# **Quality** Care Network

# **Depression Screening & Management in the Adult:**

Depression is the fourth most common diagnosis for University Hospital employed patients and dependents. Universal screening is recommended for the general population at their routine healthcare visit. Over the age of twelve, in any 2-week period, 7.6% of the United States population had depression in 2009-2012, according to the Centers for Disease Control and Prevention (CDC, National Center for Health Statistics, 2016). It is associated with "significant healthcare needs, school problems, loss of work and earlier mortality" (CDC, 2016). Furthermore, the financial cost (including workplace costs, direct costs, suicide costs and the economic burden) was estimated at \$210.5 billion in 2010, per the CDC (2017). The UH Quality Care Network (UHQCN) and the physician led board of directors developed and reviewed this Clinical Practice Guideline (CPG).

#### **Positive Screening:**

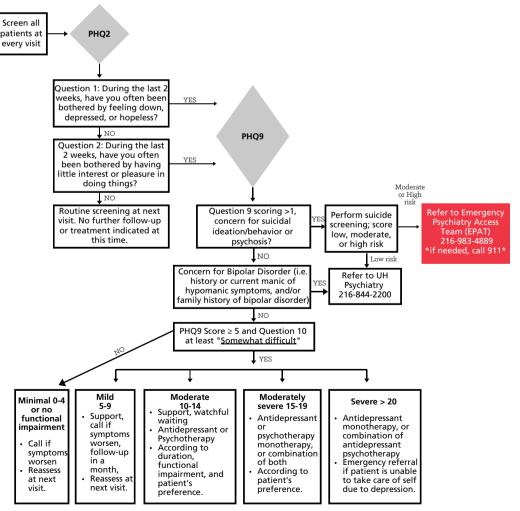
- Rule out common medical conditions which may be contributing.
- Determine the amount and frequency of substance use.
- Determine the context of the depression.
- Determine the impact on functioning - relationships, parenting, work, school, etc.
- Determine the patient's philosophy of healing: Do they prefer medications, talk therapy, complementary/nonpharmaceutical approaches.
- Ask, then Listen.
- Don't interrupt or assume.
- Don't underestimate the importance of your presence and your patience

These Clinical Practice Guidelines are guidelines only. In no way should these be used as a substitute for clinical or medical judgment.

For specialty patient populations such as elderly or post-partum patients, refer to evidenced based practice guidelines to best serve these populations' unique needs.



# **Depression Screening & Diagnosis** Begin by reviewing patient's PMH including medication and substance abuse history



November 2024

page 1

# **Diagnosis**:

Per DSM 5 (2013): Major Depressive Disorder 5+ symptoms must be present consistently nearly every day in a 2 week period and illustrate a deviation from baseline:

- Depressed mood most of the day\*
- Markedly diminished interest or pleasure in all/nearly all activities most days\*
- Significant unintended weight loss (or weight gain)
- Insomnia or hypersomnia
- Psychomotor agitation or retardation
- Fatigue or energy loss
- Feeling of worthlessness or excessive or inappropriate guilt
- Diminished ability to think, concentrate, or indecisiveness
- Recurrent thoughts of death, suicidal ideation without a specific plan, suicide attempt, or specific suicidal plan

\*One of the symptoms must be depressed mood or loss of interest/pleasure.

# Suggested Follow Up Schedule with the Primary Care Provider

- Each patient is unique. Adjust scheduling based on level of severity, degree of response to therapy, and medications, based on your clinical judgment and individual patient needs.
- Follow-up appointments are based on initial visit and screening, from weekly to monthly in a acute treatment phase.

Please note, for the patient reeiving psychotherapy this schedule refers to when they will see their Primary Care Provider in between psychotherapy appointments.

# At each visit assess for:

- Suicidal Ideation and suicidal behaviors
  - If concerned about a risk of suicide, refer to mental health professionals and arrange emergency transport, if indicated
  - If concern for bipolar disorder, refer to mental health professionals
- PHQ9 Score Compare and contrast previous PHQ9 scores at each visit to previous PHQ9
  - It's important to observe a trend in the decrease of the score
  - To calculate % change PHQ9 total score from baseline to current visit: (Baseline score minus current score) / divided by baseline score
  - Pay attention to question 9 for suicidal risk
- Symptoms of depression
- Change from patient's baseline
- Side Effect Tolerability
- Patient Feedback

If and when appropriate consider supplementing follow-up with telemedicine interventions such as telephonic follow-up based on the patient's preferences and needs.

