Sentara® Health Plans

BEHAVIORAL HEALTH GUIDELINE

ADULT DEPRESSION MEDICATION MANAGMENT GUIDELINE

Guideline History

Date Approved	08/97
Date Revised	7/08; 7/10; 7/12; 10/18
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Key Points

- ✓ Routine screening for depression is encouraged. Use the PHQ-9.
- ✓ Rule out other potential sources of depressive symptoms and treat the underlying cause (e.g., medications, other medical or psychiatric conditions).
- ✓ Assess alcohol consumption. Use of the AUDIT screening tool is recommended. (See Sentara's guideline on Alcohol Screening and Brief Intervention, available on the web site.)
- ✓ The prevalence of depression is increased in patients with medical illnesses such as diabetes, stroke, cancer and congestive heart failure. Untreated, or inadequately treated, depression may negatively impact patients' adherence to medical treatment.
- ✓ Bipolar disorder often presents initially in the depressed phase. Initiating or titrating antidepressant medication can precipitate a manic episode.
- ✓ Side effects account for as many as two-thirds of all premature discontinuations of antidepressants. Educate patients that most side effects are early onset and time limited.
- ✓ Initially the patient should be evaluated every 1-2 weeks to monitor compliance, symptom improvement and medication side effects. Assess response at 4-6 weeks and adjust therapy as indicated. Reassess response at 12 weeks. The PHQ-9 can be used to objectively measure effectiveness of treatment.
- ✓ Consider specialist consultation/referral for an incomplete response. Communicate and coordinate care with the behavioral health provider.

VA/DoD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF MAJOR DEPRESSIVE DISORDER

Department of Veterans Affairs
Department of Defense

Clinician Guideline Summary

QUALIFYING STATEMENTS

The Department of Veterans Affairs and the Department of Defense guidelines are based upon the best information available at the time of publication. They are designed to provide information and assist decision-making. They are not intended to define a standard of care and should not be construed as one. Neither should they be interpreted as prescribing an exclusive course of management.

This Clinical Practice Guideline is based on a systematic review of both clinical and epidemiological evidence. Developed by a panel of multidisciplinary experts, it provides a clear explanation of the logical relationships between various care options and health outcomes while rating both the quality of the evidence and the strength of the recommendations.

Variations in practice will inevitably and appropriately occur when clinicians take into account the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Every healthcare professional making use of these guidelines is responsible for evaluating the appropriateness of applying them in the setting of any particular clinical situation.

These guidelines are not intended to represent TRICARE policy. Further, inclusion of recommendations for specific testing and/or therapeutic interventions within these guidelines does not guarantee coverage of civilian sector care. Additional information on current TRICARE benefits may be found at www.tricare.mil or by contacting your regional TRICARE Managed Care Support Contractor.

Version 3.0 – 2016

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I. Introduction

A. Major Depressive Disorder

Depression is a common mental disorder that presents with depressed mood, loss of interest or pleasure in regular activities, decreased energy, feelings of guilt or low self-worth, disturbed sleep or appetite, and poor concentration. Major depressive disorder is the most prevalent and disabling form of depression. In addition to the immediate symptoms of depression, MDD results in poor quality of life overall, decreased productivity, and can increase mortality from suicide. Social difficulties including stigma, loss of employment, and marital conflict as a result of depression can also occur. Anxiety, posttraumatic stress disorder (PTSD), and substance misuse are common co-occurring conditions that may worsen the existing depression and complicate treatment.

Depression is considered to be a largely biological illness but can result from a combination of genetic, biological, environmental, and psychological factors. Trauma, loss of a loved one, a difficult relationship, or any stressful situation may trigger depression, but depression can also occur without an obvious trigger.

B. Depression in the General Population

According to the National Alliance on Mental Illness, an estimated 16 million American adults—almost 7% of the population—had at least one major depressive episode in the past year. Women are 70% more likely than men to experience depression, and young adults aged 18–25 are 60% more likely to have depression than people aged 50 or older.[1] Depressive disorders often start at a young age; they reduce people's functioning and often recur.[2] According to the World Health Organization (WHO), MDD (identified as unipolar depressive disorders by WHO) ranked first worldwide among the leading causes of disability (i.e., aggregate years lived with disability [YLD]).[3]

The incremental economic burden of individuals with MDD was $210.5 billion in 2010, in both direct and indirect costs, compared to $173.2 billion in 2005, an increase of 21.5% over this period.[4] Additionally, co-occurring conditions accounted for a larger percentage of the economic burden of MDD than the MDD itself.

Although depression can be a devastating illness, it often responds to treatment. There are a variety of treatment options available for people with depression including drugs and psychotherapy. Depression is frequently underdiagnosed, however; among people with severe depressive symptoms, for example, only about one-third (35%) had seen a mental health professional for treatment in the past year.[5]

C. Depression in the VA/DoD Populations

Military personnel are prone to depression, at least partially as a result of exposure to traumatic experiences, including witnessing combat, and separation from family during deployment or military trainings.[6,7] For example, based on data collected in 2011 from a de-identified cross-sectional survey of active duty soldiers, The Army Study to Assess Risk and Resilience in Servicemembers (Army STARRS) described the 30-day prevalence of MDD as 4.8% compared to less than 1%—five times higher— among a civilian comparison group.[8] A meta-analysis of 25 epidemiological studies estimated the prevalence of recent major depression based on the DSM-IV criteria at rates of 12.0% among currently deployed U.S. military personnel, 13.1% among previously deployed, and 5.7% among those never deployed.[9]

