THE UNIVERSITY OF ARIZONA | MEL AND ENID ZUCKERMAN COLLEGE OF PUBLIC HEALTH

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Medical Marijuana for the Treatment of Depression:
An Evidence Review

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Introduction

Purpose of the Evidence Review

This review evaluates evidence on cannabis use in adults for the treatment of depression. The Arizona Department of Health Services (ADHS), funded this report to assist in assessing depression as a condition to add to those that qualify for the use of medical marijuana in Arizona.

Background

Pursuant to A.R.S. § 36-2801.01, the public may petition the Arizona Department of Health Services (ADHS) to add debilitating medical conditions to those listed in A.R.S. 36-2801(3). The ADHS established the manner in which it shall consider petitions to add debilitating medical conditions in A.A.C. R9-17-106. A.A.C. R9-17-106(C) states, ADHS "shall accept requests for the addition of a medical condition to the list of debilitating medical conditions in R9-17-201 in January and July of each calendar year starting in January 2012". After receiving requests for adding conditions the ADHS requests a report on the scientific evidence on the use of cannabis for this condition from the University of Arizona College of Public Health. In addition the Department holds a public hearing to hear public testimony on the condition and its treatment with cannabis. The Department Medical Advisory Committee then considers the totality of the evidence in deciding to add a condition to the list, or not.

Scope of the Evidence Review

List of Key Questions

1. What evidence describes the benefits (including long-term benefits) of cannabis use for patients with depressive disorder? Is there evidence for the treatment of depression with medicinal marijuana or cannabis?
2. What are the approved recommended treatments for depression?
3. What is the relationship between marijuana use and depression?

Conflicts of Interest

The reviewers had no conflicts of interest to disclose.

Methods

Literature Search and Strategy

The topics of cannabis use and depression where searched in the following databases: The Cochrane Library, Ovid and PubMed MEDLINE®, Web of Science, Google Scholar, and PsycINFO. Bibliographies in the articles identified through these databases were hand searched for additional pertinent articles. A detailed description of the search terms can be found in Appendix 1.

Inclusion and Exclusion Criteria

Studies that met all of the following criteria were included:

1. Evaluated adults (≥ 18 years old) with depression
2. English language
3. Human study
4. Were relevant to one of the key questions

Studies that were excluded include those that were:

1. Animal studies
2. Editorials or opinions
3. Descriptions of biochemical and pathophysiological pathways
4. Not relevant to the key questions

The original intent was to restrict the search to clinical trials, cohort and case control studies. Due to the paucity of studies of this type found, we also included cross sectional studies and case reports.

Dates of Search

March 2012 to June 2012

Quality Assessment

Types of studies available to assess are listed and described in Appendix 2.
Observational studies were assessd using the main domains described in tools commonly used (Deeks JJ, Dinnes J, D'Amico R, Sowden AJ, Sakarovitch C, Song F, et al. Evaluating non-randomized intervention studies. Health Technology Assessment 2003;**7**(27)). The overall quality of the evidence is ranked using GRADE methodology demonstrated in Appendix 3. (Owens DK, Lohr KN, Atkins D, et al. Grading the strength of a body of evidence when comparing medical interventions. In: Agency for Healthcare Research and Quality. Methods Guide for Comparative Effectiveness Reviews. Rockville, MD. Available at: http://effectivehealthcare.ahrq.gov/healthInfo.cfm?infotype=rr&ProcessID=60.)

Results

The search resulted in a total of 155 articles between all databases. Out the 155 only 20 articles and 2 systematic reviews appeared to be relevant to the key questions. Out of the 20 articles, 9 did not meet the inclusion criteria or did not provide answers to our key questions. Each included article (total of 11) is summarized in Table 1. Systematic reviews (total of 2) are summarized in Table 2. The 9 reviewed and excluded articles are listed in Table 3.

There were a total of 11 articles that met the inclusion criteria. One was a series of case reports , two were cohort studies, 7 were cross sectional studies and one was a clinical trial of poor design.

Table 1
Articles Included in the Review

Author, Year, Title	***Description and Design of Study***	***Findings***	***Quality***
1. Denson, TF and Earleywine M. ; Decreased depression in marijuana users. Addictive Behaviors 2006;31:738-742.	Cross-Sectional Study. United States Participants solicited on internet from "drug policy organizations". Comparison via survey of 4494 people who either used either used marijuana daily (n=3323) or 1x/wk (n=861) with a control group (never used, n=310).	Users who consumed daily or occasionally had lower levels of depressive symptoms than those who never tried marijuana. Non-users had more depression than moderate users, ψ=3.2, p=.003 and heavy users ψ = 2.9, p<.001.	**Very Low Quality.** Study limitations include heavy selection bias, recall bias of participants, , and no control for confounders. It is a series of single variable analyses.
2. Gruber AJ, Pope HG, Brown M. ; Do Patients Use Marijuana As An Antidepressant? Depression 1996;4:77-80.	Case Series Review. Boston. Authors reviewed literature and presented 5 cases where they felt there was evidence of marijuana producing an antidepressant effect.	The five cases presented were of individuals ages 16 to 28, most of them with a college education. 5 cases, ages 16-28 that report anti depressant effects of marijuana. Soome used marijuana before onset of depression, some after. Most had co morbidities.	**Very Low Quality.** Article published in 1996 and is typically referenced in many updated systematic reviews on the topic.
3. Kotin J, Post RM, Goodwin FK, Δ^9 Tetrahydrocannabinol in depressed patients	Non randomized controlled clinical trial THC was given under double blind conditions to 8 depressed patients for a week and the outcomes were observed. Conducted at	Four patients showed little change in mood and reported drowsiness. Remaining four experienced adverse reactions and discontinued the intervention.	**Low Quality.** Study had a very small sample size. Inconsistency in administration of THC was noted. Duration of trial considered too short to document typical

	the NIH in Bethesda		antidepressant behavior.
4. Bovasso GB. Cannabis Use as a Risk Factor for Depressive Symptoms. American Journal of Psychiatry 2001;158:2033-2037.	**Longitudinal cohort, prospective.** **Participants (N=1,920) in the 1980 Baltimore Epidemiologic Catchment Area (ECA) study who were reassessed between 1994 and 1996 as part of a follow- up study.. The analysis focused on three groups: those who reported no depressive symptoms at baseline (N=849) and those with no diagnosis of cannabis abuse at baseline (N=1,837) vs those reporting baseline cannabis use (n=83).**	**Subjects with no history of depression but had a history of cannabis use at baseline were 4x more likely to develop depressive symptoms. Subjects with no history of cannabis use at baseline but had a history of depression did not develop cannabis abuse in the future.**	**Low to Moderate Quality.** **Depression symptomology and cannabis abuse is self reported. Imprecision is a problem as the odds ratios are found to have wide confidence Intervals. There is a large loss to follow up. Only 1920 of the original 3481 participated in the follow up. 848 had died. The study did control for multiple potential confounders.**
5. Chen CY, Wagner FA, Anthony JC. Marijuana use and the risk of major depressive episode (MDE) Epidemiological evidence from the United States National Comorbidity Survey. Social Psychiatry and Psychiatric Epidemiology 2002;37:199-206	**Cross-Sectional l Study.** **Data from 6,792 participants (15-45 yrs old) from the National Co morbidity Survey in the U.S. was analyzed.**	**The risk of first MDE was moderately associated with the number of occasions of marijuana use and with more advanced stages of marijuana use. The odds ratio was 1.6.**	**Low to Moderate Quality** **While the sample size was large and some possible confounders were controlled for, the cross sectional design is subject to recall bias from survey participants And the behaviors are self-reported .. Confounders identified: onset of marijuana use, frequency use, and social factors (unemployment status, marriage status, etc). Upgraded from very low to low-to moderate.**
6. Degenhardt L, Hall W, Lynskey M. . The relationship between cannabis use, depression and anxiety among Australian adults: findings from the National Survey of Mental Health and Well-Being. Social Psychiatry and Psychiatric Epidemiology 2001;36:219-227.	Cross-Sectional Study. Data from the Australian National Survey of Mental Health and Well-Being was analyzed (N=10,641).	There was a moderate association between cannabis use in the past 12 months and the prevalence of affective and anxiety disorders. Cannabis use did not appear to be directly related to depression or anxiety when other drug use was considered as contributing factors.	**Low to Moderate quality** A large representative sample from Australia. Major potential confounders were controlled for. Large potential for recall bias from survey participants. Self-reported behaviors. Study did not directly measure depression but a plethora of other emotional health conditions. Upgraded from very low to

			low-to - moderate.
7. Fairman BJ, Anthony JC. Are early-onset cannabis smokers at an increased risk of depression spells? Journal of Affective Disorders 2012; 138-54-62.	**Cross-Sectional Study.** **The National Surveys on Drug Use and Health (NSDUH) was used and included 173,755 participants in a 4 year time frame.**	**Cannabis smoking initiated at any age signals a modest increased risk of a spell of depression in adulthood, even when adjusted for confounding variables. Delaying cannabis onset until adulthood does not appear to diminish the cannabis- associated risk. Odds ratios were 1.7 and 1.8.**	**Low to Moderate Quality.** **Self-reported (recall) bias present. Large sample size. Potential confounding variables from other comorbid conditions or habits (tobacco smoking) were controlled for. Upgraded from very low to low-to - moderate.**
8. Harder VS, Morral AR, Arkes J. Marijuana use and depression among adults: testing for causal associations. Addiction 2006;101:1463-1472.	**Longitudinal Cohort** **Study compared differences between users and non-users of marijuana. The data used came from the U.S. National Longitudinal Survey of Youth of 1979. The survey was re-administered every year between 1979 and 1994. The number of participants was 12,686 in 1979 and 8759 in 1994. 50 potential confounders controlled for.**	**Past-year marijuana use does not significantly predict later development of depression when other variable controlled for. The associations observed between marijuana use and depression status may be caused not by continued marijuana use, but by other factors associated with both the decision to use marijuana and to depression.**	**Moderate to High Quality.** **Large sample size. Confounding variables were controlled for. Sophisticated analysis. It is unclear what years are being studied. It appears that only those responding in 1994 were studied. Limitations identified were:** **- Current treatment of depression not considered in analysis.** **- Self-reported status instrument (recall bias)** -
9. Lynskey MT Glowinsi AL, Todorov AA, et al.. Major depressive disorder (MDD), suicidal ideation, and suicide attempt in twins discordant for cannabis dependence and early-onset cannabis use. Archives of General Psychiatry 2004;61:1026-1032.	Cross-Sectional Study. A cross-sectional survey of 588 twin pairs over the age of 17 was conducted in Australia..	Individuals who were cannabis dependent had odds of suicidal ideation and suicide attempt that were 2.5 to 2.9 times higher than those of their non–cannabis dependent co-twin. Additionally, cannabis dependence was associated with elevated risks of MDD in dizygotic but not in monozygotic twins. Those who initiated cannabis use before age 17 years had elevated rates of subsequent suicide attempt (odds ratio, 3.5 [95% confidence	**Very Low Quality** Selection bias present. Possible confounders were not considered in data analysis. Article referenced in many systematic reviews.

		interval, 1.4-8.6]) but not of MDD or suicidal ideation. Early MDD and suicidal ideation were significantly associated with subsequent risks of cannabis dependence in discordant dizygotic pairs but not in discordant monozygotic pairs.	
10. Green BE,Ritter C. Marijuana Use and Depression.Journal of Health and Social Behavior 2000;41:40-49.	Cross-Sectional Study. Data from the 1985 Young Men and Drugs Survey was used. N=1,941 men. National representative sample n U.S.	Results show that early onset (in adolescent years) of marijuana use is weakly associated with increased depression in adulthood. Adult frequency of marijuana use is not significantly associated with increased depression. Participants who indicate using marijuana to cope with issue are more depressed than those who do not use it for coping.	**Low Quality** Sample size is large and is representative of men. Women are not part of the Large potential for recall bias. Few potential confounders controlled for.
11. Musty RE, Kaback L. Relationships between motivation and depression in chronic marijuana users. Life Sciences 1995; 56:2151-2158.	Cross Sectional Study. Survey disseminated to university students, which measured substance use behaviors, depression symptomology, motivation, (N=70). Chronic users (with and without depression) were compared with light users (with and without depression).	Both light and heavy users with symptoms of depression had significantly lower scores in items pertaining to motivation and sense of purpose compared to those without depressive symptoms. Study concludes that amotivational symptoms observed in heavy marijuana users in treatment are due to depression.	**Very Low Quality.** Sampling bias. Self-reported data (recall bias). Very small sample size. No potential confounders controlled for. Very low number of references and short descriptions of methodology.