# PCP Follow-up Schedule for the Patient Receiving Medication

For patients also receiving psychotherapy with medication, the psychotherapy schedule will be determined by the patient and the psychotherapy. This refers to when the patient in psychotherapy will see their Primary Care Provider. As needed, adjust PCP schedule.

#### Patient Office Visit with PHQ9 ≥ 10 and prefer medication treatment

- Initiate antidepressant therapy with a SSRI if not contraindicated.
- Provide patient with anticipatory guidance related to medication side effects.
- Counsel patient that it may take up to 4-6 weeks for medications to be fully effective.

#### 2 Week PCP Office Visit

Assess depression severity with PHQ9, suicidal risk, treatment response, and side effect tolerability including Intolerable Side Effects (ISE).

- If worsening of symptoms and/or concern for suicidal ideation refer to mental health professionals and arrange emergency transportation, if indicated.
- If ISE, may consider a different SSRI or other antidepressants.

#### 1 Month PCP Office Visit

Assess depression severity with PHQ9, suicidal risk, treatment response, and side effect tolerability.

- If PHQ9 percent change ≥ 25% from without ISE or no side effect(s), continue with the same dose of medication, and follow-up in 4 weeks;
- If PHQ9 percent change < 25% from baseline without ISE consider dose adjustment, additional medication or alternative medication and psychotherapy (if not yet initiated); If ISE, alternative medication should be considered.

#### 2 Month PCP Office Visit

Assess depression severity with PHQ9, suicidal risk, treatment response, and side effect tolerability.

- If PHQ9 percent change ≥ 50% from without ISE or no side effect(s), continue with the same treatment and follow-up in 1 month;
- If PHQ9 percent change < 50% from baseline without ISE consider dose adjustment, additional medication or alternative medication and psychotherapy (if not yet initiated); If ISE, alternative medication should be considered.

#### 3 Month PCP Office Visit

Assess depression severity with PHQ9, suicidal risk, treatment response, and side effect tolerability.

- If PHQ9 total score with < 5 without ISE, continue with the same treatment and move onto continuation phase for 6-9 months with every 1-3 month visits.
- If PHQ9 percent change ≥ 5 and percent change ≥ 50% consider dose adjustment, additional medication or alternative medication and psychotherapy, if not yet initiated.
- If PHQ9 percent change ≥ 5 and percent change < 50% strongly consider alternative medication and psychotherapy (if not yet initiated).

# PCP Follow-up Schedule for the Patient Receiving Psychotherapy

The psychotherapy schedule will be determined by the patient and psychotherapist. This refers to when the patient in psychotherapy will see their Primary Care Provider. As needed, adjust PCP schedule.

\*\*Periodically, request updates on the patient's status post referral to therapy. Frequency of updates should be decided with the therapist and based on the patients' initial depressive symptom severity and clinical judgment of the PCP.

#### Patient Office Visit with PHQ9 < 19

- Per patient's preference recommend a therapist.
- Assess if the patient needs/would like assistance scheduling with therapy, and assist the patient accordingly.

#### 2 Week PCP Office Visit

Assess for symptoms of improvement, depression severity, and suicidal risk. Re-evaluate PHQ9 at each visit. Ask if the patient has followed up with therapy at this time. Assess if the patient needs/would like assistance scheduling with therapy, and aid the patient accordingly.

- If symptom improvement and the patient has followed up with psychotherapy, the follow up interval with the PCP will be based on clinical indication.
- If no change in symptoms without follow-up therapist appointment to date follow-up visit in 2-4 weeks. A follow-up call is recommended to assist and confirm the patient has followed-up with scheduling with a therapist.
  - If symptoms worsen and PHQ9 >19 prior to seeing a therapist, an antidepressant should be strongly recommended while waiting for a therapy appointment.
- If no symptom improvement, symptom worsening or PHQ9 >19\*\* during the treatment with therapy consider initiating medication.