However, the 25 studies from which these estimates are drawn described a wide range of prevalences depending on the screening or diagnostic instrument, population, and time period used. Being female, enlisted, 17-25 years old, unmarried, and having had less than a college education were risk factors for depression.[9] In an analysis among current and former U.S. military personnel who were included in the Millennium Cohort Study and observed from July 1, 2001 to December 31, 2008, the risk of suicide increased in men and in those who were depressed.[10]

In fiscal year 2015, among Veterans served by the Veterans Health Administration (VHA), the documented prevalence of any depression (including depression not otherwise specified) was 19.8% while the documented prevalence of MDD only was 6.5%.[11]

II. Scope of the Guideline

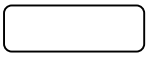
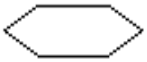
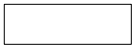
This clinical practice guideline (CPG) is designed to assist providers in managing patients with MDD. The patient population of interest for this CPG includes adults who are eligible for care in the VHA and DoD healthcare delivery system. It includes Veterans as well as deployed and non-deployed active duty Service Members. It also includes care provided by DoD and VA staff as well as care obtained by the DoD and VA from community partners. This CPG does not provide recommendations for the management of MDD in children or adolescents, or for the management of co-occurring disorders. The CPG also does not consider the management of unspecified depressive disorder, or complicated bereavement or the range of other depressive disorders identified in DSM-5: disruptive mood dysregulation disorder, persistent depressive disorder, premenstrual dysphoric disorder, substance/medication-induced depressive disorder, depressive disorder due to another medical condition, other specified depressive disorder or unspecified depressive disorder (depression not otherwise specified). The principals in this document should be strongly considered when treating these other depressive disorders and in particular, unspecified depressive disorders.

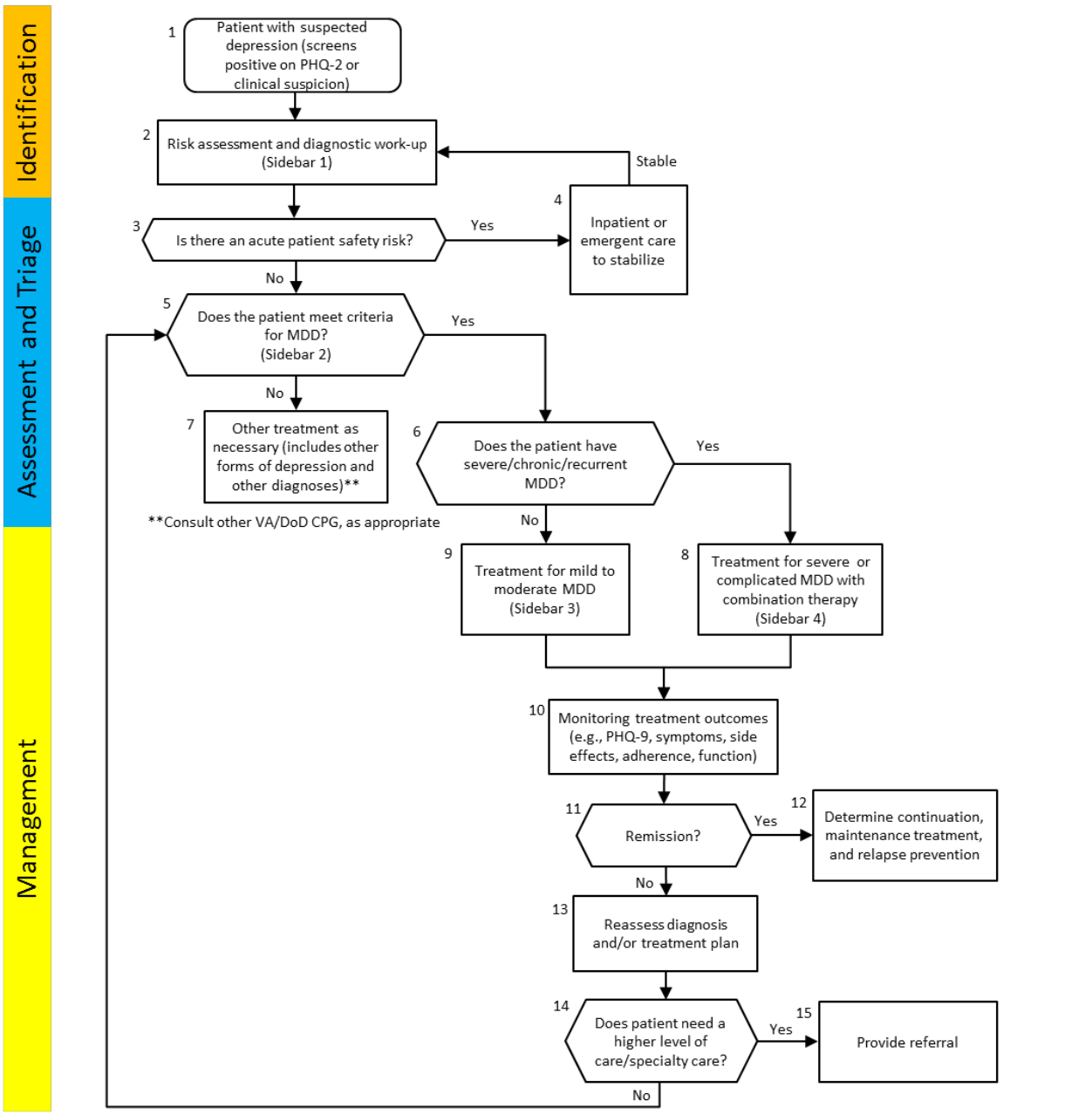
IV. Algorithm

This CPG includes an algorithm that is designed to facilitate clinical decision making for the management of MDD. The use of the algorithm format as a way to represent patient management was chosen based on the understanding that such a format can facilitate efficient diagnostic and therapeutic decision making and has the potential to affect patterns of resource use. The algorithm format allows the provider to follow a linear approach in assessing the critical information needed at the major decision points in the clinical process, and includes:

- An ordered sequence of steps of care
- Recommended observations and examinations
- Decisions to be considered
- Actions to be taken

A clinical algorithm diagrams a guideline into a step-by-step decision tree. Standardized symbols are used to display each step in the algorithm, and arrows connect the numbered boxes indicating the order in which the steps should be followed.[12]

	Rounded rectangles represent a clinical state or condition.
	Hexagons represent a decision point in the guideline, formulated as a question that can be answered Yes or No.
	Rectangles represent an action in the process of care.



Sidebar 1 - Risk Assessment and Work-up

a. Consider administration of PHQ-9
b. Evaluate for (1) suicidal and homicidal ideation, (2) history of suicide attempts, (3) presence of psychotic features
c. Rule out causes of secondary MDD (e.g., hypothyroidism, B-12 deficiency, syphilis, chronic disease)

Sidebar 3 – Considerations in Treatment of Mild/Moderate MDD

For example:

a. Select monotherapy or combination therapy: pharmacotherapy/psychotherapy
b. Treatment for special populations (e.g., treatment of co-occurring conditions, pregnant patients, geriatric patients)
c. Patient preferences (treatment refusers)
d. Consider referral

Sidebar 2 – DSM-5 Criteria

Criterion A: Five or more of the following symptoms present during the same 2-week period; at least one of the symptoms is either (1) depressed mood or (2) loss of interest/pleasure:

a. Depressed mood most of the day, nearly every day
b. Markedly diminished interest or pleasure in almost all activities most of the day, nearly every day
c. Significant weight loss when not dieting or weight gain
d. Insomnia or hypersomnia nearly every day
e. Psychomotor agitation or retardation nearly every day
f. Fatigue or loss of energy every day
g. Feelings of worthlessness or excessive inappropriate guilt
h. Diminished ability to think, concentrate, or indecisiveness, nearly every day
i. Recurrent thought of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

Criterion B: The symptoms cause significant distress or functional impairment
Criterion C: The episode is not attributable to the physiological effects of a substance or another medical condition

Sidebar 4 – Considerations in Treatment of Severe MDD

For example:

a. Recommend referral to specialty level care
b. Select combination therapy: pharmacotherapy/ psychotherapy
c. Treatment for special populations (e.g., treatment of co-occurring conditions, pregnant patients, geriatric patients)
d. Patient preferences (treatment refusers)

VI. Identification

Table 1: Patient Health Questionnaire-2 (PHQ-2) [13]

Question Number	Over the past two weeks, how often have you been bothered by any of the following problems?	Not at all	Several days	More than half the days	Nearly every day
1	Little interest or pleasure in doing things	0	1	2	3
2	Feeling down, depressed, or hopeless	0	1	2	3
For office coding: Total Score = _____+_____					

Table 2: PHQ-2 Score Interpretation [13]

PHQ-2 Score	Probability of MDD (%)	Probability of any depressive disorder (%)
1	15.4	36.9
2	21.1	48.3
3	38.4	75.0
4	45.5	81.2
5	56.4	84.6
6	78.6	92.9

VII. Assessment and Triage

Table 3: Diagnostic Criteria for Major Depressive Episode based on DSM-5 [14]

Criterion A	Five or more of the following symptoms present during the same two-week period; at least one of the symptoms is either (1) depressed mood or (2) loss of interest/ pleasure: a. Depressed mood most of the day, nearly every day b. Markedly diminished interest or pleasure in almost all activities most of the day, nearly every day c. Significant weight loss when not dieting or weight gain d. Insomnia or hypersomnia nearly every day e. Psychomotor agitation or retardation nearly every day f. Fatigue or loss of energy every day g. Feelings of worthlessness or excessive inappropriate guilt h. Diminished ability to think, concentrate, or indecisiveness, nearly every day i. Recurrent thought of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide
Criterion B	The symptoms cause significant distress or functional impairment.
Criterion C	The episode is not attributable to the physiological effects of a substance or another medical condition.

Table 4: Nine Symptom Checklist (PHQ-9)

	Over the last 2 weeks, how often have you been bothered by any of the following?	Not at all	Several days	More than half the days	Nearly every day
a	Little interest or pleasure in doing things?	0	1	2	3
b	Feeling down, depressed, or hopeless?	0	1	2	3
c	Trouble falling or staying asleep, or sleeping too much?	0	1	2	3
d	Feeling tired or having little energy?	0	1	2	3
e	Poor appetite or overeating?	0	1	2	3
f	Feeling bad about yourself—or that you are a failure or have let yourself or your family down?	0	1	2	3
g	Trouble concentrating on things, such as reading the newspaper or watching television?	0	1	2	3
h	Moving or speaking so slowly that other people could have noticed? Or the opposite—being so fidgety or restless that you have been moving around a lot more than usual?	0	1	2	3
i	Thoughts that you would be better off dead or of hurting yourself in some way?	0	1	2	3
For office coding: Total Score =_____+_____+_____+_____					

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
☐	☐	☐	☐

PHQ-9 Scoring Instructions:

Count the number (#) of boxes checked in a column. Multiply that number by the value indicated below, then add the subtotal to produce a total score. The possible range is 0-27. Use the table below to interpret the PHQ-9 score.