Systematic Reviews

Only two systematic reviews were found that directly attempted to explore the association specifically between depression and marijuana use. Both reviews were of low quality. They did not assess the quality of the studies found or use any system to rank the overall quality of the evidence.

Table 2
Systematic Reviews Included in the Review

Author, Year, Title	***Description***	***Findings***	***Quality***
1. Degenhardt L, Hall W, Lynskey M.. Exploring the association between cannabis use and depression. Addiction 2003;98;1493-1504.	Systematic review aimed at exploring the evidence on the association between cannabis use and depression.	A number of studies found a modest association between early-onset, regular cannabis use and later depression, which persisted after controlling for potential confounding variables. There was little evidence of an increased risk of later cannabis use among people with depression. They found a moderate association between heavy cannabis use and depression in cohort studies and cross-sectional studies in the general population. However, little evidence was found for an association between depression and light cannabis use. There have been a limited number of studies that have controlled for potential confounding variables in the association between heavy cannabis use and depression. These have found that the risk is much reduced by statistical control but a modest relationship remains. Heavy cannabis use and depression are associated and evidence from longitudinal studies suggests that heavy cannabis use may increase depressive symptoms among some users.	**Low quality** The search strategy and inclusion criteria were described but the articles were not systematically assessed for quality and no formal system of rating the overall quality of the evidence on each question was used.
2. Crippa JAS, Zuardi AW, & Hallak JEC. Theurapeutical use of the cannabinoids in psychiatry. Revista Brasileira de Psiquiatria • vol 32• Suppl I • may2010 • **S56-65**	The review – conducted in Brazil – reviewed the main advances related to the potential therapeutic use of cannabinoid compounds in psychiatry.	Cannabidiol compound was found to have therapeutic potential with antipsychotic, anxiolytic, and antidepressant properties. Further human control trials are necessary to confirm the findings.	**Very Low Quality** Review consisted of a search only in the PubMed, ScieELO, and Lilacs databases. Review focused primarily on animal study results. No inclusion criteria described, no system of assessing individual studies or rating the overall quality of the

			evidence. The review may not apply to our question since it focused much of its review on the active compound found in Sativa®.

Table 3 lists the remaining articles that were excluded from the analysis after review for failure address the key questions.

Table 3
Articles Reviewed but Excluded

Author, Year, Title	***Content***	***Reason Not Used***
1. Moore T, Zammit S, Lingfor-Hughes A, Barnes T, Jones P, Burke M, Lewis G. Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. The Lancet. 2007(370): 319-328.	The systematic review analyzed the evidence pertaining to cannabis use and occurrence of psychotic or affective mental health outcomes.	Did not fully include depression in its review. Greater focused on anxiety and psychotic conditions.
2. Gruber AJ, Pope HG, Brown M. Do Patients Use Marijuana As An Antidepressant? Depression 1996;4:77-80.	Reviews the evidence from RCTs for pharmacologic and psychological approaches to the treatment of cannabis use among individuals with psychotic or depressive disorders.	Does not address a key question.
3. Robson P. Therapeutic aspects of cannabis and cannabinoids. The British Journal of Psychology. 2001;178:107-115.	Review of the evidence to assess the therapeutic profile of cannabis and cannabinoids.	Content does not address the questions. Focus is primarily on anxiety, pain treatment, and analgesics effects of cannabis.
4. Ware MA, Adams H, Guy GW. The medicinal use of cannabis in the UK: Results of a nationwide survey. Int J Clin Pract. 2005;59(3):291-295.	Cross Sectional l Study. Report on the results of a self-administered questionnaire study conducted in the United Kingdom between 1998 and 2002. N=2969. Documented medicinal use of cannabis by patients with chronic pain, multiple sclerosis and depression, arthritis and neuropathy.	Article does not address the question.. Only use patterns are documented,
5. Zammit S, Moore T, Lingford-Hughes A, Barnes T, Jones P, Lewis G. Effects of cannabis use on outcomes of psychotic disorders: a systematic review. British Journal of Psychology. 2008;193:357-363.	The article is a systematic review of the evidence pertaining to whether cannabis affects outcome of psychotic disorders.	Article does not address depression.
6. Degenhardt L, Tennant C, Gilmour S, Schofield D, Nash L, Hall W, & McKay D. The temporal dynamics of relationships between cannabis, psychosis and depression among young adults with psychotic	The aim of the study was to examine the temporal relationships over 10 months between cannabis use and symptoms of psychosis and depression in people with schizophrenia and related disorders.	Article did not fully address depression. The association between marijuana and depression is not clearly stated nor is it a major focus within the article. Does not

disorders: findings from a 10-month prospective study. Psychological Medicine. 2007;37:927-934.	N=101. The study discovered that cannabis use predicted a small but statistically significant increase in symptoms of psychosis, but not depression, after controlling for other differences between cannabis users and non-users. Symptoms of depression and psychosis did not predict cannabis use.	address a key question.
7. . Milani R, Parrot A, Turner J, Fox H. Gender differences in self-reported anxiety, depression, and somatization among ecstasy/MDMA polydrug users, alcohol/tobacco users, and nondrug users. Addictive Behaviros. 2004(29);965-971.	Cross-Sectional Study. The present investigation (N=768) explores gender variability in patterns of drug use in relation to self-reported depression, anxiety, and somatization. The study discovered that heavy illegal drug users are represented by a preponderance of males than females.	Does not answer key questions. Small communication format of article does not provide much detail.
8. Moreira, F, Grieb M, & Lutz B. Central side-effects of therapies based on CB1 cannabinoid receptor agonists and antagonists: focus on anxiety and depression. Best Practices and Research Clinical Endocronology and Metabolism. 2009(23);133-144.	A review of current therapies biopharmaceutical focus.	Article does not answer key questions. Review is on the therapeutic use of synthesized THC not medical marijuana.
9. Vlahov D, Galea S, Ahern J, Resnick H, Boscarino J, Gold J, Bucuvalas, M & Kilpatrick D. Consumption of Cigarettes, Alcohol, and Marijuana Among New York City Residents Six Months After the September 11 Terrorist Attacks. The American Journal of Drug and Alcohol Abuse. 2004(30);2:385-407.	Phone interview surveys of residents in New York City 6 to 9 months post 9/11 events. Interview asked consumption behavior questions. Study discovered that prevalence of PTSD and Depression in a segment of the population was declining over time while substance use was increasing.	Does not address key questions.

Conclusion

There is insufficient evidence to answer any of the key questions. There is no credible evidence regarding the effectiveness, or harms of marijuana for the treatment of depression. There may be an association between marijuana use and depression but it is not know if one causes the other or if both are linked to some unknown third factor. The one clinical trial found was so poorly designed that it provides no useful information. No other studies addressed the use of marijuana to treat depression. There appears to be a correlation between marijuana use and depression although the strength of this association is low to modest and it is not possible to tell if one causes the other if both are related to other variables.

Major Recommendations for the Effective Treatment of Depression

The National Guideline Clearinghouse was searched for guidelines on the treatment of depression. The most recent and pertinent guideline found was by the American Psychiatric Association (APA).

Practice guideline for the treatment of patients with major depressive disorder. 3rd ed. Arlington (VA): American Psychiatric Association (APA);
2010 http://guideline.gov/content.aspx?id=24158&search=depression+and+major+depression+disorder

The guideline is attached as appendix 5.

Appendix 1: Search Terms

Initial Terms used

1. cannabis
2. depression
3. tetrahydrocannabinol

Mesh Terms

Marijuana Smoking

- Smoking, Marijuana
- Marihuana Smoking
- Smoking, Marihuana
- **Cannabis Smoking**
- Smoking, Cannabis
- Hashish Smoking
- Smoking, Hashish

Mesh Terms

Cannabis

Entry Terms:

- Cannabi
- Hemp Plant
- Hemp Plants
- Plant, Hemp
- Plants, Hemp
- Cannabis indica
- Cannabis indicas
- indica, Cannabis
- indicas, Cannabis
- Marihuana
- Marihuanas
- Marijuana
- Marijuanas
- Ganja
- Ganjas
- Hashish
- Hashishs
- Hemp
- Hemps
- Bhang
- Bhangs
- Cannabis sativa
- Cannabis sativas
- sativa, Cannabis
- sativas, Cannabis

Mesh Terms

Depression

Entry Terms:

- Depressions
- Depressive Symptoms
- Depressive Symptom
- Symptom, Depressive
- Symptoms, Depressive
- Emotional Depression
- Depression, Emotional
- Depressions, Emotional
- Emotional Depressions

Mesh Terms
Depressive Disorder
Entry Terms
- Depression, Postpartum
- Depressive Disorder, Major
- Depressive Disorder, Treatment-Resistant
- Dysthymic Disorder
- Seasonal Affective Disorder

Appendix 2: Taxonomy of Study Designs

BOX 1 *Taxonomy of study designs to assess the effectiveness of an intervention*

Experimental designs
A study in which the investigator has control over at least some study conditions, particularly decisions concerning the allocation of participants to different intervention groups.

1. ***Randomised controlled trial***
   Participants are randomly allocated to intervention or control groups and followed up over time to assess any differences in outcome rates. Randomisation with allocation concealment ensures that on average known and unknown determinants of outcome are evenly distributed between groups.
2. ***Quasi-randomised trial***
   Participants are allocated to intervention or control groups by the investigator, but the method of allocation falls short of genuine randomisation and allocation concealment (e.g. allocated by date of birth, hospital record number, etc.)
3. ***Non-randomised trial/quasi-experimental study***
   The investigator has control over the allocation of participants to groups, but does not attempt randomisation (e.g. patient or physician preference). Differs from a 'cohort study' in that the intention is experimental rather than observational.

