and select studies to include in the review, as well as to extract quantitative data from each study. In addition, although not a hard and fast standard, the IOM notes that systematic reviews become outdated at 5.5 years. Following such guidance restricted our ability to incorporate those reviews that did not meet such standards, regardless of the quality of the review in all other aspects. However, when such restrictions led to a major lack of information on which to base recommendations (see Method section as well as section below on constraints using the IOM standards), we did include meta-analyses that did not meet such standards but that did meet quality criteria per AMSTAR review.

Attempting to follow the standards and guidance set forth by the IOM can be limiting if systematic reviews are not available (see section below for additional detail), despite the existence of multiple individual studies. As such, developing clinical practice guidelines that are “trustworthy” can be difficult. On one hand, it becomes crucial to follow scientifically sound protocols, such as the IOM guidance. On the other hand, doing so can limit the ability to develop clinical practice guidelines in such a manner that includes all potentially relevant data. For example, several meta-analyses that are viewed by many as supportive of the efficacy of various psychotherapies for depression are actually considered outdated or do not meet the rigorous IOM standards. As such, although information about the potential viability and efficacy of such therapies are at times in the “collective conscious” of the health professions at large, it

may not be included in current clinical practice guidelines. The lack of studies to help answer questions regarding comparative effectiveness and the efficacy and relevance of various treatments for ethnic minority populations is particularly challenging. The situation is even more complex as single studies need to be evaluated for quality (as with a meta-analysis or similar endeavor) and typically do not have sufficient strength of evidence alone to draw robust conclusions.

This state of affairs leads to a scientific and professional dilemma—should the panel have used IOM guidance? In the absence of any other "gold standard," the answer is "yes" given that the ultimate goal is to produce a scientifically sound clinical practice guideline. Alternatively, future efforts to create differing clinical practice guideline development guidance, whether they are slight variations of the current IOM standards or something created by other agencies or professional groups, may yield more viable approaches. The development of the original CONSORT (Consolidated Standards of Reporting Trials) statement guidelines provided standards for reporting clinical trials in order to foster transparency and scholarship. Because the original CONSORT was developed for the general medical field, various extensions have been developed to better suit differing populations, methodological approaches, and content. Relevant to this clinical practice guideline, a formal extension of the CONSORT guidelines is currently being developed by an international consensus group to be relevant and appropriate for clinical trials specific to social and psychological interventions, including psychotherapy trials (hence the title Consolidated Standards of Reporting Trials—for Social and Psychological Intervention Trials; Montgomery et al., 2013). In this vein, it is possible that the current IOM guidance may be the starting point but not the final best approach for developing clinical practice guidelines that involve predominantly psychotherapy research. The nature of both funding sources (e.g., requirements to receive grants) and aspects of research design (e.g., inability to blind participants to the treatment they receive) may require different criteria for

evaluating the quality of research. This is, however, perhaps also an empirical question. In the meantime, to pursue a scientifically sound path, adopting the IOM guidance is considered to be the best current approach. However, it is also important to acknowledge limitations. The full reports for each of these development standards are available online (IOM, 2011a; IOM, 2011b).

The panel was committed to ensuring the scientific rigor of the development process by following the IOM standards for guideline development while simultaneously generating a guideline that was based on an adequate inclusion of the research literature. When reviewing the original umbrella review of treatments conducted by an evidence-based practice center for the panel, it became clear that a large number of systematic reviews and meta-analyses were not included in that umbrella review due to not meeting the IOM standards, yet frequently these were the only reviews covering a key domain. The panel determined it could not create an adequately meaningful guideline without broadening the inclusion parameters and determined to consider reviews that did not utilize a dual review process for selecting articles for inclusion. All other requirements were maintained, such as excluding reviews including trials that were not appropriately controlled. While single review increases the risk of bias in article selection (Edwards et al., 2002), the panel in reviewing the literature determined that the guideline would not adequately cover the PICOTS (Population, Interventions, Comparators, Outcomes, Timing, Settings) without some expansion of the available literature, and this modification was the most scientifically defensible of all options. All identified reviews not conducted or evaluated by an evidence-based practice center were evaluated by a scientist external to the guideline development process using the AMSTAR criteria before including the reviews in the evidence base.