Not at all (#) _____ x 0 = _____
Several days (#) _____ x 1 = _____
More than half the days (#) _____ x 2 = _____
Nearly every day (#) _____ x 3 = _____
Total score: _____

VIII. Treatment Setting

Table 5: Summary of Evidence-based Elements of the Collaborative Care Model for MDD* [15-21]

Essential	Optimal	Equivocal	Not Recommended
Interdisciplinary, team approach to brief, problem-focused care	Access to evidence-based psychosocial services (e.g., behavioral activation, motivational interviewing, problem solving therapy, brief CBT)	Requiring or focusing on direct hand-offs from the primary care provider to the team	Consultation-liaison or co-located care without systematic follow-up
Structured protocols, including screening, case identification, and longitudinal measurement	Availability to provide crisis intervention	Acceptance of stable patients from specialty care	Assessment and triage (i.e., walk-in) model (no follow up)
Systematic follow-up (registries, measure-guided treatment)	Facilitated self-management		
Patient education and activation including adherence monitoring	A program that offers additional behavioral health services including brief alcohol interventions	Use of a prescribing provider (psychiatrists, certified registered nurse practitioner [CRNP]) for psychotropic medications (separate from supervision)	
Supervision by psychiatrist/prescriber	Open accessibility to primary care providers and patients		
Data-driven quality improvement	Referral management for more severe symptoms		

*Work Group's synthesis of collaborative care model for MDD based on literature available through January 2015.
Abbreviations: CBT: Cognitive Behavioral Therapy, CRNP: Certified Registered Nurse Practitioner

IX. Management

Table 6: Classification of MDD Symptoms Severity and Risk Modifiers

Severity Level	PHQ-9 Total Score	Number of Symptoms According to DSM-5	Functional Impairment
Mild	10-14	2	Mild
Moderate	15-19	3	Moderate
Severe	≥20	4 or 5	Severe
Modifiers			
Complications	Co-occurring PTSD, substance use disorder (SUD), psychosis, suicide risk, mania, significant social stressors, significant anxiety		
Chronicity	More than two years of symptoms despite treatment		
Treatment-Resistant Depression	At least two adequate treatment trials and lack of full response to each [22]		

Table 7: Definitions of Evidence-based Psychotherapy

Evidence-based Psychotherapy	Definition
Cognitive behavioral therapy (CBT)	Interventions that treat MDD by teaching patients to modify both thinking and behavior. Patients learn to track their thinking and activities and identify the affective and behavioral consequences of those thoughts and activities. Patients then learn techniques to change thinking that contributes to depression and schedule activities to improve mood. CBT can also be administered via computer-based programs in which case it is known as computer-based cognitive behavioral therapy (CCBT).
Interpersonal therapy (IPT)	IPT is derived from attachment theory and treats MDD by focusing on improving interpersonal functioning and exploring relationship-based difficulties. IPT addresses the connection between patients' feelings and current difficulties in their relationships with people in their life by targeting four primary areas - interpersonal loss, role conflict, role change, and interpersonal skills.
Mindfulness-based cognitive therapy (MBCT)	MBCT integrates traditional CBT interventions with mindfulness-based skills, including and mindfulness meditation, imagery, experiential exercises, and other techniques that aid patients in experiencing affect without necessarily attempting to change it. With regard to cognitions, unlike cognitive therapy, MBCT does not so much seek to modify or eliminate dysfunctional thoughts as to become more detached and able to observe thoughts as objects.
Behavioral therapy (BT)	BT for major depression refers to a class of psychotherapy interventions which treat MDD by teaching patients to increase rewarding activities. Patients learn to track their activities and identify the affective and behavioral consequences of those activities. Patients then learn techniques to schedule activities to improve mood. BT emphasizes training patients to monitor their symptoms and behaviors to identify the relationships between them.
Behavioral activation (BA)	BA is a particular version of BT which targets the link between avoidant behavior and depression and expands the treatment component of BT.
Acceptance and commitment therapy (ACT)	ACT is a manualized psychotherapy intervention derived from relational frame theory that emphasizes acceptance of emotional distress and engagement in goal directed behaviors. A key feature of these interventions is acceptance rather than avoidance of emotional pain. This acceptance is thought to reduce affective symptom severity. To facilitate effective behavior change, ACT emphasizes identification of personal values and learning to act based on those values in spite of inevitable distress as opposed to having behaviors be focused on avoiding pain and adversity.
Problem-solving therapy (PST)	PST is defined as a discrete, time-limited, structured psychological intervention that focuses on learning to cope with specific problem areas and where therapist and patient work collaboratively to identify and prioritize key problem areas; to break problems down into specific, manageable tasks; to problem solve; and to develop appropriate coping behaviors for problems. The intervention is short-term and the mode of action is hypothesized as skills acquisition.