Observational designs
A study in which natural variation in interventions (or exposure) among study participants is investigated to explore the effect of the interventions (or exposure) on health outcomes.

4. ***Controlled before-and-after study***
   A follow-up study of participants who have received an intervention and those who have not, measuring the outcome variable both at baseline and after the intervention period, comparing either final values if the groups are comparable at baseline, or change scores. It can also be considered an experimental design if the investigator has control over, or can deliberately manipulate, the introduction of the intervention.
5. ***Concurrent cohort study***
   A follow-up study that compares outcomes between participants who have received an intervention and those who have not. Participants are studied during the same (concurrent) period either prospectively or, more commonly, retrospectively.
6. ***Historical cohort study***
   A variation on the traditional cohort study where the outcome from a new intervention is established for participants studied in one period and compared with those who did not receive the intervention in a previous period, i.e. participants are not studied concurrently.
7. ***Case–control study***
   Participants with and without a given outcome are identified (cases and controls respectively) and exposure to a given intervention(s) between the two groups compared.
8. ***Before-and-after study***
   Comparison of outcomes from study participants before and after an intervention is introduced. The before and after measurements may be made in the same participants, or in different samples. It can also be considered an experimental design if the investigator has control over, or can deliberately manipulate, the introduction of the intervention.
9. ***Cross-sectional study***
   Examination of the relationship between disease and other variables of interest as they exist in a defined population at one particular time point.
10. ***Case series***
    Description of a number of cases of an intervention and outcome (no comparison with a control group).

Appendix 3: GRADE Method

Study Design	Quality of Evidence	Lower if	Higher if
Randomized trial →	High	Risk of bias -1 Serious -2 Very serious	Large effect +1 Large +2 Very large
	Moderate	Inconsistency -1 Serious -2 Very serious	Dose response +1 Evidence of a gradient
Observational study →	Low	Indirectness -1 Serious -2 Very serious	All plausible confounding +1 Would reduce a demonstrated effect or +1 Would suggest a spurious effect when results show no effect
	Very low	Imprecision -1 Serious -2 Very serious Publication bias -1 Likely -2 Very likely	

Owens DK, Lohr KN, Atkins D, et al. Grading the strength of a body of evidence when comparing medical interventions. In: Agency for Healthcare Research and Quality. Methods Guide for Comparative Effectiveness Reviews. Rockville, MD. Available at: http://effectivehealthcare.ahrq.gov/healthInfo.cfm?infotype=rr&ProcessID=60.

Appendix 4: Articles Found in the Search

1

1. Abel EL. Retrieval of information after use of marihuana. *Nature*. 1971;231(5297):58.
2. Ablon SL, Goodwin FK. High frequency of dysphoric reactions to tetrahydrocannabinol among depressed patients. *Am J Psychiatry*. 1974;131(4):448-453.
3. Amtmann D, Weydt P, Johnson KL, Jensen MP, Carter GT. Survey of cannabis use in patients with amyotrophic lateral sclerosis. *Am J Hosp Palliat Care*. 2004;21(2):95-104.
4. Arendt M, Munk-Jorgensen P. Heavy cannabis users seeking treatment- prevalence of psychiatric disorders. *Soc Psychiatry Psychiatr Epidemiol*. 2004;39(2):97-105. doi: 10.1007/s00127-004-0719-7.
5. Ayd FJ,Jr. Doxepin with other drugs. *South Med J*. 1973;66(4):465-471.
6. Baker A, Hides L, Lubman D.Treatment of Cannabus Use Among People With Psychotic or Depressive Disorders: A Systematic Review. *Journal of Clinical Psychiatry*. 2010;71(3):247-254.
7. Barnett G, Chiang CW, Licko V. Effects of marijuana on testosterone in male subjects. *J Theor Biol*. 1983;104(4):685-692.
8. Bellville JW, Gasser JC, Miyake T, Aqleh K. Tolerance to the respiratory effects of marijuana in man. *J Pharmacol Exp Ther*. 1976;197(2):326-331.
9. Bellville JW, Swanson GD, Aqleh KA. Respiratory effects of delta-9-tetrahydrocannabinol. *Clin Pharmacol Ther*. 1975;17(5):541-548.
10. Benowitz NL, Jones RT, Lerner CB. Depression of growth hormone and cortisol response to insulin-induced hypoglycemia after prolonged oral delta-9-tetrahydrocannabinol administration in man. *J Clin Endocrinol Metab*. 1976;42(5):938-941.
11. Blevins RD, Regan JD. Delta-9-tetrahydrocannabinol: Effect on macromolecular synthesis in human and other mammalian cells. *Arch Toxicol*. 1976;35(2):127-135.
12. Bourne PG. The viet nam veteran: Psychosocial casualties. *Psychiatry Med*. 1972;3(1):23-27.
13. Bovasso GB. Cannabis Use As A Risk Factor for Depressive Symptoms. *American Jorunal of Psychiatry*. 2001;158:2033-2037.
14. Boyd P. Problems and treatment of drug abuse in adolescence. *Proc R Soc Med*. 1975;68(9):566-570.
15. Brill NQ, Crumpton E, Grayson HM. Personality factors in marihuana use: A preliminary report. *Arch Gen Psychiatry*. 1971;24(2):163-165.
16. Burke EL, Eichberg RH. Personality characteristics of adolescent users of dangerous drugs as indicated by the minnesota multiphasic personality inventory. *J Nerv Ment Dis*. 1972;154(4):291-301.
17. Campbell I. The amotivational syndrome and cannabis use with emphasis on the canadian scene. *Ann N Y Acad Sci*. 1976;282:33-36.
18. Carlini EA, Santos M, Claussen U, Bieniek D, Korte F. Structure activity relationship of four tetrahydrocannabinols and the pharmacological activity of five semi-purified extracts of cannabis sativa. *Psychopharmacologia*. 1970;18(1):82-93.
19. Carlson ET. Cannabis indica in 19th-century psychiatry. *Am J Psychiatry*. 1974;131(9):1004-1007.
20. Chen CY, Wagener FA, Anthony JC. Marijauana use and the risk of major depressive epidose (MDE): epidemiological evidence from the United States National Comorbdity Survey. *Social Psychiatry and Psychiatric.* 2002;37:199-206.
21. Cherek DR, Thompson T. Effects of delta1-tetrahydrocannabinol on schedule-induced aggression in pigeons. *Pharmacol Biochem Behav*. 1973;1(5):493-500.
22. Cohen S. Marijuana. does it have a possible therapeutic use?. *JAMA*. 1978;240(16):1761-1763.
23. Cohen S. Therapeutic aspects. *NIDA Res Monogr*. 1977;(14)(14):194-225.
24. Comitas L. Cannabis and work in jamaica: A refutation of the amotivational syndrome. *Ann N Y Acad Sci*. 1976;282:24-32.
25. Connor JP, Gullo MJ, Feeney GF, Young RM. Validation of the cannabis expectancy questionnaire (CEQ) in adult cannabis users in treatment. *Drug Alcohol Depend*. 2011;115(3):167-174. doi: 10.1016/j.drugalcdep.2010.10.025.
26. Cornelius JR, Aizenstein HJ, Hariri AR. Amygdala reactivity is inversely related to level of cannabis use in individuals with comorbid cannabis dependence and major depression. *Addict Behav*. 2010;35(6):644-646. doi:

10.1016/j.addbeh.2010.02.004.
27. Crippa JAS, Zuardi AW, Hallak JEC. Theurapeutical use of the cannabinoids in psychiatry. *Revista Brasileira de Psiquiatria.* 2010(32);1:S56-65.
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NGC banner

Guideline Summary NGC-8093

Guideline Title

Practice guideline for the treatment of patients with major depressive disorder, third edition.

Bibliographic Source(s)

American Psychiatric Association (APA). Practice guideline for the treatment of patients with major depressive disorder. 3rd ed. Arlington (VA): American Psychiatric Association (APA); 2010 Oct. 152 p. [1170 references]

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: American Psychiatric Association practice guideline for the treatment of patients with major depressive disorder. Am J Psychiatry 2000 Apr;157(4 Suppl):1-45. [325 references]

FDA Warning/Regulatory Alert

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- March 28, 2012 – Celexa (citalopram hydrobromide) : The U.S. Food and Drug Administration (FDA) is clarifying dosing and warning recommendations for the antidepressant Celexa (citalopram hydrobromide; also available in generic form). In August 2011, FDA issued a Drug Safety Communication (DSC) stating that citalopram should no longer be used at doses greater than 40 mg per day because it could cause potentially dangerous abnormalities in the electrical activity of the heart. Citalopram use at any dose is discouraged in patients with certain conditions because of the risk of QT prolongation, but because it may be important for some of those patients to use citalopram, the drug label has been changed to describe the particular caution that needs to be taken when citalopram is used in such patients. The revised drug label also describes lower doses that should be used in patients over 60 years of age.

Scope

Disease/Condition(s)

Major depressive disorder

Guideline Category

Evaluation

Management

Treatment

Clinical Specialty

Psychiatry

Intended Users

Physicians

Guideline Objective(s)

To summarize the specific approaches to treatment of individuals with major depressive disorder

Target Population

Individuals with major depressive disorder

Interventions and Practices Considered

Evaluation/Management

1. Establishing and maintaining a therapeutic alliance
2. Psychiatric assessment
3. Safety evaluation including evaluation of suicide risk, level of self-care and dependent care, and risk or harm to self and others
4. Establishing appropriate treatment setting including hospitalization if appropriate
5. Evaluation of functional impairment and quality of life
6. Coordinating care with other clinicians, monitoring status, and tailoring treatment to specific patient needs
7. Assessment of and acknowledgment of potential barriers to treatment

8. Patient and family education

Treatment

1. Pharmacotherapy
   - Selective serotonin reuptake inhibitors (SSRI)
   - Serotonin norepinephrine reuptake inhibitors (SNRI)
   - Mirtazapine
   - Bupropion
   - Nonselective monoamine oxidase inhibitors (MAOIs)
2. Somatic therapies such as electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), vagus nerve stimulation
3. Psychotherapy
   - Cognitive-behavioral therapy (CBT)
   - Interpersonal psychotherapy
   - Psychodynamic therapy
   - Marital and family therapy
   - Problem-solving therapy in individual and in group formats
4. Combination of medications and psychotherapy
5. Complementary and alternative therapies
   - St. John's wort
   - *S*-adenosyl methionine
   - Omega-3 fatty acids
   - Folate
   - Light therapy
   - Acupuncture

Major Outcomes Considered

- Control of depressive symptoms
- Rate of remission, relapse, and recurrence of major depression
- Morbidity and mortality due to major depression
- Side effects of treatment