Even with this expansion, there were some domains that were inadequately addressed. For example, there was only one study of psychodynamic therapy identified in the child and

adolescent literature reviews (Trowell et al., 2007), despite it being a common modality in the community (i.e., the IMPACT study in the United Kingdom; see Midgley & Kennedy, 2011). In another example, studies of newer therapies such as schema-focused therapy, emotion-focused therapy, and acceptance and commitment therapy, although used in the community for treating depression, were not reviewed. These newer therapies were not covered in existing meta-analyses that were of high enough quality per AMSTAR standards and thus were not considered for a recommendation by the panel. Use of smartphone-based treatment was not reviewed due to inadequate comparison conditions in the general adult population. Studies of play therapy varied greatly in definition of intervention (the one study of acceptable quality focused on war-abducted youth, raising questions of generalizability). Medication as a comparator across the age populations varied greatly in terms of quality of treatment and conformity to standards of practice, with the physician members of the panel noting that in some cases the standard doses were below recommended doses, or the medication was not used in current practice (e.g., nefazodone). These limitations restricted the nature of the recommendations the panel could make.

Panel members did discuss whether there were ways to effectively include research that did not depend on randomized controlled designs as generally those studies do not meet the quality inclusion criteria for systematic review. In domains where there are limited randomized controlled trials available, it may be reasonable to develop preliminary recommendations based on well-designed correlational studies, particularly if there is longitudinal data available. The panel does recommend review of guideline development processes to ensure emerging best practices are captured in APA's processes and determine if specific modification may be indicated for guidelines related to mental and behavioral health. For example, maintaining a double-blind condition in a psychotherapy study is not possible (the provider and participant

know the intervention being provided), and this leads to such studies being judged as lower quality.

Limitations of Existing Treatment Research Literature

In creating this guideline, the panel had an opportunity to identify a number of domains in which there are extensive needs for future research.

Extensive evidence for a variety of treatments. Depression is one of the disorders most widely studied in psychotherapy research, with over 400 randomized clinical trials for depression across the last 3 decades (Cuijpers, van Straten, Warmerdam, & Andersson, 2008). However, while a large number of studies focused on the efficacy of one approach, cognitive-behavioral therapy (CBT), fewer studies have examined other widely utilized treatments including psychodynamic therapy, interpersonal psychotherapy, behavioral activation, problem-solving therapy, and emotion-focused therapy, among others. Most of these treatments have demonstrated preliminary efficacy necessitating the need for further study. In addition, while the largest body of literature is for CBT, the definition of CBT is not the same across all CBT studies. This heterogeneity limits the ability to make conclusions about the CBT model. It is imperative that the field generate more evidence to support different psychotherapies (with preliminary efficacy as this is crucial for the advancement of the scientific field, diversification of education, and training opportunities for and adherence to scientific calls for personalized approaches to treatment). There is also interest and awareness of growing areas in complementary and alternative medicine such as those included in this review and others that were not included (such as emotional support animals).

Secondary outcomes. Symptomatic change (or reductions in the severity and duration of symptoms) has been widely considered the gold standard for improvement in treatments of depression. However, it is important to consider patients' improvement beyond symptom change. Very few studies have focused on investigating treatment gains in a wide range of

functional domains of patient-centered outcomes, such as quality of life, employment status, integration in the community, social engagement, satisfaction in interpersonal relationships, etc.

Long-term outcomes of psychotherapy. There is still lack of sufficient evidence on the enduring long-term effects of treatments for depression. While some evidence suggests that effects of some psychotherapies persist longer than the effects of medication (e.g., Hollon & Ponniah, 2010; Cuijpers et al., 2013; Fonagy et al., 2015), there is still a need for data from long-term follow-ups with multiple time points. In that respect, understanding long-term change trajectories could also help researchers develop interventions that are focused on relapse prevention.

Treatment for patients with comorbid medical conditions. While there is a large body of literature demonstrating the relation between various medical conditions (e.g., obesity, cardiovascular disease, chronic pain, cancer) and depression, few randomized controlled trials have been conducted targeting depression among these populations. One of the reasons is that randomized controlled trials have had strict exclusion criteria, leaving outpatients suffering from comorbid conditions. Randomized controlled trials with strict exclusion criteria have led to a better understanding of efficacy of treatments for this clearly defined and fairly homogenous population. However, less is known about patient populations who do not fit this category. Therefore, future research should examine some of the more commonly co-occurring physical ailments of depression like stroke, diabetes, and cancer, as well as subsyndromal depression and substance use disorders.