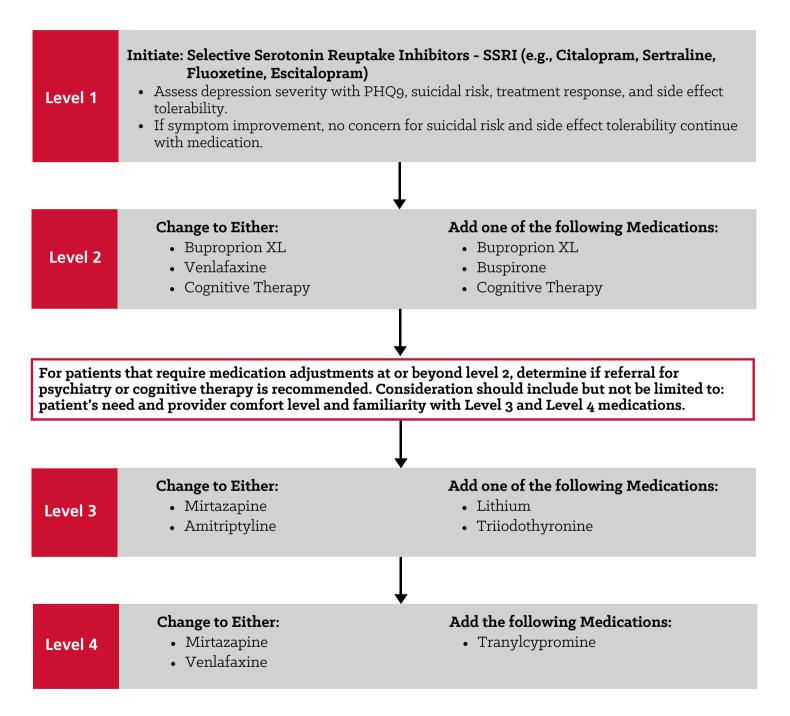
#### 3 Month PCP Office Visit

Assess for symptoms of improvement depression severity and suicidal risk. Re-evaluate PHQ9.

- If PHQ9 score improved and symptoms improved continue with treatment and follow up every 3- 6 months.
- If no symptom improvement with worsening PHQ9 score, and/or PHQ9 ≥10 consider initiating medication, and psychiatry referral.

# STAR\*D Study

The Sequenced Treatment Alternative to Relieve Depression (STAR\*D) Study conducted by the National Institute of Mental Health (NIMH) in order to "determine the effectiveness of different treatments for people with major depression who have not responded to initial treatment with an antidepressant".



#### **Common Initial Oral Dosages for Adults < 60**

Selective Serotonin	Reuptake	Inhibitors	(SSRIs)
---------------------	----------	------------	---------

Citalopram 20 mg daily	\$
Escitalopram 10 mg daily	Ś
Fluoxetine 20 mg daily	¢
Paroxetine 20mg daily	¢
Sertraline 50mg daily	\$
Serotonin-Norepinephrine Inhibitors (SNRIs)	
Venlafaxine XR (Extended Release) 37.5mg-75mg daily	\$\$
Desvenlafaxine 50mg daily	\$\$\$
Duloxetine 30mg daily	\$\$
Levomilnacipran 20mg daily	\$\$\$
Miscellaneous Antidepressants	
Bupropion HCL XL (24-hour) 150mg every 24 hours	
Bupropion HCL SR (12-hour XL) (Sustained Release)150mg 2x daily	\$
*For Bupropion HCL SR, one a day for the first 3 days, then 2x daily (every 12 hours)	\$
Mirtazapine 15mg daily	*
M. Estended Beleves	\$

XL=Extended Release XR=Extended Release SR=Extended Release

#### Cost Estimates

\*Please note these are estimates. When determining costs, please keep in mind the patient's unique insurance situation.

\$ = Cheapest (Under \$100/30 day supply)
 \$ = Under \$150/30 day supply
 \$\$ = \$200-300/30 day supply
 \$\$\$ = \$300+/30 day supply
 \$\$\$\$ = \$400+/30 day supply

When starting medications, pay attention to specific guidance related to initiating treatment therapy. Certain medications may have required wash-out periods.