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Relevant updates to the literature were identified through a MEDLINE literature search for articles published since the second edition of the guideline, published in 2000. For this edition of the guideline, literature was identified through a computerized search of MEDLINE, using PubMed, for the period from January 1999 to December 2006. Using the MeSH headings depression or depressive disorder, as well as the key words major depression, major depressive disorder, neurotic depression, neurotic depressive, dysthymia, dysthymic, dysthymic disorder, endogenous depression, endogenous depressive, melancholia, melancholic, psychotic depression, atypical depression, seasonal depression, postpartum depression, postpartum depressive symptoms, unipolar depression, unipolar depressive, or pseudodementia yielded 39,157 citations. An additional 8,272 citations were identified by using the key words depression or depressive in combination with the MeSH headings affective disorders or psychotic or the key words psychosis, psychotic, catatonic, catatonia, mood disorder, mood disorders, affective disorder, or affective disorders. These citations were limited to English language articles on human treatments using the MeSH headings central nervous system stimulants, hypnotics and sedatives, anticonvulsants, tranquilizing agents, electric stimulation therapy, electroconvulsive therapy, psychotherapy, antidepressive agents, and monoamine oxidase inhibitors or the key words antidepressant, antidepressants, antidepressive, antidepressive agents, antidepressive agents, second generation, antidepressive agents tricyclic, antidepressive agents, tricyclic, fluoxetine, citalopram, escitalopram, paroxetine, sertraline, venlafaxine, duloxetine, mirtazapine, nefazodone, trazodone, imipramine, desipramine, nortriptyline, protriptyline, doxepin, trimipramine, amitriptyline, phenelzine, tranylcypromine, isocarboxazid, moclobemide, antipsychotic agents, testosterone, thyroid, tri iodothyronine, thyroxine, omega 3, *s* adenosyl methionine, *s* adenosylmethionine, St. John's wort, hypericum, selegiline, anticonvulsant, anticonvulsants, antipsychotic, antipsychotic agent, antianxiety, anti anxiety, benzodiazepine, benzodiazepines, zolpidem, sedative, sedatives, hypnotic, hypnotics, zaleplon, eszopiclone, valproate, valproic acid, divalproex, carbamazepine, oxcarbazepine, gabapentin, topiramate, lamotrigine, lithium, modafinil, methylphenidate, Adderall, amphetamine, amphetamines, dextroamphetamine, atomoxetine, electroconvulsive, vagal nerve stimulation, vagus nerve stimulation, VNS, rTMS, rapid transcranial magnetic, repetitive transcranial magnetic stimulation, magnetic stimulation, deep brain stimulation, psychotherapy, psychotherapeutic, psychotherapies, behavior therapy, behaviour therapy, cognitive therapy, cognitive behavior therapy, cognitive behavioral analysis system, cognitive behavioral therapy, cognitive

behaviour therapy, cognitive behavioural therapy, psychoanalytic, interpersonal therapy, interpersonal psychotherapy, group therapy, family therapy, marital therapy, couples therapy, psychoanalysis, psychodynamic, aversive therapy, desensitization, exposure therapy, relaxation techniques, or progressive muscle relaxation. This yielded 13,506 abstracts, which were screened for relevance with a very modest threshold for inclusion, then reviewed by the Work Group.

The Psychoanalytic Electronic Publishing database (http://www.p-e-p.org) was also searched using the terms major depression or major depressive. This search yielded 112 references. The Cochrane databases were also searched for the key word depression, and 168 meta-analyses were identified. Additional, less formal, literature searches were conducted by American Psychiatric Association (APA) staff and individual Work Group members and included references through May 2009. Sources of funding were considered when the Work Group reviewed the literature.

The broad scope of this guideline and the substantial evidence base resulted in some practical tradeoffs. One such tradeoff worth highlighting is the decision to build upon literature reviews of the first and second editions of the guideline, rather than re-do them. This decision is acknowledged to have resulted in an emphasis of study in this guideline on newer treatments, because the majority of studies about older treatments, including tricyclic antidepressants and monoamine oxidase inhibitors, were published in decades prior to 1999. Readers are advised that the reviews of this older literature are described in the previous editions of the guideline. The Work Group for this edition considered the previous editions during their evidence review, but for practical reasons, that effort is less well documented than the group's analysis of the newer literature. The treatment recommendations of this guideline, however, were developed to reflect the complete evidence base.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus (Committee)

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Evidence tables were developed that reviewed the key features of each identified study, including funding source, study design, sample sizes, subject characteristics, treatment characteristics, and treatment outcomes.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

This practice guideline was developed under the direction of the Steering Committee on Practice Guidelines. The development process is detailed in a document entitled "APA Guideline Development Process," which is available from the American Psychiatric Association (APA) Department of Quality Improvement and Psychiatric Services. Key features of this process include the following:

- A comprehensive literature review to identify all relevant randomized clinical trials as well as less rigorously designed clinical trials and case series when evidence from randomized trials was unavailable.
- Development of evidence tables that reviewed the key features of each identified study, including funding source, study design, sample sizes, subject characteristics, treatment characteristics, and treatment outcomes.
- Initial drafting of the guideline by a work group ("Work Group") that included psychiatrists with clinical and research expertise in major depressive disorder.
- Production of multiple revised drafts with widespread review; 15 organizations and 71 individuals submitted comments.
- Review of the final draft by an Independent Review Panel of experts with no relationships with industry, who were charged to evaluate the guideline recommendations for bias from potential conflicts of interest.
- Approval by the APA Assembly and Board of Trustees.
- Planned revisions at regular intervals.

This document represents a synthesis of current scientific knowledge and rational clinical practice regarding the treatment of patients with major depressive disorder. It strives to be as free as possible of bias toward any theoretical approach to treatment. In order for the reader to appreciate the evidence base behind the guideline recommendations and the weight that should be given to each recommendation, the summary of treatment recommendations is keyed according to the level of confidence with which each recommendation is made. Each rating of clinical confidence considers the strength of the available evidence. When evidence from randomized controlled trials and meta-analyses is limited, the level of confidence may also incorporate other clinical trials and case reports as well as clinical consensus with regard to a particular clinical decision. In the listing of cited references, each reference is followed by a letter code in brackets that indicates the nature of the supporting evidence.

Rating Scheme for the Strength of the Recommendations

Each recommendation is identified as falling into one of three categories of endorsement, indicated by a bracketed Roman numeral following the statement. The three categories represent varying levels of clinical confidence:

[**I**] Recommended with substantial clinical confidence.

[**II**] Recommended with moderate clinical confidence.

[**III**] May be recommended on the basis of individual circumstances.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

Iterative guideline drafts were broadly circulated to and reviewed by the Steering Committee, other experts, allied organizations, and the American Psychiatric Association (APA) membership; reviewers were asked to disclose their own potential conflicts of interest relevant to evaluating their comments. Over 1,000 comments were received and were addressed by substantive revisions by the Work Group. Oversight of the draft review and revision process was provided by the chair and vice-chair of the Steering Committee and by the Medical Editor, none of whom had relationships with industry.

In response to a 2009 report by the Institute of Medicine, which advocated that professional organizations that develop and disseminate practice guidelines should adopt a new policy that members of guideline work groups have no significant relationships with industry, the following process was implemented: An independent review panel of experts ("Independent Review Panel") having no current relationships with industry also reviewed the guideline and was charged with identifying any possible bias. The Independent Review Panel found no evidence of bias.

This practice guideline was approved in May 2010 and published in October 2010.

Recommendations

Major Recommendations

Each recommendation is identified as falling into one of three categories of endorsement, indicated by a bracketed Roman numeral following the statement. Definitions of the categories of endorsement are provided at the end of the "Major Recommendations" field.

Psychiatric Management

Psychiatric management consists of a broad array of interventions and activities that psychiatrists should initiate and continue to provide to patients with major depressive disorder through all phases of treatment [**I**].

Establish and Maintain a Therapeutic Alliance

In establishing and maintaining a therapeutic alliance, it is important to collaborate with the patient in decision making and attend to the patient's preferences and concerns about treatment [**I**]. Management of the therapeutic alliance should include awareness of transference and counter-transference issues, even if these are not directly addressed in treatment [**II**]. Severe or persistent problems of poor alliance or nonadherence to treatment may be caused by the depressive symptoms themselves or may represent psychological conflicts or psychopathology for which psychotherapy should be considered [**II**].

Complete the Psychiatric Assessment

Patients should receive a thorough diagnostic assessment in order to establish the diagnosis of major depressive disorder, identify other psychiatric or general medical conditions that may require attention, and develop a comprehensive plan for treatment [**I**]. This evaluation generally includes a history of the present illness and current symptoms; a psychiatric history, including identification of past symptoms of mania, hypomania, or mixed episodes and responses to previous treatments; a general medical history; a personal history including information about psychological development and responses to life transitions and major life events; a social, occupational, and family history (including mood disorders and suicide); review of the patient's prescribed and over-the-counter medications; a review of systems; a mental status examination; a physical examination; and appropriate diagnostic tests as indicated to rule out possible general medical causes of depressive symptoms [**I**]. Assessment of substance use should evaluate past and current use of illicit drugs and other substances that may trigger or exacerbate depressive symptoms [**I**].

Evaluate the Safety of the Patient

A careful and ongoing evaluation of suicide risk is necessary for all patients with major depressive disorder [**I**]. Such an assessment includes specific inquiry about suicidal thoughts, intent, plans, means, and behaviors; identification of specific psychiatric symptoms (e.g., psychosis, severe anxiety, substance use) or general medical conditions that may increase the likelihood of acting on suicidal ideas; assessment of past and, particularly, recent suicidal behavior; delineation of current stressors and potential protective factors (e.g., positive reasons for living, strong social support); and identification of any family history of suicide or mental illness [**I**]. In addition to assessing suicide risk per se, it is important to assess the patient's level of self-care, hydration, and nutrition, each of which can be compromised by severe depressive symptoms [**I**]. As part of the assessment process, impulsivity and potential for risk to others should also be evaluated, including any history of violence or violent or homicidal ideas, plans, or intentions [**I**]. An evaluation of the impact of the depression on the patient's ability to care for dependents is an important component of the safety

evaluation [**I**]. The patient's risk of harm to him- or herself and to others should also be monitored as treatment proceeds [**I**].

Establish the Appropriate Setting for Treatment

The psychiatrist should determine the least restrictive setting for treatment that will be most likely not only to address the patient's safety, but also to promote improvement in the patient's condition [**I**]. The determination of an appropriate setting for treatment should include consideration of the patient's symptom severity, co-occurring psychiatric or general medical conditions, available support system, and level of functioning [**I**]. The determination of a treatment setting should also include consideration of the patient's ability to adequately care for him- or herself, to provide reliable feedback to the psychiatrist, and to cooperate with treatment of the major depressive disorder [**I**]. Measures such as hospitalization should be considered for patients who pose a serious threat of harm to themselves or others [**I**]. Patients who refuse inpatient treatment can be hospitalized involuntarily if their condition meets the criteria of the local jurisdiction for involuntary admission [**I**]. Admission to a hospital or, if available, an intensive day program, may also be indicated for severely ill patients who lack adequate social support outside of a hospital setting, who have complicating psychiatric or general medical conditions, or who have not responded adequately to outpatient treatment [**I**]. The optimal treatment setting and the patient's likelihood of benefit from a different level of care should be reevaluated on an ongoing basis throughout the course of treatment [**I**].