Table 8: Antidepressant Dosing[1] and Monitoring [23]

Class	Agent	Initial Dose	Titration Schedule[2]	Max. Dose/day	Initial Dose or Guidance: Special Populations			
					Geriatric	Renal	Hepatic	Pregnancy FDA Cat.
SSRIs	Citalopram	20 mg once a day	20 mg weekly	40 mg; 20 mg geriatric	10-20 mg once a day	Avoid: CrCl <20 ml/min	↓ dose	C
	Escitalopram	10 mg once a day	10 mg weekly	20 mg	5-10 mg once a day	Avoid: CrCl <20 ml/min	10 mg once a day	C
	Fluoxetine	20 mg once a day	20 mg every 2 weeks	80 mg	10 mg once a day	↓ dose and/or ↓ frequency	↓ dose 50%	C
	Fluoxetine weekly	90 mg once a week	N/A	90 mg	90 mg once a week	No change	Avoid	C
	Paroxetine	20 mg once a day	20 mg weekly	50 mg	10 mg once a day	10 mg once a day	10 mg once a day	D
	Paroxetine CR	25 mg once a day	12.5 mg weekly	62.5 mg; 50 mg geriatric	12.5 mg; once a day	12.5 mg once a day	12.5 mg once a day	D
	Sertraline	50 mg once a day	50 mg weekly	200 mg	25 mg once a day	25 mg once a day	↓ dose	C
	Vilazodone	10 mg once a day	10 mg weekly	20-40 mg	5 mg	No change	No change	C

[1] All dose oral except selegiline patch
[2] Recommended minimum time between dose increases

Class	Agent	Initial Dose	Titration Schedule[2]	Max. Dose/day	Initial Dose or Guidance: Special Populations			
					Geriatric	Renal	Hepatic	Pregnancy FDA Cat.
SNRIs	Duloxetine	20-30 mg twice a day	20-30 mg weekly	60 mg	20 mg once or twice a day	Avoid if CrCl <30 ml/min	Avoid	C
	Venlafaxine IR	37.5 mg twice a day	75 mg weekly	225-375 mg	25mg once or twice a day	↓dose based on CrCl	↓ dose 50%	C
	Venlafaxine XR	75 mg once a day	75 mg weekly	225 mg	37.5-75 mg once a day	↓dose based on CrCl	↓ dose 50%	C
	Levomilnacipran	20 mg once a day	20-40 mg every 2 days	120 mg	Refer to adult dosing, Consider CrCl	Max doses less if CrCl <60ml/min	No change	C
	Desvenlafaxine	50 mg once a day	Unnecessary	100 mg; no benefit at doses >50 mg per day	Consider CrCl	CrCl <30 ml/min, 25mg once daily	No change	C
5-HT3 receptor antagonist	Vortioxetine	10 mg once a day	10 mg once daily	5-20mg	5-20 mg once a day	No change	Severe: not recommended	C
NDRIs	Bupropion IR	100 mg twice a day	100 mg weekly	450 mg	37.5mg twice a day	Has not been studied	Severe: 75 mg/day	C
	Bupropion SR	150 mg once a day	150 mg weekly	200 mg twice daily	100 mg once a day		100 mg once a day or 150 mg every other day; Mod to severe: use with extreme caution	C
	Bupropion XR	150 mg once a day	150 mg weekly	450 mg	150 mg once a day			C

Class	Agent	Initial Dose	Titration Schedule[2]	Max. Dose/day	Initial Dose or Guidance: Special Populations			
					Geriatric	Renal	Hepatic	Pregnancy FDA Cat.
5-HT2 receptor antagonist	Trazodone	50 mg three times a day	50 mg weekly	600 mg	25-50 mg at bedtime	Has not been studied	Unknown	C
	Nefazodone	100 mg twice a day	100 mg weekly	600 mg	50 mg twice a day	No change	Avoid	C
Noradrenergic antagonist	Mirtazapine	15 mg daily at bedtime	15 mg weekly	45 mg	7.5 mg at bedtime	Caution in renal impairment	Cl ↓ 30%	C
TCAs	Amitriptyline	25-50 mg daily single dose at bedtime or in divided doses	Weekly	300 mg	10–25 mg at bedtime	No change	Lower dose and slower titration recommended	C
	Imipramine	25 mg 1- 4 times a day	Weekly	300 mg	10-25 mg at bedtime	No change		Unclassified
	Nortriptyline	25 mg 3-4 times a day	Weekly	150 mg	30-50 mg/day	No change		Unclassified
	Desipramine	25-50 mg once daily or in divided doses	Weekly	300 mg; 150 mg geriatric	10-25 mg once a day	No change		Unclassified
	Doxepin	25-50 mg daily at bedtime or twice a day	Weekly	300 mg	Low dose, once daily	No change		C

Class	Agent	Initial Dose	Titration Schedule[2]	Max. Dose/day	Initial Dose or Guidance: Special Populations			
					Geriatric	Renal	Hepatic	Pregnancy FDA Cat.
MAOIs	Isocarboxazid	10 mg twice a day	10 mg/day every 2-4 days to 40 mg/day. After first week, may increase by up to 20 mg/week to a maximum of 60 mg/day.	60 mg	10 mg twice a day	Avoid in any renal impairment. Contraindicated in severe	Contraindicated in patients with a history of liver disease or abnormal LFTs	C
	Phenelzine	15 mg 3 times a day	Increase rapidly, based on patient tolerance, to 60-90 mg/day	90 mg; 60 mg geriatric	7.5 mg once a day	Avoid if severe	Avoid	Undetermined
	Selegiline patch	6 mg/24 hours	3 mg/24 hours every 2 weeks	12 mg/24 hours	6 mg/24 hours	Use in patients with a CrCl <15 ml/min has not been studied	Mild to mod: no adjustment; Severe: not studied	C
	Tranylcypromine	10 mg twice a day	10 mg weekly	60 mg	10 mg twice a day	No change	Avoid	C