Additionally, when discontinuing therapy, certain medications may have weaning periods that are indicated.

Take time to educate and counsel patients appropriately related to this. Consider using tools such as the Teach-Back Method, where the patients teaches back the information that you shared with them. This gives the provider the opportunity to assess the patient's understanding and provide appropriate redirection accordingly.



## **Common Side Effects**

For more detailed information, please see Appendix B. For a comprehensive list of side effects refer to your drug reference guide.

- Anticholinergic
- Drowsiness
- Insomnia/agitation
- Orthostatic hypotension
- QTc Prolongation
- Gastrointestinal toxicity
- Weight gain
- Sexual dysfunction

Patients should be counseled and provided anticipatory guidance related to treatment efficacy potential side effects. Please note, this is NOT meant to be an extensive list. Consider patient specific drug interactions and patient specific needs. **Pharmacological Management** should be determined based on the individual patient's needs.

 For any questions related to medication management, consult with the UH Ambulatory Psychiatric Clinic at 216-844-2400 or 1-800-UH4Care

#### **Treatment & Management:**

If remission is achieved, continue the same treatment including the same medication(s) dose for 6-12 months from the first major depressing episode to prevent relapse.

• Note: An adequate treatment trial with a medication is commonly defined as the maximal recommended dose for a minimum period of 6-8 weeks.

\*\*For patients < 25 years old, refer to pediatric guidelines and for elderly, refer to best practice guidelines.

# Integrative Health: Non-Pharmacological Tools

# In addition to pharmacological management and therapy, educate the patient on lifestyle and behavioral changes.

- Exercise
- Sleep hygiene
- Healthy diet
- Stress management
- Light therapy for Seasonal Affective Disorder (SAD)
- Meditation/Mindfulness
  - "The Mindfulness and Acceptance Workbook for Depression" by Robinson & Strosahl
  - "The Mindul Way Through Depression" by Williams, Teasdale, Segal, & Cabot-Zinn

#### **UH Connor Integrative Health Network**

For more information related to integrative health, referring a patient, or patient schedule, call: 216-285-4070

#### **Social Determinants of Health Assessment**

In order to engage and empower patients to be active in their care, it is also necessary to assess Social Determinants of Health (SDOH). Patients can be unwillingly impacted by SDOH, which will impact a patients' capacity to adhere to their treatment plan.

Keep this in mind and assess accordingly to provide proper referrals to encircle the patients with support to achieve their optimal health. Consider:

- The patient's own understanding and perceptions can impact their willingness and capacity to understand their disease process and engage in their treatment plan.
- Culture, community/beliefs/family
- Behavioral and or psychological barriers that may be influencing and perpetuating lifestyle habits.
- Health literacy and comprehension related to educational resources
- Formulary inclusion and ability to afford medications

#### **Resources**

- <u>National Suicide Prevention Lifeline</u>: 1-800-274-8255
- PHQ-9 Screening Tool
- SAMSHA PHQ9 Screener & Scoring Tool
- Ohio Mental Health & Addiction Services
- CoverMyMeds
- WHO Handouts on Depression
- <u>National Institute of Mental Health</u>
   <u>Depression: What You Need to Know</u>

# Interventional Treatments for Major Depressive Disorder or Bipolar Depression at University Hospitals

Treatment	Indications	Referral	Coverage
Repetitive Transcranial Magnetic stimulation (rTMS)	Major depressive disorder fails at least 2 antidepressants from 2 different classes	Primary care physicians, psychiatrists, or nurse practitioners who manage patient's antidepressant(s)	Medicare – medical necessity Medicaid – pre-authorization Private insurer – pre-authorization
Intranasal esketamine (SPRAVATO)	Major depressive disorder fails at least 2 antidepressants from 2 different classes	Psychiatrists or nurse practitioners who manages patient's antidepressant(s)	Medicare – medical necessity Medicaid – pre-authorization Private insurer – pre-authorization
Electroconvulsive therapy (ECT)	Major depressive disorder or bipolar depression with at least moderate severity	Psychiatrists or nurse practitioners who manages patient's psychotropics	Medicare – medical necessity Medicaid – pre-authorization Private insurer – pre-authorization
Ketamine infusion	Major depressive disorder or bipolar depression	Psychiatrists or nurse practitioners who manages patient's psychotropics	Self-pay

Information current as of September, 2024. For more information, contact Dr. Kerming Gao

#### Documentation

Depression metrics relate to medication compliance, depression screenings, and appropriate follow-up.