Evaluate Functional Impairment and Quality of Life

Major depressive disorder can alter functioning in numerous spheres of life including work, school, family, social relationships, leisure activities, or maintenance of health and hygiene. The psychiatrist should evaluate the patient's activity in each of these domains and determine the presence, type, severity, and chronicity of any dysfunction [**I**]. In developing a treatment plan, interventions should be aimed at maximizing the patient's level of functioning as well as helping the patient to set specific goals appropriate to his or her functional impairments and symptom severity [**I**].

Coordinate the Patient's Care with Other Clinicians

Many patients with major depressive disorder will be evaluated by or receive treatment from other health care professionals in addition to the psychiatrist. If more than one clinician is involved in providing the care, all treating clinicians should have sufficient ongoing contact with the patient and with each other to ensure that care is coordinated, relevant information is available to guide treatment decisions, and treatments are synchronized [**I**].

In ruling out general medical causes of depressive symptoms, it is important to ensure that a general medical evaluation has been done [**I**], either by the psychiatrist or by another health care professional. Extensive or specialized testing for general medical causes of depressive symptoms may be conducted based on individual characteristics of the patient [**III**].

Monitor the Patient's Psychiatric Status

The patient's response to treatment should be carefully monitored [**I**]. Continued monitoring of co-occurring psychiatric and/or medical conditions is also essential to developing and refining a treatment plan for an individual patient [**I**].

Integrate Measurements into Psychiatric Management

Tailoring the treatment plan to match the needs of the particular patient requires a careful and systematic assessment of the type, frequency, and magnitude of psychiatric symptoms as well as ongoing determination of the therapeutic benefits and side effects of treatment [**I**]. Such assessments can be facilitated by integrating clinician- and/or patient-administered rating scale measurements into initial and ongoing evaluation [**II**].

Enhance Treatment Adherence

The psychiatrist should assess and acknowledge potential barriers to treatment adherence (e.g., lack of motivation or excessive pessimism due to depression; side effects of treatment; problems in the therapeutic relationship; logistical, economic, or cultural barriers to treatment) and collaborate with the patient (and if possible, the family) to minimize the impact of these potential barriers [**I**]. In addition, the psychiatrist should encourage patients to articulate any fears or concerns about treatment or its side effects [**I**]. Patients should be given a realistic notion of what can be expected during the different phases of treatment, including the likely time course of symptom response and the importance of adherence for successful treatment and prophylaxis [**I**].

Provide Education to the Patient and the Family

Education about the symptoms and treatment of major depressive disorder should be provided in language that is readily understandable to the patient [**I**]. With the patient's permission, family members and others involved in the patient's day-to-day life may also benefit from education about the illness, its effects on functioning (including family and other interpersonal relationships), and its treatment [**I**]. Common misperceptions about antidepressants (e.g., they are addictive) should be clarified [**I**]. In addition, education about major depressive disorder should address the need for a full acute course of treatment, the risk of relapse, the early recognition of recurrent symptoms, and the need to seek treatment as early as possible to reduce the risk of complications or a full-blown episode of major depression [**I**]. Patients should also be told about the need to taper antidepressants, rather than discontinuing them precipitously, to minimize the risk of withdrawal symptoms or symptom recurrence [**I**]. Patient education also includes general promotion of healthy behaviors such as exercise, good sleep hygiene, good nutrition, and decreased use of tobacco, alcohol, and other potentially deleterious substances [**I**]. Educational tools such as books, pamphlets, and trusted web sites can augment the face-to-face education provided by the clinician [**I**].

Acute Phase

Choice of an Initial Treatment Modality

Treatment in the acute phase should be aimed at inducing remission of the major depressive episode and achieving a full return to the patient's baseline level of functioning [**I**]. Acute phase treatment may include pharmacotherapy, depression-focused psychotherapy, the combination of medications and psychotherapy, or other somatic therapies such as electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), or light therapy, as described in the sections that follow. Selection of an initial treatment modality should be influenced by clinical features (e.g., severity of symptoms, presence of co-occurring disorders or psychosocial stressors) as well as other factors (e.g., patient preference, prior treatment experiences) [**I**]. Any treatment should be integrated with psychiatric management and any other treatments being provided for other diagnoses [**I**].

Pharmacotherapy

An antidepressant medication is recommended as an initial treatment choice for patients with mild to moderate major depressive disorder [**I**] and definitely should be provided for those with severe major depressive disorder unless ECT is planned [**I**]. Because the effectiveness of antidepressant medications is generally comparable between classes and within classes of medications, the initial selection of an antidepressant medication will largely be based on the anticipated side effects, the safety or tolerability of these side effects for the individual patient, pharmacological properties of the medication (e.g., half-life, actions on cytochrome P450 enzymes, other drug interactions), and additional factors such as medication response in prior episodes, cost, and patient preference [**I**]. For most patients, a selective serotonin reuptake inhibitor (SSRI), serotonin norepinephrine reuptake inhibitor (SNRI), mirtazapine, or bupropion is optimal [**I**]. In general, the use of nonselective monoamine oxidase inhibitors (MAOIs) (e.g., phenelzine, tranylcypromine, isocarboxazid) should be restricted to patients who do not respond to other treatments [**I**], given the necessity for dietary restrictions with these medications and the potential for deleterious drug-drug interactions. In patients who prefer complementary and alternative therapies, S-adenosyl methionine (SAMe) [**III**] or St. John's wort [**III**] might be considered, although evidence for their efficacy is modest at best, and careful attention to drug-drug interactions is needed with St. John's wort [**I**].

Once an antidepressant medication has been initiated, the rate at which it is titrated to a full therapeutic dose should depend upon the patient's age, the treatment setting, and the presence of co-occurring illnesses, concomitant pharmacotherapy, or medication side effects [**I**]. During the acute phase of treatment, patients should be carefully and systematically monitored on a regular basis to assess their response to pharmacotherapy, identify the emergence of side effects (e.g., gastrointestinal symptoms, sedation, insomnia, activation, changes in weight, and cardiovascular, neurological, anticholinergic, or sexual side effects), and assess patient safety [**I**]. The frequency of patient monitoring should be determined based upon the patient's symptom severity (including suicidal ideas), co-occurring disorders (including general medical conditions), cooperation with treatment, availability of social supports, and the frequency and severity of side effects with the chosen treatment [**II**]. If antidepressant side effects do occur, an initial strategy is to lower the dose of the antidepressant or to change to an antidepressant that is not associated with that side effect [**I**].

Other Somatic Therapies

ECT is recommended as a treatment of choice for patients with severe major depressive disorder that is not responsive to psychotherapeutic and/or pharmacological interventions, particularly in those who have significant functional impairment or have not responded to numerous medication trials [**I**]. ECT is also recommended for individuals with major depressive disorder who have associated psychotic or catatonic features [**I**], for those with an urgent need for response (e.g., patients who are suicidal or nutritionally compromised due to refusal of food or fluids) [**I**], and for those who prefer ECT or have had a previous positive response to ECT [**II**].

Bright light therapy might be used to treat seasonal affective disorder as well as nonseasonal depression [**III**].

Psychotherapy

Use of a depression-focused psychotherapy alone is recommended as an initial treatment choice for patients with mild to moderate major depressive disorder [**I**], with clinical evidence supporting the use of cognitive-behavioral therapy (CBT) [**I**], interpersonal psychotherapy [**I**], psychodynamic therapy [**II**], and problem-solving therapy [**III**] in individual [**I**] and in group [**III**] formats. Factors that may suggest the use of psychotherapeutic interventions include the presence of significant psychosocial stressors, intrapsychic conflict, interpersonal difficulties, a co-occurring axis II disorder, treatment availability, or—most important—patient preference [**II**]. In women who are pregnant, wish to become pregnant, or are breastfeeding, a depression-focused psychotherapy alone is recommended [**II**] and depending on the severity of symptoms, should be considered as an initial option [**I**]. Considerations in the choice of a specific type of psychotherapy include the goals of treatment (in addition to resolving major depressive symptoms), prior positive response to a specific type of psychotherapy, patient preference, and the availability of clinicians skilled in the specific psychotherapeutic approach [**II**]. As with patients who are receiving pharmacotherapy, patients receiving psychotherapy should be carefully and systematically monitored on a regular basis to assess their response to treatment and assess patient safety [**I**]. When determining the frequency of psychotherapy sessions for an individual patient, the psychiatrist should consider multiple factors, including the specific type and goals of psychotherapy, symptom severity (including suicidal ideas), co-occurring disorders, cooperation with treatment, availability of social supports, and the frequency of visits necessary to create and maintain a therapeutic relationship, ensure treatment adherence, and monitor and address depressive symptoms and suicide risk [**II**]. Marital and family problems are common in the course of major depressive disorder, and such problems should be identified and addressed, using marital or family therapy when indicated [**II**].

Psychotherapy Plus Antidepressant Medication

The combination of psychotherapy and antidepressant medication may be used as an initial treatment for patients with moderate to severe major depressive disorder [**I**]. In addition, combining psychotherapy and medication may be a useful initial treatment even in milder cases for patients with psychosocial or interpersonal problems, intrapsychic conflict, or co-occurring Axis II disorder [**II**]. In general, when choosing an antidepressant or psychotherapeutic approach for combination treatment, the same issues should be considered as when selecting a medication or psychotherapy for use alone [**I**].

Assessing the Adequacy of Treatment Response

In assessing the adequacy of a therapeutic intervention, it is important to establish that treatment has been administered for a sufficient duration and at a sufficient frequency or, in the case of medication, dose [**I**]. Onset of benefit from psychotherapy tends to be a bit more gradual than that from medication, but no treatment should continue unmodified if there has been no symptomatic improvement after 1 month [**I**]. Generally, 4–8 weeks of treatment are needed before concluding that a patient is partially responsive or unresponsive to a specific intervention [**II**].

Strategies to Address Nonresponse

For individuals who have not responded fully to treatment, the acute phase of treatment should not be concluded prematurely [**I**], as an incomplete response to treatment is often associated with poor functional outcomes. If at least a moderate improvement in symptoms is not observed within 4–8 weeks of treatment initiation, the diagnosis should be reappraised, side effects assessed, complicating co-occurring conditions and psychosocial factors reviewed, and the treatment plan adjusted [**I**]. It is also important to assess the quality of the therapeutic alliance and treatment adherence [**I**]. For patients in psychotherapy, additional factors to be assessed include the frequency of sessions and whether the specific approach to psychotherapy is adequately addressing the patient's needs [**I**]. If medications are

prescribed, the psychiatrist should determine whether pharmacokinetic [I] or pharmacodynamic [III] factors suggest a need to adjust medication doses. With some TCAs, a drug blood level can help determine if additional dose adjustments are required [I].

After an additional 4–8 weeks of treatment, if the patient continues to show minimal or no improvement in symptoms, the psychiatrist should conduct another thorough review of possible contributory factors and make additional changes in the treatment plan [I]. Consultation should also be considered [II].