Treatment for racially, ethnically, and gender diverse populations. Despite the increasing awareness of the importance of accessibility of mental health care for racially, ethnically, and gender diverse persons and the emphasis on multiculturalism, the panel was unable to address depression within groups of people of color and other diverse groups across age cohorts. For example, there is a growing yet limited body of knowledge regarding

conceptualizations of the etiology of depression in people of color (Sontag-Padilla et al., 2016; Stein et al., 2010), the diagnosis of depression in adults and youth of color (Breland-Noble, Al-Mateen, & Singh, 2016; Breland-Noble, Sotomayor, & Burriss, 2015), and most effective delivery methods of treatment for these populations (Camacho et al., 2015). Unfortunately, there is a dearth of evidence regarding treatment engagement and outcomes for most racial ethnic groups in the U.S. (including adults and youth), thereby restricting the panel's ability to account for treatment response variability in relation to racial and ethnic group diversity within the current guideline.

Future research must expand its inclusion of underserved and underrepresented populations in depression treatment research. There is particular need for more comprehensive sampling of these populations (e.g., often the youth of color included in studies are disproportionately from communities experiencing individual-level and neighborhood-level socioeconomic disadvantage). Within these studies, it is imperative that researchers identify culturally relevant means of assessing depression in racially diverse populations. Doing so would more accurately identify individuals in need of treatment and utilize measures that are sensitive to the symptom changes of these populations throughout the course of treatment. Also, further research is needed to examine culturally relevant outcomes of standardized interventions as well as interventions targeted specifically to the needs of these diverse groups, such as school-based mental health services for minority youth (Atkins, Frazier, Adil, & Talbott, 2003; Bear, Finer, Guo, & Lau, 2014; Langley, Nadeem, Kataoka, Stein, & Jaycox, 2010). Given preliminary evidence suggesting that ethnicity moderates treatment effects (e.g., Barber et al., 2012), researchers should focus on studying process and outcomes of psychotherapies among racially, ethnically, and gender diverse populations (Perry, Chaplo, & Baucom, 2017). Of note, there are special issues to consider when conducting research with diverse groups (APA, 2017b; Council of National Psychological Associations for the Advancement of Ethnic Minority

Interests, 2007). These issues include training in multicultural competency to properly conduct research with such individuals, using culturally relevant and appropriate assessment tools for a given group or subgroup, and including individuals of a particular minority population of research focus within a larger stakeholder framework.

Cohort specific limitations: *Child and adolescent*. Broadly, additional studies of psychotherapy interventions in general for diverse children with depression that include long-term follow-up are needed. While the field recognizes the benefits of interpersonal psychotherapy (adapted for adolescents) and CBT for youth, the literature is currently insufficient for definitively stating which therapies are most efficacious for specific populations (e.g., preadolescents, young children, and children of color). Also, more studies with children and with adolescents comparing active interventions are needed.

In addition, the meta-analyses and reviews included a number of indicated prevention focused studies in the analyses assessing the evidence base for depression interventions. These study participants endorsed depression symptoms albeit subsyndromal but elevated enough that they were considered depressed. However, the target outcome for indicated prevention studies is prevention of increasing symptom severity and acquisition of a depression diagnosis rather than recovery or remission from diagnosed depression. Combining prevention and intervention studies within meta-analyses may have obscured differences in outcomes of similar treatments with different targets, reducing the confidence in strength of effectiveness for a given treatment approach.

***Limitations in older adults*.** Three of the most salient limitations of the intervention literature to date in late-life depression treatment and prevention concern (1) the underrepresentation of racial and ethnic minority participants, (2) the relative dearth of participants among the “oldest old” strata of society (i.e., those older than 75 or 80), and (3) the paucity of information on treatment response modifiers. There is increasing interest in testing

measures of medical morbidity and of cognitive impairment as moderators of treatment response, with early promising leads in these domains. Moreover, comparative effectiveness research is needed to address the treatment of depression in patients for whom treatments fail in later life.