Remember to Document:

- Annual PHQ2 Depression Screenings
- If answering yes to either PHQ2 Depression Screening questions, document follow-up PHQ9 screening
- Appropriate follow-up plan
- Diagnosis of depression when clinically indicated
- For patients that have achieved remission, remember to document accordingly when clinically indicated.
  - For example, for a patient that's in remission for major depression, documentation is required that will correct the initial diagnosis of major depression, then a code entry for major depression in remission once PHQ-9 < 5.</li>

#### UH Ambulatory Psychiatry Clinic

General Intake Referral

intake referral line to

consultation request,

information or call.

Line: 216-844-2400

• Call the general

refer a patient,

or to request additional

physician

#### Schedule with a UH Quality Care Network

# UH Provider App

- On your telephone or mobile device, download the UH Provider App.
  - Use this App to refer to a specialist.



#### CLINICAL PRACTICE GUIDELINE

#### References

American Psychiatric Association. (2013). Depressive Disorders. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Retrieved from: http://dsm.psychiatryonline.org/doi/full/10.1176/appi.books.9780890425596.dsm04#BCFHDJJH.

Centers for Disease Control and Prevention. (2016). Depression: Overview. Retrieved from: https://www.cdc.gov/mentalhealth/basics/mental-illness/depression.htm.

Centers for Disease Control and Prevention. (2016). National Centers for Health Statistics: Depression. Retrieved from: https://www.cdc.gov/nchs/fastats/depression.htm.

Dunn, J.D. and Tierney, J. G. (2006) A step therapy algorithm for the treatment and management of Chronic Depression. The American Journal of Managed Care. Volume 12(12). Retrieved from: http://www.ajmc.com/journals/supplement/2006/2006-10-vol12-n12suppl/oct06-2378ps335-s344?p=3.

Goldenberg, Neal. (2016). Guidelines for managing depression in primary care. Presentation to UH Primary Care Institute (5 March 2016).

Intermountain Health. (2015). Care process model: Management of depression-2015 update. Retrieved from: https://intermountainhealthcare.org/ext/Dcmnt?ncid=51061767.

Kroenke K, Spitzer RL, Williams JBW. The PHQ-9: Validity of a brief depression severity measure. J Gen Intern Med 2001; 16:606-613.

National Council Quality Assurance. (2017): Hedis 2018: Volume 1: Narrative. Retrieved from: http://www.ncqa.org/hedis-quality-measurement/hedis-measures/hedis-2018.

National Institute of Mental Health. NIMH Practical Clinical Trials: Sequenced Treatment Alternatives to Relieve Depression (STAR\*D) Study. Retrieved from: https://www.nimh.nih.gov/funding/clinical-research/practical/stard/index.shtml.

Simon, G. Roy-Byrne, P.P, & Solomon, D. (2017) Unipolar major depression in adults: Choosing initial treatment. Up To Date. Retrieved from: https://www.uptodate.com/contents/unipolar-major-depression-in-adults-choosing-initial-treatment? search=STAR\*D&source=search\_result&selectedTitle=2~16&usage\_type=default&display\_rank=2.

Williams, J. and J. Nieuwsma. (2017). Screening for depression in adults. Up To Date. Retrieved from: https://www.uptodate.com/contents/screening-for-depression-in-adults/print? source=search\_result&search=Depression&selectedTitle=2~150.

Special thanks to the CPG Development Team: Reviewed and revised September 2024 by Keming Gao, MD and Sona Kirpekar, MD. The 2021 CPG was developed by Patrick Runnels, MD, MBA, Sandeep Palakodeti, MD, MPH, Todd Zeiger, MD, Randy Jernejcic, MD, MMM, Deanna Cox, MSN, MBA, RN, Esther Thatcher, PhD, RN, and Taylor Dews. The original CPG was developed by Brad Hillard, DO, Robert Ronis, MD, PhD, Keming Gao, MD, PhD, Joseph Calabrese, MD, Patrick Runnels, MD, Adan Francoise, MD, Todd Zeiger, MD, William Steiner, MD, George Topalsky, MD, Tammy Brand PharmD, RPh, and Deanna Cox, BSN, MSN, RN. The UH Quality Care Network (UHQCN) and the physician led board of directors developed and reviewed this Clinical Practice Guideline (CPG).