A number of strategies are available when a change in the treatment plan seems necessary. For patients treated with an antidepressant, optimizing the medication dose is a reasonable first step if the side effect burden is tolerable and the upper limit of a medication dose has not been reached [II]. Particularly for those who have shown minimal improvement or experienced significant medication side effects, other options include augmenting the antidepressant with a depression-focused psychotherapy [I] or with other agents [II] or changing to another non-MAOI antidepressant [I]. Patients may be changed to an antidepressant from the same pharmacological class (e.g., from one SSRI to another SSRI) or to one from a different class (e.g., from an SSRI to a tricyclic antidepressant [TCA]) [II]. For patients who have not responded to trials of SSRIs, a trial of an SNRI may be helpful [II]. Augmentation of antidepressant medications can utilize another non-MAOI antidepressant [II], generally from a different pharmacological class, or a non-antidepressant medication such as lithium [II], thyroid hormone [II], or a second-generation antipsychotic [II]. Additional strategies with less evidence for efficacy include augmentation using an anticonvulsant [III], omega-3 fatty acids [III], folate [III], or a psychostimulant medication [III], including modafinil [III]. If anxiety or insomnia are prominent features, consideration can be given to anxiolytic and sedative-hypnotic medications [III], including buspirone, benzodiazepines, and selective gamma-aminobutyric acid (GABA) agonist hypnotics (e.g., zolpidem, eszopiclone). For patients whose symptoms have not responded adequately to medication, ECT remains the most effective form of therapy and should be considered [I]. In patients capable of adhering to dietary and medication restrictions, an additional option is changing to a nonselective MAOI [II] after allowing sufficient time between medications to avoid deleterious interactions [I]. Transdermal selegiline, a relatively selective MAO B inhibitor with fewer dietary and medication restrictions, or transcranial magnetic stimulation could also be considered [II]. Vagus nerve stimulation (VNS) may be an additional option for individuals who have not responded to at least four adequate trials of antidepressant treatment, including ECT [III].

For patients treated with psychotherapy, consideration should be given to increasing the intensity of treatment or changing the type of therapy [II]. If psychotherapy is used alone, the possible need for medications in addition to or in lieu of psychotherapy should be assessed [I]. Patients who have a history of poor treatment adherence or incomplete response to adequate trials of single treatment modalities may benefit from combined treatment with medication and a depression-focused psychotherapy [II].

Continuation Phase

During the continuation phase of treatment, the patient should be carefully monitored for signs of possible relapse [I]. Systematic assessment of symptoms, side effects, adherence, and functional status is essential [I] and may be facilitated through the use of clinician- and/or patient-administered rating scales [II]. To reduce the risk of relapse, patients who have been treated successfully with antidepressant medications in the acute phase should continue treatment with these agents for 4–9 months [I]. In general, the dose used in the acute phase should be used in the continuation phase [II]. To prevent a relapse of depression in the continuation phase, depression-focused psychotherapy is recommended [I], with the best evidence available for cognitive-behavioral therapy.

Patients who respond to an acute course of ECT should receive continuation pharmacotherapy [I], with the best evidence available for the combination of lithium and nortriptyline. Alternatively, patients who have responded to an acute course of ECT may be given continuation ECT, particularly if medication or psychotherapy has been ineffective in maintaining remission [II].

Maintenance Phase

In order to reduce the risk of a recurrent depressive episode, patients who have had three or more prior major depressive episodes or who have chronic major depressive disorder should proceed to the maintenance phase of treatment after completing the continuation phase [I]. Maintenance therapy should also be considered for patients with additional risk factors for recurrence, such as the presence of residual symptoms, ongoing psychosocial stressors, early age at onset, and family history of mood disorders [II]. Additional considerations that may play a role in the decision to use maintenance therapy include patient preference, the type of treatment received, the presence of side effects during continuation therapy, the probability of recurrence, the frequency and severity of prior depressive episodes (including factors such as psychosis or suicide risk), the persistence of depressive symptoms after recovery, and the presence of co-occurring disorders [II]. Such factors also contribute to decisions about the duration of the maintenance phase [II]. For many patients, particularly for those with chronic and recurrent major depressive disorder or co-occurring medical and/or psychiatric disorders, some form of maintenance treatment will be required indefinitely [I].

During the maintenance phase, an antidepressant medication that produced symptom remission during the acute phase and maintained remission during the continuation phase should be continued at a full therapeutic dose [II]. If a depression-focused psychotherapy has been used during the acute and continuation phases of treatment, maintenance treatment should be considered, with a reduced frequency of sessions [II]. For patients whose depressive episodes have not previously responded to acute or continuation treatment with medications or a depression-focused psychotherapy but who have shown a response to ECT, maintenance ECT may be considered [III]. Maintenance treatment with vagus nerve stimulation is also appropriate for individuals whose symptoms have responded to this treatment modality [III].

Due to the risk of recurrence, patients should be monitored systematically and at regular intervals during the maintenance phase [I]. Use of standardized measurement aids in the early detection of recurrent symptoms [II].

Discontinuation of Treatment

When pharmacotherapy is being discontinued, it is best to taper the medication over the course of at least several weeks [I]. To minimize the likelihood of discontinuation symptoms, patients should be advised not to stop medications abruptly and to take medications with them when they travel or are away from home [I]. A slow taper or temporary change to a longer half-life antidepressant may reduce the risk of discontinuation syndrome [II] when discontinuing antidepressants or reducing antidepressant doses. Before the discontinuation of active treatment, patients should be informed of the potential for a depressive relapse and a plan should be established for seeking treatment in the event of recurrent symptoms [I]. After discontinuation of medications, patients should continue to be monitored over the next several months and should receive another course of adequate acute phase treatment if symptoms recur [I].

For patients receiving psychotherapy, it is important to raise the issue of treatment discontinuation well in advance of the final session [**I**], although the exact process by which this occurs will vary with the type of therapy.

Clinical Factors Influencing Treatment

Psychiatric Factors

For suicidal patients, psychiatrists should consider an increased intensity of treatment, including hospitalization when warranted [**I**] and/or combined treatment with pharmacotherapy and psychotherapy [**II**]. Factors to consider in determining the nature and intensity of treatment include (but are not limited to) the nature of the doctor-patient alliance, the availability and adequacy of social supports, access to and lethality of suicide means, the presence of a co-occurring substance use disorder, and past and family history of suicidal behavior [**I**].

For patients who exhibit psychotic symptoms during an episode of major depressive disorder, treatment should include a combination of antipsychotic and antidepressant medications or ECT [**I**]. When patients exhibit cognitive dysfunction during a major depressive episode, they may have an increased likelihood of future dementia, making it important to assess cognition in a systematic fashion over the course of treatment [**I**].

Catatonic features that occur as part of a major depressive episode should be treated with a benzodiazepine [**I**] or barbiturate [**II**], typically in conjunction with an antidepressant [**II**]. If catatonic symptoms persist, ECT is recommended [**I**]. To reduce the likelihood of general medical complications, patients with catatonia may also require supportive medical interventions, such as hydration, nutritional support, prophylaxis against deep vein thrombosis, turning to reduce risks of decubitus ulcers, and passive range of motion to reduce risk of contractures [**I**]. If antipsychotic medication is needed, it is important to monitor for signs of neuroleptic malignant syndrome, to which patients with catatonia may have a heightened sensitivity [**II**].

When patients with a major depressive disorder also have a co-occurring psychiatric illness, the clinician should address each disorder as part of the treatment plan [**I**]. Benzodiazepines may be used adjunctively in individuals with major depressive disorder and co-occurring anxiety [**II**], although these agents do not treat depressive symptoms, and careful selection and monitoring is needed in individuals with co-occurring substance use disorders [**I**].

In patients who smoke, bupropion [**I**] or nortriptyline [**II**] may be options to simultaneously treat depression and assist with smoking cessation. When possible, a period of substance abstinence can help determine whether the depressive episode is related to substance intoxication or withdrawal [**II**]. Factors that suggest a need for antidepressant treatment soon after cessation of substance use include a family history of major depressive disorder and a history of major depressive disorder preceding the onset of the substance use disorder or during periods of sobriety [**II**].

For patients who have a personality disorder as well as major depressive disorder, psychiatrists should institute treatment for the major depressive disorder [**I**] and consider psychotherapeutic and adjunctive pharmacotherapeutic treatment for personality disorder symptoms [**II**].

Demographic and Psychosocial Factors

Several aspects of assessment and treatment differ between women and men. Because the symptoms of some women may fluctuate with gonadal hormone levels, the evaluation should include a detailed assessment of mood changes across the reproductive life history (e.g., menstruation, pregnancy, birth control including oral contraception use, abortions, menopause) [**I**]. When prescribing medications to women who are taking oral contraceptives, the potential effects of drug-drug interactions must be considered [**I**]. For women in the perimenopausal period, SSRI and SNRI antidepressants are useful in ameliorating depression as well as in reducing somatic symptoms such as hot flashes [**II**]. Both men and women who are taking antidepressants should be asked whether sexual side effects are occurring with these medications [**I**]. Men for whom trazodone is prescribed should be warned of the risk of priapism [**I**].

The treatment of major depressive disorder in women who are pregnant or planning to become pregnant requires a careful consideration of the benefits and risks of available treatment options for the patient and the fetus [**I**]. For women who are currently receiving treatment for depression, a pregnancy should be planned, whenever possible, in consultation with the treating psychiatrist, who may wish to consult with a specialist in perinatal psychiatry [**I**]. In women who are pregnant, planning to become pregnant, or breast-feeding, depression-focused psychotherapy alone is recommended [**II**] and should always be considered as an initial option, particularly for mild to moderate depression, for patients who prefer psychotherapy, or for those with a prior positive response to psychotherapy [**I**]. Antidepressant medication should be considered for pregnant women who have moderate to severe major depressive disorder as well as for those who are in remission from major depressive disorder, are receiving maintenance medication, and are deemed to be at high risk for a recurrence if the medication is discontinued [**II**]. When antidepressants are prescribed to a pregnant woman, changes in pharmacokinetics during pregnancy may require adjustments in medication doses [**I**]. Electroconvulsive therapy may be considered for the treatment of depression during pregnancy in patients who have psychotic or catatonic features, whose symptoms are severe or have not responded to medications, or who prefer treatment with ECT [**II**]. When a woman decides to nurse, the potential benefits of antidepressant medications for the mother should be balanced against the potential risks to the newborn from receiving antidepressant in the mother's milk [**I**]. For women who are depressed during the postpartum period, it is important to evaluate for the presence of suicidal ideas, homicidal ideas, and psychotic symptoms [**I**]. The evaluation should also assess parenting skills for the newborn and for other children in the patient's care [**I**].

In individuals with late-life depression, identification of co-occurring general medical conditions is essential, as these disorders may mimic depression or affect choice or dosing of medications [**I**]. Older individuals may also be particularly sensitive to medication side effects (e.g., hypotension, anticholinergic effects) and require adjustment of medication doses for hepatic or renal dysfunction [**I**]. In other respects, treatment for depression should parallel that used in younger age groups [**I**].

The assessment and treatment of major depressive disorder should consider the impact of language barriers, as well as cultural variables that may influence symptom presentation, treatment preferences, and the degree to which psychiatric illness is stigmatized [**I**]. When antidepressants are prescribed, the psychiatrist should recognize that ethnic groups may differ in their metabolism and response to medications [**II**].