Despite establishing that some psychotherapies are beneficial to older adults, the research literature is at best limited. Moderators of effect, such as health and cognitive status, are poorly understood. The majority of older adults included in treatment studies are younger older adults, and little is known about the benefits of treatment for those in the eighth and ninth decades of life. Finally, as is common across all age cohorts, the diversity of patient samples is minimal.

Last, family caregiver burden in the context of late-life depression is a significant public health issue. This underscores the importance of engaging family members in the process of care, both as sources of reliable information about how a loved one with depression is doing, and also to foster engagement in and adherence to treatment for a sufficient period of time to realize and to sustain meaningful benefit. Family caregivers are frequently demoralized by their loved one's depression and welcome the opportunity to learn more about the illness and its treatment and resources for self-care.

Older adult patients for whom treatment fails. Similar to the general adult population, there is also a great need for comparative effectiveness research because, as suggested by the Nelson et al. (2008) meta-analysis, existing treatments may benefit no more than half of older adults with major depression. Further, as noted above, there is limited information about moderators of treatment response (which treatment for which patient). Some practitioners advocate switching class of antidepressant, while others argue for the use of augmentation strategies. The data do not provide conclusive evidence for either switching or augmentation strategies.

Judging from the statistic numbers-needed-to-treat reported in randomized, placebo-controlled trials, antidepressant pharmacotherapy appears to be more effective in long-term or maintenance treatment (over 2–3 years), with respect to preventing recurrence of major depressive episodes, than in short-term use (up to 12 weeks) with respect to rates of response or remission. A meta-analysis by Kok and colleagues (Kok, Heeren, & Nolen, 2011; Kok, Nolen, & Heeren, 2012) estimated a number needed to treat of 3.4. The clinical relevance of this observation is considerable, given the risk for a chronic, relapsing course in late-life depression (Kok & Reynolds, 2017). There is yet, however, no strong evidence-based consensus about which patients need maintenance pharmacotherapy, apart from those with three or more episodes of major depression.

The modest efficacy of antidepressant pharmacotherapy needs to be weighed against side-effect burden and adverse effects, especially in frail older adults with medical poly-morbidity. Potential safety concerns in older adults treated with antidepressants include drug–drug interactions, hyponatremia, falls and fractures, gastrointestinal bleeding, cardiovascular effects, and bone metabolism/osteoporosis. At the same time, however, evidence-based management of late-life depression in primary care patients (where most patients are treated), in which both pharmacotherapy and learning-based psychotherapies (interpersonal psychotherapy and problem-solving therapy) are offered, has demonstrated moderately higher levels of treatment response and remission versus care as usual (Bruce et al., 2004; Unützer et al., 2002). It has further demonstrated reduction in long-term rates of mortality from co-occurring medical conditions (Gallo et al., 2013). Thus, both the short- and long-term risks and benefits of antidepressant pharmacotherapy in older adults, together with patient preferences, need to be carefully weighed in shared decision-making with patients and families.

Need for a Clearer Taxonomy of Psychotherapies

The great deal of variability in what is grouped in a review as a particular form of psychotherapy (e.g., cognitive therapy, psychodynamic therapy, etc.) also interferes with establishing clear treatment guidelines. The panel, in some cases, had difficulty determining what was included in categories in reviews and how the determinations were made and, at times, questioned whether treatments should be grouped together. For example, group and individual psychodynamic psychotherapy were grouped together in a meta-analysis (Driessen et al., 2015) with an outcome suggesting less efficacy than other treatment approaches. However, when only individual treatments were analyzed, there was no difference between psychodynamic and other treatment approaches (Driessen et al., 2015) which is consistent with Barber et al. (2012). Similarly, a well-defined model of psychotherapy, emotion-focused therapy, was grouped in reviews under “non-specific and supportive models” (Cuijpers, Driessen, et al., 2012a). Experts indicate that this is a mis-categorization, but the categorization resulted in masking potential evidence regarding efficacy of this intervention.