#### © 2024 University Hospitals Health System, Inc.

Disclaimer: The contents of University Hospitals Quality Care Network ("QCN") clinical practice guidelines ("CPGs") are to be used as practical and deliberatively brief guides for licensed QCN provider participants. CPGs are not strict protocols and do not replace a licensed QCN provider participant's clinical judgment nor are they meant to be a replacement for licensed QCN provider participant's training, experience, continuing medical education and self-study on the latest literature and drug information. QCN has made every effort to ensure that the information provided inCPGs are based upon best available scientific evidence at the time of publication. Nonetheless, the CPGs should never be relied on as a substitute for proper assessment with respect to the particular circumstances of each case and the needs of each patient. QCN accepts no responsibility for any inaccuracies in a CPG, evidence based changes to best practices after publication of a CPG, or outcomes of any treatment regime recommended within a CPG. Send feedback to: Patrick Runnels, MD, MBA, UH Population Health Chief Medical Officer (Patrick.Runnels1@UHhospitals.org).

# **Uuality** Care Network

# Appendix A: Columbia-Suicide Severity Rating Scale

Screen with Triage Points for Primary Care

Ask questions that are in bold and underlined.		Past month	
Ask Questions 1 and 2	YES	NO	
1) <u>Have you wished you were dead or wished you could go to sleep and not wake up?</u>			
2) Have you had any actual thoughts of killing yourself?			
If YES to 2, ask questions 3, 4, 5, and 6. If NO to 2, go directly to question 6.			
3) <u>Have you been thinking about how you might do this?</u> e.g. "I thought about taking an overdose but I never made a specific plan as to when where or how I would actually do itand I would never go through with it."			
4) <u>Have you had these thoughts and had some intention of acting on them?</u> as opposed to "I have the thoughts but I definitely will not do anything about them."			
5) <u>Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?</u>			
<ul> <li>6) Have you ever done anything, started to do anything, or prepared to do anything to end your life?</li> <li>Examples: Collected pills, obtained a gun, gave away valuables, wrote a will or suicide note, took out pills but didn't swallow any, held a gun but changed your mind or it was grabbed from your hand, went to the roof but didn't jump; or actually took pills, tried to shoot yourself, cut yourself, tried to hang yourself, etc.</li> <li>If YES, ask: Was this within the past 3 months?</li> </ul>			

#### Response Protocol to C-SSRS Screening

Item 1 Behavioral Health Referral Item 2 Behavioral Health Referral Item 3 Behavioral Health Consult (Psychiatric Nurse/Social Worker) and consider Patient Safety Precautions Item 4 Behavioral Health Consultation and Patient Safety Precautions Item 5 Behavioral Health Consultation and Patient Safety Precautions Item 6 Behavioral Health Consult (Psychiatric Nurse/Social Worker) and consider Patient Safety Precautions Item 6 Behavioral Health Consult (Psychiatric Nurse/Social Worker) and consider Patient Safety Precautions Item 6 3 months ago or less: Behavioral Health Consultation and Patient Safety Precautions

Reference: Columbia Lighthouse Project. (2018). Columbia-Suicide Severity Rating Scale: Screen with Triage Points for Primary Care. Available at https://cssrs.columbia.edu/

#### Appendix B: Side Effects of Antidepressant Medications

\*For a comprehensive list of side effects, refer to your drug reference guide.