Abbreviations: 5-HT = serotonin, BID = twice a day, CrCl = creatinine clearance, CR = controlled release, IR = immediate release, LFT = liver function test, MAOI = monoamine oxidase inhibitor, mg = milligram, min = minute, ml = milliliter, N/A= not applicable, NDRI= norepinephrine and dopamine reuptake inhibitor, QD = once a day, QHS = once before bedtime, QID = four times a day, QOD = every other day, SNRI = serotonin norepinephrine reuptake inhibitor, SR = sustained-release, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant, TDM = therapeutic drug monitoring, XR = extended-release

Table 8: Antidepressant Dosing and Monitoring

Class	Agent	Initial Dose	Titration Schedule	Max Dose/day	Geriatric	Renal	Hepatic	Pregnancy FDA Cat.
NMDA [1] non-competitive	Esketamine (Spravato)	56 mg twice weekly	May increase dose to 84 mg twice weekly (after first dose) based on response. Beginning on week 5, use previous dose (56 or 84 mg) and decrease to once weekly. At week 9, continue previous dose once weekly or decrease to every 2 weeks	84 mg twice a week	28-84 mg twice weekly for 4 weeks	Has not been studied	Mild-moderate: has not been studied Severe: not recommended	Not assigned – use is not recommended in pregnancy
GABA [2] A Receptor Positive Modulator	Brexanolone (Zulresso)	0-4 hours: 30 mcg/kg/hour	4 to 24 hours: 60 mcg/kg/hour 24 to 52 hours: 90 mcg/kg/hour; may reduce dose to 60 mcg/kg/hour based on tolerability 52 to 56 hours: 60 mcg/kg/hour 56 to 60 hours: 30 mcg/kg/hour	90 mcg/kg/hr.	Not listed	Avoid if eGFR<15 mL/min/1.73 m^2	No adjustment	Not assigned
Second Generation (Atypical) Antipsychotic	Brexpiprazole (Rexulti)	0.5-1 mg once daily	Titrate at weekly intervals based on response and tolerability to 1 mg once daily (if initial dose is 0.5 mg), followed by an increase to the target dose of 2 mg once daily	3 mg once daily	0.5 mg once daily	If CrCl <60 mL/min: 2 mg once daily max dose	Moderate to severe: 2 mg once daily max dose	C

D/NRI* AND NMDA	Dextromethorphan HBr and Bupropion HCl (Auvelity)	Dextromethorphan 45 mg/ bupropion 105 mg once daily	After 3 days, increase to dextromethorphan 45 mg/bupropion 105 mg twice daily, administered at least 8 hours apart	Dextromethorphan 90 mg/bupropion 210 mg	Refer to adults dosing	If eGFR 30-59 mL/min/1.73 m^2: dextro 45mg/bupropion 105 mg If eGFR <30 mL/min/1.73 m^2: avoid	Severe: not recommended	Not assigned – use is not recommended in pregnancy

Table 9: Antidepressant Adverse Event Profiles [23]

Drug Class or Drug	Amine Update		Anti-cholinergic Activity	Sedation (H1 activity)	Orthostatic Hypotension (alpha-1 act.)	Cardiac Conduction Effects	GI Effects	Weight Gain	Comments
	5HT	NE							
SSRIs	+++	0/+	0/++	0/ +	0	0/+	+++	0/+	▪ Sexual dysfunction common ▪ Citalopram and escitalopram dose-related conduction effects ▪ Paroxetine most anticholinergic; avoid in elderly ▪ Paroxetine and fluoxetine CYP2D6 and CYP2B6 inhibitors ▪ Vilazodone CYP2C8 2C1 and 2D6 inhibitor
SNRIs	++/+++	++/+++	0/+	0/+	0/++	0/+	++/+++	0/+	▪ Sexual dysfunction common ▪ Venlafaxine NE activity dose-related ▪ Desvenlafaxine active metabolite of venlafaxine
Bupropion	0/+	0/+	0	0	0	0	++	0	▪ Risk of seizures is dose-related; avoid if seizure history, bulimia or eating disorder ▪ CYP2D6 inhibitor
Trazodone Nefazodone	+++	0/+	0	+++	0	0/+	++	0/+	▪ Very sedating ▪ Nefazodone associated with a higher risk of hepatotoxicity ▪ Nefazodone CYP3A4 inhibitor
Mirtazapine	0/+	0/+	0	+++	0/+	0	0/+	+++	▪ Doses >15 mg less sedating ▪ May stimulate appetite
Vortoxetine	+++	++	0	0	0	0	+++	0	