Issues relating to the family situation and family history, including mood disorders and suicide, can also affect treatment planning and are an important element of the initial evaluation [**I**]. A family history of bipolar disorder or acute psychosis suggests a need for increased attention to possible signs of bipolar illness in the patient (e.g., with antidepressant treatment) [**I**]. A family history of recurrent major depressive disorder increases the likelihood of recurrent episodes in the patient and supports a need for maintenance treatment [**II**]. Family history of a response to a particular antidepressant may sometimes help in choosing a specific antidepressant for the patient [**III**]. Because

problems within the family may become an ongoing stressor that hampers the patient's response to treatment, and because depression in a family is a major stress in itself, such factors should be identified and strong consideration given to educating the family about the nature of the illness, enlisting the family's support, and providing family therapy, when indicated [**II**].

For patients who have experienced a recent bereavement, psychotherapy or antidepressant treatment should be used when the reaction to a loss is particularly prolonged or accompanied by significant psychopathology and functional impairment [**I**]. Support groups may be helpful for some bereaved individuals [**III**].

Co-occurring General Medical Conditions

In patients with major depressive disorder, it is important to recognize and address the potential interplay between major depressive disorder and any co-occurring general medical conditions [**I**]. Communication with other clinicians who are providing treatment for general medical conditions is recommended [**I**]. The clinical assessment should include identifying any potential interactions between medications used to treat depression and those used to treat general medical conditions [**I**]. Assessment of pain is also important as it can contribute to and co-occur with depression [**I**]. In addition, the psychiatrist should consider the effects of prescribed psychotropic medications on the patient's general medical conditions, as well as the effects of interventions for such disorders on the patient's psychiatric condition [**I**].

In patients with preexisting hypertension or cardiac conditions, treatment with specific antidepressant agents may suggest a need for monitoring of vital signs or cardiac rhythm (e.g., electrocardiogram [ECG] with TCA treatment; heart rate and blood pressure assessment with SNRIs and TCAs) [**I**]. When using antidepressant medications with anticholinergic side effects, it is important to consider the potential for increases in heart rate in individuals with cardiac disease, worsening cognition in individuals with dementia, development of bladder outlet obstruction in men with prostatic hypertrophy, and precipitation or worsening of narrow angle glaucoma [**I**]. Some antidepressant drugs (e.g., bupropion, clomipramine, maprotiline) reduce the seizure threshold and should be used with caution in individuals with preexisting seizure disorders [**II**]. In individuals with Parkinson's disease, the choice of an antidepressant should consider that serotonergic agents may worsen symptoms of the disease [**II**], that bupropion has potential dopamine agonist effects (benefitting symptoms of Parkinson's disease but potentially worsening psychosis) [**II**], and that selegiline has antiparkinsonian and antidepressant effects but may interact with L-dopa and with other antidepressant agents [**I**]. In treating the depressive syndrome that commonly occurs following a stroke, consideration should be given to the potential for interactions between antidepressants and anticoagulating (including antiplatelet) medications [**I**]. Given the health risks associated with obesity and the tendency of some antidepressant medications to contribute to weight gain, longitudinal monitoring of weight (either by direct measurement or patient report) is recommended [**I**], as well as calculation of body mass index (BMI) [**II**]. If significant increases are noted in the patient's weight or BMI, the clinician and patient should discuss potential approaches to weight control such as diet, exercise, change in medication, nutrition consultation, or collaboration with the patient's primary care physician [**I**]. In patients who have undergone bariatric surgery to treat obesity, adjustment of medication formulations or doses may be required because of altered medication absorption [**I**]. For diabetic patients, it is useful to collaborate with the patient's primary care physician in monitoring diabetic control when initiating antidepressant therapy or making significant dosing adjustments [**II**]. Clinicians should be alert to the possibility of sleep apnea in patients with depression, particularly those who present with daytime sleepiness, fatigue, or treatment-resistant symptoms [**II**]. In patients with known sleep apnea, treatment choice should consider the sedative side effects of medication, with minimally sedating options chosen whenever possible [**I**]. Given the significant numbers of individuals with unrecognized human immunodeficiency virus (HIV) infection and the availability of effective treatment, consideration should be given to HIV risk assessment and screening [**I**]. For patients with HIV infection who are receiving antiretroviral therapy, the potential for drug-drug interactions needs to be assessed before initiating any psychotropic medications [**I**]. Patients who are being treated with antiretroviral medications should be cautioned about drug-drug interactions with St. John's wort that can reduce the effectiveness of HIV treatments [**I**]. In patients with hepatitis C infection, interferon can exacerbate depressive symptoms, making it important to monitor patients carefully for worsening depressive symptoms during the course of interferon treatment [**I**]. Because tamoxifen requires active 2D6 enzyme function to be clinically efficacious, patients who receive tamoxifen for breast cancer or other indications should generally be treated with an antidepressant (e.g., citalopram, escitalopram, venlafaxine, desvenlafaxine) that has minimal effect on metabolism through the cytochrome P450 2D6 isoenzyme [**I**]. When depression occurs in the context of chronic pain, SNRIs and TCAs may be preferable to other antidepressive agents [**II**]. When ECT is used to treat major depressive disorder in an individual with a co-occurring general medical condition, the evaluation should identify conditions that could require modifications in ECT technique (e.g., cardiac conditions, hypertension, central nervous system lesions) [**I**]; these should be addressed insofar as possible and discussed with the patient as part of the informed consent process [**I**].

Definitions:

Categories of Endorsement

[**I**] Recommended with substantial clinical confidence.

[**II**] Recommended with moderate clinical confidence.

[**III**] May be recommended on the basis of individual circumstances.

Clinical Algorithm(s)

None provided

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

This document represents a synthesis of current scientific knowledge and rational clinical practice regarding the treatment of patients with major depressive disorder.

In order for the reader to appreciate the evidence base behind the guideline recommendations and the weight that should be given to each recommendation, the summary of treatment recommendations is keyed according to the level

of confidence with which each recommendation is made (see "Major Recommendations" field). Each rating of clinical confidence considers the strength of the available evidence. When evidence from randomized controlled trials and meta-analyses is limited, the level of confidence may also incorporate other clinical trials and case reports as well as clinical consensus with regard to a particular clinical decision. In the listing of cited references, each reference is followed by a letter code in brackets that indicates the nature of the supporting evidence:

- **[A]** *Randomized, double-blind clinical trial*. A study of an intervention in which subjects are prospectively followed over time; there are treatment and control groups; subjects are randomly assigned to the two groups; both the subjects and the investigators are blind to the assignments.
- **[A-]** *Randomized clinical trial*. Same as above but not double-blind.
- **[B]** *Clinical trial*. A prospective study in which an intervention is made and the results of that intervention are tracked longitudinally; study does not meet standards for a randomized clinical trial.
- **[C]** *Cohort or longitudinal study*. A study in which subjects are prospectively followed over time without any specific intervention.
- **[D]** *Case-control study*. A study in which a group of patients and a group of control subjects are identified in the present and information about them is pursued retrospectively or backward in time.
- **[E]** *Review with secondary data analysis*. A structured analytic review of existing data, e.g., a meta-analysis or a decision analysis.
- **[F]** *Review*. A qualitative review and discussion of previously published literature without a quantitative synthesis of the data.
- **[G]** *Other*. Textbooks, expert opinion, case reports, and other reports not included above.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate treatment of major depressive disorder

Potential Harms

Antidepressants

- *Selective Serotonin Reuptake Inhibitors (SSRIs)*: Side effects include gastrointestinal issues, activation/insomnia, sexual side effects, headaches, extrapyramidal side effects, falls, effects on weight, serotonin syndrome, drug interactions, and discontinuation syndrome.
- *Serotonin norepinephrine reuptake inhibitors (SNRIs)*: Side effects are similar to SSRIs. Dose-related hypertension may occur. Discontinuation symptoms are sometime protracted.
- *Bupropion*: Side effects include headaches, tremors, and seizures.
- *Mirtazapine*: The most common side effects include dry mouth, sedation, and weight gain. Mirtazapine increases cholesterol levels in some patients.
- *Trazodone*: The most common side effect is sedation. Trazodone can also cause cardiovascular side effects.
- *Nefazodone*: Side effects include dry mouth, nausea, constipation, orthostasis, and visual alterations. Sedation is also common. Hepatic toxicity has also been reported. These reports led the U.S. Food and Drug Administration to require a black box warning in the labeling of nefazodone, warning of possible liver failure leading to transplant and/or death.
- *Tricyclic Antidepressants (TCAs)*: Side effects include cardiovascular effects, anticholinergic effects, sedation, weight gain, myoclonus, seizures, falls, and medication interactions.
- *Monoamine Oxidase Inhibitors*: Side effects include cardiovascular effects, weight gain, sexual side effects, and headaches, insomnia, and sedation. Food-drug and drug-drug interactions can produce hypertensive crises and serotonin syndrome, which can be life-threatening.

See the original guideline document for further details on potential side effects of antidepressants, including information about risk of suicidal thoughts and behaviors.

Somatic Therapies

- *Electroconvulsive Therapy (ECT)*: Headaches and muscle aches are common. ECT may have cardiovascular side effects. It can also be associated with cognitive effects and anterograde amnesia.
- *Transcranial Magnetic Stimulation (TMS)*: Transient scalp discomfort and headaches were the most commonly reported side effects.

Other Non-pharmacological Therapies

- *Psychotherapy* carries its own "side effects." A psychotherapy that requires considerable time or patients may be poorly tolerated. The work of psychotherapy itself may generate anxiety or other strong feelings, which may be difficult for patients to manage.
- *Complementary and Alternative Treatments*: An important consideration with St. John's wort is the potential for drug-drug interactions.
- *Light Therapy*: Monitoring for mania and hypomania may be appropriate with initiation of light therapy, as hypomania was been reported.

Contraindications

Contraindications

- The combined use of a monoamine oxidase inhibitor (MAOI) with a selective serotonin reuptake inhibitor (SSRI) is contraindicated because it can lead to a potentially lethal interaction: the serotonin syndrome. Combining other serotonergic agents with an MAOI, including serotonin norepinephrine reuptake inhibitors (SNRIs), St. John's wort, or tricyclic antidepressants (TCAs), can also lead to the serotonin syndrome. When an SSRI is being changed to an MAOI or vice versa, a minimum washout time must be allowed.
- The vagus nerve stimulation (VNS) device may affect the operation of other implanted devices such as cardiac pacemakers or defibrillators and other procedures such as diathermy, and whole body or radiofrequency receive-only magnetic resonance imaging (MRI) are contraindicated. VNS is also contraindicated in the presence of bilateral or left cervical vagotomy.
- Enlarged prostate size and other causes of bladder outlet obstruction are relative contraindications to the use of antidepressant medication compounds with antimuscarinic effects.
- Bupropion is contraindicated in patients who have had anorexia nervosa or bulimia nervosa because of elevated risk of seizures.