Drug	Anticholinergic	Drowsiness	Insomnia/ agitation	Orthostatic hypotension	QTc prolongation*	Gastrointestinal toxicity	Weight gain	Sexual dysfunction
Selective serotonin	Selective serotonin reuptake inhibitors (SSRIs) <sup>1</sup>							
Citalopram	0	0	1+	1+	1+ <sup>Δ</sup>	1+ (all SSRIs: see <sup>¶</sup> )	1+	3+
Escitalopram	0	0	1+	1+	1+	1+	1+	3+
Fluoxetine	0	0	2+	1+	1+	1+	1+	3+
Paroxetine	1+	1+	1+	2*	0 to 1+	1+	2+	4+
Sertraline	0	0	2*	1+	0 to 1+	2+0	1+	3+
Atypical agents								
Bupropion	0	0	2+ (immediate release) 1+ (sustained release)	0	1+	1+	0	0
Mirtazapine	1+	4+	0	0	1+	0	4+	1+
Serotonin-norepine	ephrine reuptake inh	ibitors (SNRIs) <sup>%</sup>	0				_	-
Desvenlafaxine <sup>N</sup>	0	0	1+	0	0	2+	unknown	1+
Duloxetine	0	0	1+	0	0	2+1	0-1+	1+
Levomilnacipran <sup>w</sup>	0 <sup>‡</sup>	0	0-1+	0-1+	0	2+1	0	1+
Venlafaxine¥	0	1+	1+	0	1+	2+	0-1+	3+

Scale: 0 = none; 1+ = slight; 2+ = low; 3+ = moderate; 4+ = high; ND = inadequate data.

\* Risk of QTc prolongation or torsades de pointes is also elevated with advanced age, female sex, heart disease, congenital long QT syndrome, hypokalemia or hypomagnesemia, elevated serum drug

concentrations (eg, drug overdose, interacting drugs, organ failure) and combination of drugs with QTc prolonging effects. Refer to topic on acquired long QT syndrome.

¶ All SSRIs and SNRIs are associated with transient nausea and gastrointestinal discomfort upon initiation or dose increase.

△ Based upon reports of dose related QTc prolongation and arrhythmia, the maximum recommended dose of citalopram is 20 mg for patients at increased risk of elevated citalopram serum concentrations. Sertraline is associated with higher rates of diarrhea.

¥ May cause persistent dose-related increases in blood pressure (primarily diastolic) and heart rate. Monitor blood pressure regularly.

\* Levomilnacipran has dose dependent effects on urinary hesitancy.

ΔΔ Gastrointestinal forms of anticholinergic side effects include: dry mouth, constipation, epigastric distress, decreased esophagogastric tone. Refer to "Anticholinergic" data for frequency rankings.

None of the SNRIs have anticholinergic activity. However, SNRIs can produce anticholinergic-like effects (which appear to be mediated by noradrenergic effects on the autonomic nervous system) such
 as dry mouth and constipation, and should be used with caution in narrow angle glaucoma. In addition, levomilnacipran is associated with urinary hesitancy.

Data from:

- Nelson JC. Tricyclic and tetracyclic drugs. In: The American Psychiatric Publishing Textbook of Psychopharmacology, 4th ed, Schatzberg AF, Nemeroff CB (Ed), American Psychiatric Publishing, Washington, DC 2009. p.263.
- 2. Wenzel-Seifert K, Wittmann M, Haen E: QTc prolongation by psychotropic drugs and the risk of torsade de pointes. Dtsch Arztebi Int 2011; 108:687.
- Reichenpfader U, Gartlehner G, Morgan LC, et al. Sexual dysfunction associated with second generation antidepressants in patients with major depressive disorder: Results from a systematic review with network meta-analysis. Drug Saf 2014; 37:19.
- 4. Howland RH. A benefit-risk assessment of agomelatine in the treatment of major depression. Drug Saf 2011; 34:709.
- Lexicomp Online. Copyright © 1978-2018 Lexicomp, Inc. All Rights Reserved.
- Baldwin DS, Chrones L, Florea I, et al. The safety and tolerability of vortioxetine: Analysis of data from randomized placebo-controlled trials and open-label extension studies. J Psychopharmacol 2016; 30:242.

Graphic 62488 Version 17.0

Retrieved from https://www.uptodate.com/contents/search?partner=LCO&search=star%20d%20trial

https://www.uptodate.com/contents/image?imageKev=PC%2F62488&topicKev=PSYCH%2F14685&search=star%20d%20trial&source=outline\_link&selectedTitle=1"13"