Other times, the same or similar labels were used to describe approaches that are actually quite different from each other. For instance, although conceptually similar, psychoanalysis, psychoanalytic psychotherapy, brief psychodynamic psychotherapy, and interpersonal psychotherapy are also different regarding emphasis, focus, strategies, length of treatment, and hypothesized mechanisms of action. Although this labeling issue exists and was recognized by the panel, the panel strove to use labels similar to the investigators in order to maintain consistency with the language used by investigators as well as to maintain a sufficient sampling of studies under each treatment approach. However, it is possible that the outcomes of meta-analyses and reviews might be different based on alternate groupings of interventions (i.e., cognitive therapy alone or combined with cognitive-behavioral therapy or behavioral therapy for analyses) potentially resulting in different evaluations of effectiveness. Given this

possibility, there is a need for formal efforts at developing a more universal taxonomy of psychotherapies that can better categorize shared and unique features of interventions incorporated in specific treatments. The panel strongly recommends that researchers carefully operationalize and specifically define the treatment approach that they are investigating and label accordingly. The problem is compounded by the fact that it is often hard to know how the actual treatments were delivered, how adherent the therapists were, and how much "borrowing" from other treatment modalities was done.

Need for Rigorous Comparisons of Treatments and Treatment Modality

Despite the increasing number of studies and meta-analyses comparing different treatments, the differences, process, and outcome data on different treatments remains elusive (Cuijpers, 2015; Cuijpers et al., 2008), and more rigorous treatment comparisons of psychological interventions are needed. One of the most challenging and yet pressing needs is developing methods to evaluate the contribution of specific aspects of psychotherapy models compared with the shared or nonspecific aspects. In particular, designs that use a general form of psychotherapy that represents the shared components of effective models as a control condition would contribute to improving the ability to separate out the unique contributions of specific models. Fewer studies have compared the efficacy of individual modalities of treatment versus group modalities. One of the biggest research gaps in terms of treatment implications is the evaluation of either the efficacy of treatments delivered in a group format or comparisons of a treatment delivered in an individual format to treatment in a group format. Given how frequently group is the modality of treatment in certain settings (i.e., Veteran's Administration and psychiatric hospitals), better data on its comparability to traditional individual therapy is imperative.

Another important domain is assessing new models of delivering previously supported approaches. This includes delivery in new environments (e.g., primary care, in home) and

through the use of new technologies (e.g., phone, video-conferencing, Internet, smartphone apps). The panel found that some reviews lumped different settings or technologies together, limiting the panel's ability to make comparisons.

Improving Methodology and Reporting in Treatment Studies

Along these lines, it is critical that randomized controlled trials testing theoretically sound interventions be designed using the principles of available study design guidelines (e.g., Consolidated Standards of Reporting Trials, Journal Article Reporting Standards—Altman et al., 2001; Appelbaum et al., 2018; Levitt et al., 2018). The design features that the panel encourages researchers to adopt include: adequate control conditions (waitlist controls can artificially inflate effect sizes; Furukawa et al., 2014); clear definitions of both active and control conditions; extended long-term follow-up; comparisons between treatment modalities (e.g., group vs. individual); direct comparisons of dosage differences (e.g., number, length, or frequency of sessions) for psychotherapies; definition and assessment of training in the intervention; and assessment of competence in and fidelity to the intervention. The panel was concerned that many studies included in reviews provided an insufficient summary/description of important components of their study design. Specifically, a number of studies did not provide information on the training and competence of the providers, which again limits the ability to determine strength of recommendations, as it is not known whether the treatment was adequately delivered when under evaluation. In addition, the panel supports articles including links to archives and appendices to facilitate transparency and replicability, especially when journals allow very limited number of words. This can be particularly helpful with publication of treatment manuals associated with specific interventions. The panel also supports incorporating a section on harms and burdens in reports on psychotherapy trials, consistent with the standard practice in pharmacotherapy research. Throughout the process of completing this guideline, the inability to assess harms and burdens of specific interventions was a major obstacle to having

confidence in recommendations for psychotherapies. In terms of outcomes, the panel notes the need for longer term outcomes and supports researchers using the 5R model (response, remission, recovery, relapse and recurrence; Frank et al., 1991) for defining symptom outcomes. End of treatment response and remission (e.g., brief period of symptom improvement) are typically reported (Frank et al., 1991). However, recovery (e.g., depressive episode has been in remission for an extended period of time), relapse (e.g., re-emergence of depressive episode during a prior period of remission) and recurrence (e.g., re-emergence of symptoms during a prior period of recovery) are also meaningful outcomes for evaluating treatments but are much less commonly reported. Yet the outcomes of recovery, relapse, and recurrence are critical for understanding the endurance of treatment effects (Frank et al., 1991). The panel also supports expanded incorporation of clinical significance (i.e., evaluating whether change of treatment leads to clinically meaningful difference such as changing from meeting diagnostic criteria to no longer meeting criteria) for evaluating outcomes in addition to the traditional use of statistical significance.