Qualifying Statements

Qualifying Statements

- The American Psychiatric Association (APA) Practice Guidelines are not intended to be construed or to serve as a standard of medical care. Standards of medical care are determined on the basis of all clinical data available for an individual patient and are subject to change as scientific knowledge and technology advance and practice patterns evolve. These parameters of practice should be considered guidelines only. Adherence to them will not ensure a successful outcome for every individual, nor should they be interpreted as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate recommendation regarding a particular clinical procedure or treatment plan must be made by the psychiatrist in light of the clinical data, the psychiatric evaluation, and the diagnostic and treatment options available. Such recommendations should incorporate the patient's personal and sociocultural preferences and values in order to enhance the therapeutic alliance, adherence to treatment, and treatment outcomes.
- The Work Group and the Steering Committee differed on how to rate the strength of recommendation for psychodynamic psychotherapy. Based on their review of the available empirical evidence on the use of psychodynamic psychotherapy in individuals with major depressive disorder, the Work Group gave this treatment a level III rating, i.e., "may be recommended on the basis of individual circumstances." The Steering Committee gave a level II rating, "recommended with moderate clinical confidence," based on the long history of clinical experience with psychodynamic psychotherapy as well as findings from several studies of patients who had depressive symptoms but not major depressive disorder per se.
- The broad scope of this guideline and the substantial evidence base resulted in some practical tradeoffs. One such tradeoff worth highlighting is the decision to build upon literature reviews of the first and second editions of the guideline, rather than re-do them. This decision is acknowledged to have resulted in an emphasis of study in this guideline on newer treatments, because the majority of studies about older treatments, including tricyclic antidepressants and monoamine oxidase inhibitors, were published in decades prior to 1999. Readers are advised that the reviews of this older literature are described in the previous editions of the guideline. The Work Group for this edition considered the previous editions during their evidence review, but for practical reasons, that effort is less well documented than the group's analysis of the newer literature. The treatment recommendations of this guideline, however, were developed to reflect the complete evidence base.
- Medications discussed in this practice guideline may not have an indication from the U.S. Food and Drug Administration for the disorder or condition for which they are recommended. Off-label use of medications by individual physicians is permitted and common. Decisions about off-label use can be guided by the evidence provided in the APA practice guideline, other scientific literature, and clinical experience.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Quick Reference Guides/Physician Guides

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

American Psychiatric Association (APA). Practice guideline for the treatment of patients with major depressive disorder. 3rd ed. Arlington (VA): American Psychiatric Association (APA); 2010 Oct. 152 p. [1170 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

1993 (revised 2010 Oct)

Guideline Developer(s)

American Psychiatric Association - Medical Specialty Society

Source(s) of Funding

American Psychiatric Association (APA)

Guideline Committee

Work Group on Major Depressive Disorder

Composition of Group That Authored the Guideline

Work Group Members: Alan J. Gelenberg, MD, Chair; Marlene P. Freeman, MD; John C. Markowitz, MD; Jerrold F. Rosenbaum, MD; Michael E. Thase, MD; Madhukar H. Trivedi, MD; Richard S. Van Rhoads, MD, Consultant

Financial Disclosures/Conflicts of Interest

Work Group members were selected on the basis of their expertise and integrity, and they agreed to disclose all potential conflicts of interest before and during their work on this guideline to the Steering Committee on Practice Guidelines and to each other. Employees of industry were not included on the group, and the group was balanced to include some persons with minimal industry relationships. As disclosed below, from initiation of work in 2005 to approval of the guideline in 2010, some members of the Work Group on Major Depressive Disorder had relationships with industry for which they received research grants or income from consulting or speaking related to treatments discussed in the guideline.

The Work Group on Major Depressive Disorder reports the following potentially competing interests for the period from May 2005 to May 2010:

- Dr. Gelenberg reports consulting for Eli Lilly and Company, Pfizer, Best Practice, AstraZeneca, Wyeth, Cyberonics, Novartis, Forest Pharmaceuticals, Inc., GlaxoSmithKline, ZARS Pharma, Jazz Pharmaceuticals, Lundbeck, Takeda Pharmaceuticals North America, Inc., eResearch Technology, Dey Pharma, PGxHealth, and Myriad Genetics. He reports serving on speakers bureaus for Pfizer, GlaxoSmithKline, and Wyeth. He reports receiving research grant funding from Eli Lilly and Company, Pfizer, and GlaxoSmithKline. He reports stock ownership in Healthcare Technology Systems.
- Dr. Freeman reports that she received research support from the Meadows Foundation, the National Institute for Mental Health, the U.S. Food and Drug Administration, the Institute for Mental Health Research, Forest, GlaxoSmithKline and Eli Lilly and Company (investigator-initiated trials), and Pronova Biocare (research materials). She received an honorarium for case-based peer-reviewed material for AstraZeneca's website. She reports consulting for Ther-Rx, Reliant, and Pamlab. She reports receiving an honorarium for speaking at an APA continuing medical education program that was sponsored by Forest and an honorarium for speaking at a continuing medication education program sponsored by KV Pharmaceuticals. She reports receiving an honorarium from Leerink Swann for participating in a focus group.
- Dr. Markowitz reports consulting for Ono Pharmaceutical Co., Ltd. (2005). He reports receiving research support from Forest Pharmaceuticals, Inc. (2005). He reports receiving grant support from the National Institute of Mental Health (2005–2013), the National Alliance for Research in Schizophrenia and Depression (2005), and MINT: Mental Health Initiative (2005). He reports receiving royalties from American Psychiatric Publishing, Inc. (2005–2010), Basic Books (2005–2010), Elsevier (2005–2010), and Oxford University Press (2007–2010).
- Dr. Rosenbaum reports attending advisory boards for Bristol-Myers Squibb, Cephalon, Cyberonics, Forest Pharmaceuticals, Inc., Eli Lilly and Company, MedAvante, Neuronetics, Inc., Novartis, Orexigen Therapeutics, Inc., Organon BioSciences, Pfizer, Roche Diagnostics, Sanofi-aventis, Shire, and Wyeth. He reports consulting for Auspex Pharmaceuticals, Compellis Pharmaceuticals, EPIX Pharmaceuticals, Neuronetics, Inc., Organon BioSciences, Somaxon, and Supernus Pharmaceuticals, Inc. He reports receiving honoraria from lectureships for Boehringer Ingleheim, Bristol-Myers Squibb, Cyberonics, Forest Pharmaceuticals, Inc., Eli Lilly and Company, and Schwartz Pharma. He was involved in the creation of the Massachusetts General Hospital Psychiatry Academy (MGH-PA) and has served as a panelist in four satellite broadcast programs. MGH-PA programs that have industry support are always multi-sponsored, and curriculum development by the Academy is independent of sponsorship; the curricula from January 2005 to March 2009 included sponsorship support from AstraZeneca, Bristol-Myers Squibb, Cephalon, Eli Lilly and Company, Forest Pharmaceuticals, Inc., GlaxoSmithKline, Janssen Medical Affairs LLC, Ortho-McNeil Pharmaceutical, sanofi-aventis, Shire, and Wyeth. He reports equity holdings in Compellis Pharmaceuticals, MedAvante, and Somaxon.
- Dr. Thase reports that he provided scientific consultation to AstraZeneca, Bristol-Myers Squibb, Eli Lilly &

Company, Forest Pharmaceuticals, Inc., Gerson Lehman Group, GlaxoSmithKline, Guidepoint Global, H. Lundbeck A/S, MedAvante, Inc., Neuronetics, Inc., Novartis, Otsuka, Ortho-McNeil Pharmaceuticals, PamLab, L.L.C., Pfizer (formerly Wyeth-Ayerst Laboratories), Schering-Plough (formerly Organon), Shire U.S., Inc., Supernus Pharmaceuticals, Takeda (Lundbeck), and Transcept Pharmaceuticals. He was a member of the speakers bureaus for AstraZeneca, Bristol-Myers Squibb, Eli Lilly and Company, GlaxoSmithKline, Pfizer (formerly Wyeth-Ayerst Laboratories), and Schering-Plough (formerly Organon). He received grant funding from Eli Lilly and Company, GlaxoSmithKline, the National Institute of Mental Health, the Agency for Healthcare Research and Quality, and Sepracor, Inc. He had equity holdings in MedAvante, Inc., and received royalty income from American Psychiatric Publishing, Inc., Guilford Publications, Herald House, Oxford University Press, and W.W. Norton and Company. His wife was employed as the group scientific director for Embryon (formerly Advogent), which does business with Bristol-Myers Squibb and Pfizer/Wyeth.

- Dr. Trivedi reports that he was a consultant to or on speaker bureaus for Abbott Laboratories, Inc., Abdi Ibrahim, Akzo (Organon Pharmaceuticals, Inc.), AstraZeneca, Bristol-Myers Squibb Company, Cephalon, Inc., Cyberonics, Inc., Eli Lilly and Company, Evotec, Fabre Kramer Pharmaceuticals, Inc., Forest Pharmaceuticals, GlaxoSmithKline, Janssen Pharmaceutica Products, L.P., Johnson & Johnson P.R.D., Meade-Johnson, Medtronic, Neuronetics, Otsuka Pharmaceuticals, Parke-Davis Pharmaceuticals, Inc., Pfizer, Inc., Sepracor, Shire Development, Solvay Pharmaceuticals, VantagePoint, and Wyeth-Ayerst Laboratories. He received research support from the Agency for Healthcare Research and Quality, Corcept Therapeutics, Inc., Cyberonics, Inc., Merck, National Alliance for Research in Schizophrenia and Depression, National Institute of Mental Health, National Institute on Drug Abuse, Novartis, Pharmacia & Upjohn, Predix Pharmaceuticals (Epix), Solvay Pharmaceuticals, Inc., and Targacept.
- Dr. Van Rhoads reports no competing interests.

The Independent Review Panel, including Drs. Reus, DePaulo, Fawcett, Schneck, and Silbersweig, report no competing interests. The Independent Review Panel reviewed this guideline to assess potential biases and found no evidence of influence from the industry and other relationships of the Work Group disclosed above. The Steering Committee on Practice Guidelines also reviewed this guideline and found no evidence of influence from these relationships. The development process for this guideline, including the roles of the Work Group, Independent Review Panel, Steering Committee, American Psychiatric Association (APA) Assembly, and APA Board of Trustees is described in "Overview of Guideline Development Process" on p. 11 in the original guideline document.

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: American Psychiatric Association practice guideline for the treatment of patients with major depressive disorder. Am J Psychiatry 2000 Apr;157(4 Suppl):1-45. [325 references]

Guideline Availability

Electronic copies: Available from the American Psychiatric Association's Web site.

Availability of Companion Documents

The following are available:

- Treating major depressive disorder. A quick reference guide. Washington (DC): American Psychiatric Association (APA); 2010. 28 p. Electronic copies: Available from the American Psychiatric Association (APA) Web site (by subscription only).
- American Psychiatric Association practice guideline development process. Arlington (VA): APA; 2004. Available from the APA Web site. Also available in a PDA version.

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on December 15, 2010. The information was verified by the guideline developer on January 7, 2011. This summary was updated by ECRI Institute on May 20, 2011 following the U.S. Food and Drug Administration advisory on antipsychotic drugs. This summary was updated by ECRI Institute on September 12, 2011 following the U.S. Food and Drug Administration advisory on Celexa (citalopram hydrobromide). This summary was updated by ECRI Institute on April 16, 2012 following the updated U.S. Food and Drug Administration advisory on Celexa (citalopram hydrobromide).

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