Table 9: Antidepressant Adverse Event Profiles

Drug Class/ Drug	GI Effects	Weight Gain/Loss	Comments
NMDA Receptor Antagonist Spravato	Prevalence >10%: Dysgeusia, nausea, vomiting Prevalence <10%: constipation, diarrhea, xerostomia	Weight gain	-Increased SBP and DBP - Nervous system effects: dissociation, anxiousness, numbness, spinning, dizziness can occur during and after administration -Sexual dysfunction can occur -Suicidal tendencies in adults ≤24 years
GABA A Receptor Positive Modulator Zulresso	Diarrhea, dyspepsia, and xerostomia all <10% prevalence	Weight loss	-Excessive sedation and sudden loss of consciousness that requires stopping infusion -Flushing and hot flashes -Dizziness, presyncope, and vertigo also very common
Second Generation (Atypical) Antipsychotic Brexpiprazole	Abdominal pain, constipation, diarrhea, dyspepsia, flatulence, increased appetite, nausea, sialorrhea, xerostomia all 10% prevalence	Weight gain	-inner sense of restlessness -Akathisia -Increased risk of death for older patients with dementia-related psychosis -Increased risk of suicidal thoughts and actions
D/NRI* AND NMDA Auvelity	Diarrhea, Nausea, decreased appetite, constipation All GI side effects <10% prevalence, except nausea >10%	Weight loss	-Dizziness is most common ADE -Nausea is most common GI related ADE -Sexual dysfunction can occur -Excessive sweating and fatigue -Suicidal ideation and suicidal tendencies in pediatric and young adult populations -Anxiety also seen in trials

* Dopamine/Norepinephrine reuptake inhibitor; 1 NMDA N-Methyl-D-Aspartate receptor antagonist; 2 GABA Gamma-Aminobutyric Acid

- **Spravato is non formulary for both Medicaid and commercial formulary.**

  PA Spravato Medical BH.pdf (sitecorecontenthub.cloud)

  PASpravato_Medicaid.pdf (sitecorecontenthub.cloud)

- **Zulresso (brexanolone)- is non formulary for both Medicaid and commercial formulary.**

  PAZulresso_BH.pdf (sitecorecontenthub.cloud)

  PAZulresso_BH_Medicaid.pdf (sitecorecontenthub.cloud)

- **Rexulti (Brexpiprazole)- is non formulary for both Medicaid and commercial formulary.** PAAtypicalAntipsychotics.pdf (sitecorecontenthub.cloud)

  PAAtypicalAntipsychotics_Medicaid.pdf (sitecorecontenthub.cloud)

- **Auvelity (Dextromethorphan & Bupropion)- is non formulary for both Medicaid and commercial formulary.**

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Drug Class or Drug	Amine Update		Anti-cholinergic Activity	Sedation (H1 activity)	Orthostatic Hypotension (alpha-1 act.)	Cardiac Conduction Effects	GI Effects	Weight Gain	Comments
	5HT	NE							
TCAs	+/+++	+/+++	+/+++	0/+++	+/+++	++/+++	0/+	0/++	▪ Desipramine and nortriptyline more tolerable; least sedating, anticholinergic and orthostatic hypotension ▪ Therapeutic blood concentrations established for desipramine, imipramine, and nortriptyline
MAOIs	0	0	0	0/+	0/+	0	0/+	0/+	▪ Requires a low tyramine diet except selegiline 6 mg/24 hours patch ▪ Contraindicated with sympathomimetics and other antidepressants ▪ Observe appropriate washout times when switching from or to another class of antidepressant

Key: +++ = strong effect, ++ = moderate effect, + = minimal effect, 0 = no effect

Abbreviations: MAOI = monoamine oxidase inhibitor, SNRI = serotonin norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant

Table 10: Augmentation, Adjunct and Alternative Pharmacotherapy [23]

Class	Agent	Initial Dose	Titration Schedule[3]	Max. Dose/day	Initial Dose or Guidance: Special Populations			
					Geriatric	Renal	Hepatic	Pregnancy FDA Cat.
SGAs	Aripiprazole	2-5 mg once a day	2-5 mg after ≥1 week	15 mg	2 mg once a day	No change	No change	C
	Olanzapine	2.5-5 mg once a day	2.5-5 mg weekly	20 mg	2.5 mg once a day	No change	No change	C
	Quetiapine	50 mg once a day for 1 day	100 mg daily as tolerated	300 mg	50 mg once a day	No change	Initial 25 or 50 mg once a day	C
	Risperidone	0.25-0.5 mg once a day	0.5 mg daily	3 mg	0.25 mg once a day	Adjust if CrCl <30 ml/min	Severe: Caution	C
	Ziprasidone	20 mg twice a day	20 mg twice a day every 2-4 days	160 mg	20 mg twice a day	No change	Caution	C
5-HT1A & -HT2 agonist	Buspirone	7.5 mg twice a day	7.5 mg twice a day weekly	60 mg	7.5 mg twice a day	Avoid if severe	Avoid if severe	B
Lithium	Lithium	300 mg 1-2 times a day	300 mg weekly	1200 mg	150mg once or twice a day	↓ dose 25% - 75%	No change	D
Thyroid hormone	Liothyronine	25 µg once a day	May be increased to 50 µg/day after ~1 week	50 µg	5 µg once a day; increase by 5 µg/day every 2 weeks	No change	No change	A
Herbal	St. John's wort	300 mg 2-3 times a day	Unknown	1200 mg	Unknown	Has not been studied	Has not been studied	Avoid

Abbreviations: 5-HT = serotonin, CrCl = creatinine clearance, mg = milligram, µg = microgram, SGA = Second Generation Antipsychotic