Testing Moderators and Mediators of Treatment Outcome

Some psychotherapy research demonstrated that, after treatment completion, more than half of patients remained depressed (Thase et al., 1997), and of those who improved by the end of treatment, about 40% experienced a relapse in depressive symptoms (Steinert, Hofmann, Kruse, & Leichsenring, 2014). Little is known about the reasons behind patient deterioration or lack of improvement, and less still about how to help patients achieve and maintain treatment gains. The panel believes that researchers should focus their efforts on outcomes as well as on the identification of moderators of treatment outcomes to identify characteristics that predict treatment failure/success. More specifically, if a given treatment protocol has been found to be efficacious, for example, in comparison to no treatment, a large portion of the sample may still have not responded fully (or at all). Testing the moderator variables associated with who does

and does not respond to a treatment is a next step in improving the ability to develop and improve treatments, although doing so will require much larger sample sizes in order to have sufficient power to test those hypotheses. Moderator variables can include a wide range of patient characteristics (e.g., sex, age, symptom severity, comorbidity, religion, physical health status), treatment-related factors (e.g., therapist competency, setting, treatment dose), and person-centered outcomes (e.g., treatment preferences, treatment cost and accessibility). Also, it will be important for the field to consider developing innovative ways to match patients with treatments. Last, studies should examine the efficacy of a step-wise approach like switching patients from medication to types of psychotherapies (or vice versa) in cases of treatment failure (see Rush et al., 2006, for preliminary evidence). Ultimately, the goal of such research is to better understand how to make the treatment more effective for all persons or to better understand for which individuals the treatment is not recommended.

Funding Needs

Given the complexity and large amount of resources required to conduct scientifically valid randomized clinical trials (Barber, 2009; Nezu & Nezu, 2008), it is understandable that available high-quality research is limited. Funding is highly competitive and thus available to a relatively small number of investigators. To address the many questions raised in this document, it will require more investment in complex and expensive research across many investigative teams. In particular, key questions of moderators and mediators of treatment response require much larger sample sizes than are typical of current psychotherapy research studies.

Conclusion

Overall these limitations require caution and conservative recommendations given the gaps in the depression intervention literature. Thus, while the panel makes recommendations based on following the IOM (2011a) criteria for rigorous guideline development, the panel is aware of the limits of its assessment and scope of its recommendations. The field is strongly urged to address significant issues related to study design and standardization of methodology (e.g., consistent inclusion of racially diverse populations, and consistency in defining treatments and measurement of outcomes). Further the field is encouraged to generate additional research and reviews on humanistic therapies, emotion-focused therapy, and different treatment modalities. Altogether, the current guideline makes an important contribution to the field and complements existing knowledge by addressing treatment of depression from childhood through older adulthood, including an examination of psychotherapeutic interventions. Moreover, this guideline was developed following the IOM (2011a) standards for trustworthy guideline development. Finally, this guideline is an outgrowth of APA's evidence-based practice policy and is predicated on the three domains noted in earlier work by both the IOM (2011a & 2011b) and APA (2006) integrating the best available research; practitioner expertise; and patient culture, values and preferences.

Conflicts of Interest

Prior to final appointment to the panel, candidates completed a conflict of interest (COI) form that was then reviewed by the advisory steering committee or APA staff to ensure there were no identified conflicts that would prohibit participation, with the understanding that some "adversarial conflict" representing different points of views was to be expected and encouraged in this process. While intellectual affiliations were expected, no panel members had been singularly identified with particular approaches to intervention nor had significant known financial conflicts. Once the panel was formed, all panel members completed an educational module on conflicts of interest that underscored the importance of identifying and managing any potential conflicts, both financial and intellectual. The APA conflicts of interest policy and disclosure form are included in the appendix.

All panel members and staff affiliated with development of the depression clinical practice guideline updated their conflicts of interest form on an annual basis and were asked to provide more timely updates if changes in their disclosures were perceived to be relevant to the development of the guideline. All were asked to disclose all potential conflicts of interest with the understanding that these would be reviewed and evaluated, and a decision would be made regarding how to manage identified conflicts. Conflicts of interest included not only possibilities for financial or professional gain, but also strong intellectual viewpoints that might then limit someone from objectively reviewing the evidence. Emphasis was placed on disclosing all potential conflicts and allowing the staff and chair (or other appropriate entity in the case of the chair) to review the disclosures and determine whether or not such information could reasonably be construed as to be a source of possible influence on the guideline development process. Furthermore, on first joining the initiative and at the initial face-to-face meeting, panel members were asked to verbalize their conflicts, so all present would be familiar with the diversity of

perspectives and range of possible influences. This practice continued at subsequent face-to-face meetings.

All authors were required to disclose their intellectual interests, financial and professional interests, interests related to APA, and other relevant interests. They were also required to disclose interests of family members, defined as “a spouse, domestic partner, parent, child, or other relative with whom [they] have a comparably close tie.” Authors were asked to disclose the following potential conflicts of interest: scientific/educational/professional communications, communications to a general audience, roles at APA or other organizations, relevant honoraria, endorsements, research funding or royalties, payment for services or training, and serving as expert witnesses. None of the reported potential conflicts of interest precluded a nominated candidate from serving on the guideline development panel. Excluding all guideline development panel candidates with any potential conflicts of interest risks excluding the level and type of expertise needed to fully evaluate treatment benefits and risks. The most knowledgeable individuals can be conflicted because of expertise in their areas of interest, and they may possess both financial and intellectual conflicts of interest from participating in research and serving as consultants to industry. However, these experts may possess unique insight into appropriate health care needs and recommendations.

There is growing recognition that financial relations to the pharmaceutical industry threaten the integrity of research and of clinical practice guidelines. However, the issue is still contentious, and exclusion of all potential guideline development panel members with such conflicts may itself be seen as biased against pharmacological treatments or particular medical specialties. Similarly, experts with respect to psychotherapy tend to have intellectual passions for specific types of psychosocial interventions that also constitute potential conflicts. Yet, such individuals may be difficult to replace because of their unique insights, as well as their status in the eyes of key stakeholders (IOM, 2011b). Hence, rather than exclude topic experts and risk

minimizing expertise, APA follows the principle of adversarial collaboration in which competing interests are balanced on panels and committees, rather than avoided. This approach is also used by other leading developer of clinical practice guidelines, such as the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines (American College of Cardiology Foundation & American Heart Association, 2010; IOM, 2011b).

Conflict of interest forms for all authors are available by request for public review.

Author Disclosures

The Clinical Practice Guideline Development Panel reported the following disclosures during the development and approval of this guideline. The following points, drawn from panelists' disclosures, were among the information noted in assessing and managing potential financial and intellectual conflicts of interest.

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Michael “Misha” Kessler is a published and award-winning advocate and public speaker, social entrepreneur, and software developer. His personal experiences with mental health challenges as a young adult became the foundation of his career, motivating him to find creative solutions to pressing issues in the mental health space, uniting principles of consumer autonomy and user-oriented design. Mr. Kessler founded Remedient, a digital marketing and design firm for mental health professionals, which aims to create greater digital accessibility for consumers; Seven Summits for Suicide Prevention, a biennial mountain climbing charity and fundraiser, which donates 100% of proceeds to small budget suicide prevention nonprofits; and Crisis International, a global resource directory and knowledge base for suicide intervention and postvention needs.

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Forrest Scogin, Jr., PhD, is a clinical psychologist and a professor in the Department of Psychology at the University of Alabama. He formerly directed a Graduate Psychology Education grant from the Health Resources and Service Administration's Bureau of Health Professions that developed interdisciplinary training and proactive models for the provision of psychological services to underserved populations in primary care clinics.

Conflict of interest forms for all authors are available by request for public review.

Developer

American Psychological Association–Depression Guideline Development Panel. The Depression Guideline Development Panel is a multidisciplinary Panel of experts.

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