[3] Recommended minimum time between dose increases

XI. References

1. National Alliance on Mental Illness. *Depression*. 2015; https://www.nami.org/Learn-More/Mental-Health-Conditions/Depression. Accessed December 7, 2015.
2. Marcus M, Yasamy MT, Ommeren MV, Chisholm D, Saxena S. Depression. A global public health concern. *WHO Department of Mental Health and Substance Abuse.*1-4. http://www.who.int/mental_health/management/depression/who_paper_depression_wfmh_2012.pdf
3. *Global health estimates 2014 summary tables: YLD by cause, age and sex, 2000-2012.* World Health Organization, Geneva;June 2014. http://www.who.int/healthinfo/global_burden_disease/en/.
4. Greenberg PE, Fournier AA, Sisitsky T, Pike CT, Kessler RC. The economic burden of adults with major depressive disorder in the United States (2005 and 2010). *J Clin Psychiatry.* Feb 2015;76(2):155-162.
5. Pratt L, Brody D. Depression in the U.S. household population, 2009–2012. *Hyattsville, MD: National Center for Health Statistics.* 2014;NCHS data brief, No. 172.
6. *Depression and the military*. March 29, 2012; http://www.healthline.com/health/depression/military-service#1. Accessed November 15, 2015.
7. Hoge CW, Auchterlonie JL, Milliken CS. Mental health problems, use of mental health services, and attrition from military service after returning from deployment to Iraq or Afghanistan. *JAMA.* Mar 1 2006;295(9):1023-1032.
8. Kessler RC, Heeringa SG, Stein MB, et al. Thirty-day prevalence of DSM-IV mental disorders among nondeployed soldiers in the US Army: Results from the Army study to assess risk and resilience in service members (Army STARRS). *JAMA Psychiatry.* 2014;71(5):504-513.
9. Gadermann AM, Engel CC, Naifeh JA, et al. Prevalence of DSM-IV major depression among U.S. Military personnel: Meta-analysis and simulation. *Mil Med.* Aug 2012;177(8 Suppl):47-59.
10. LeardMann CA, Powell TM, Smith TC, et al. Risk factors associated with suicide in current and former US military personnel. *JAMA.* 2013;310(5):496-506.
11. Veterans Health Administration Mental Health Services. Preliminary findings regarding prevalence and incidence of major depressive Disorder (MDD), non-MDD depression diagnoses, and any depression diagnosis in FY2015 among Veterans. Veterans Health Administration Mental Health Services; 2015.
12. Society for Medical Decision Making Committee on Standardization of Clinical Algorithms. Proposal for clinical algorithm standards. *Med Decis Making.* Apr-Jun 1992;12(2):149-154.
13. Kroenke K, Spitzer RL, Williams JB. The Patient Health Questionnaire-2: Validity of a two-item depression screener. *Med Care.* Nov 2003;41(11):1284-1292.
14. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM), 5th ed. Washington, DC: American Psychiatric Association; 2013.
15. O'Connor EA, Whitlock EP, Gaynes BN. Screening for and treatment of suicide risk relevant to primary care--in response. *Ann Intern Med.* Aug 20 2013;159(4):307-308.
16. Coventry PA, Hudson JL, Kontopantelis E, et al. Characteristics of effective collaborative care for treatment of depression: A systematic review and meta-regression of 74 randomised controlled trials. *PLoS One.* 2014;9(9):e108114.
17. Thota AB, Sipe TA, Byard GJ, et al. Collaborative care to improve the management of depressive disorders: A community guide systematic review and meta-analysis. *Am J Prev Med.* May 2012;42(5):525-538.

18. Cape J, Whittington C, Bower P. What is the role of consultation-liaison psychiatry in the management of depression in primary care? A systematic review and meta-analysis. *Gen Hosp Psychiatry.* May-Jun 2010;32(3):246-254.
19. van Straten A, Hill J, Richards DA, Cuijpers P. Stepped care treatment delivery for depression: A systematic review and meta-analysis. *Psychol Med.* Mar 26 2014:1-16.
20. Firth N, Barkham M, Kellett S. The clinical effectiveness of stepped care systems for depression in working age adults: A systematic review. *J Affect Disord.* Jan 1 2015;170:119-130.
21. van der Feltz-Cornelis CM, Van Os TW, Van Marwijk HW, Leentjens AF. Effect of psychiatric consultation models in primary care. A systematic review and meta-analysis of randomized clinical trials. *J Psychosom Res.* Jun 2010;68(6):521-533.
22. Rush AJ, Fava M, Wisniewski SR, et al. Sequenced treatment alternatives to relieve depression (STAR*D): Rationale and design. *Control Clin Trials.* Feb 2004;25(1):119-142.
23. Lexi-Drugs, Hudson, Ohio: Lexi-Comp, Inc. Accessed March 30, 2016.
24. Kupfer DJ. Recurrent depression: Challenges and solutions. *J Clin Psychiatry.* 1991;52:28-34.
25. Andrews J, Guyatt G, Oxman AD, et al. Grade guidelines: 14. Going from evidence to recommendations: The significance and presentation of recommendations. *J Clin Epidemiol.* Jul 2013;66(7):719-725.
26. Andrews JC, Schunemann HJ, Oxman AD, et al. Grade guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. *J Clin Epidemiol.* Jul 2013;66(7):726-735.
27. *The guidelines manual.* London: National Institute for Health and Care Excellence;2012. http://www.nice.org.uk/article/pmg6/resources/non-guidance-the-guidelines-manual-pdf.
28. Martinez Garcia L, McFarlane E, Barnes S, Sanabria AJ, Alonso-Coello P, Alderson P. Updated recommendations: An assessment of NICE clinical guidelines. *Implement Sci.* 2014;9:72.

Resource: Brochure "Understanding Depression: A Resource for Providers and Patients"
https://www.healthquality.va.gov/guidelines/MH/mdd/_MDDTool4Depression4x6BookletNewStyle121516508.pdf