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Antidepressant Medication Management and Quality Update for Patients with Major Depression, Part I

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MDD Overview

How to you treat antidepressant induced hyponatremia?

Question of the Month

Severity of hyponatremia is classified as acute or chronic, differentiated by sodium levels and patient symptoms. Mild-to-moderate hyponatremia is a more chronic and asymptomatic condition and is defined as a sodium concentration of 120 to 135 mEq/L. Severe hyponatremia is a medical emergency and is usually defined as a sodium concentration of <120 mEq/L or hyponatremia with symptoms that may include seizures, coma, and respiratory arrest. After severity is assessed, the patient's volume status is classified as hypervolemic, euvolemic, or hypovolemic.

The reported incidence of SSRI-induced hyponatremia ranges from 0.5-32%, and the risk is most highly correlated with patient-specific risk factors including older age (>65 years), female sex, concomitant use of diuretics, low body weight, and lower baseline serum sodium concentration. Euvolemic hyponatremia caused by SIADH is due to increased release of antidiuretic hormone (ADH). SIADH has been associated with many drugs often used in psychiatric patients, including nicotine, barbiturates, carbamazepine, antipsychotics, and antidepressants. In euvolemic patients, hyponatremia is most often due to SIADH, and patients typically have urine sodium levels >40 mEq/L. Patients presenting with SIADH are usually asymptomatic unless the sodium level is below 120 mEq/L. Free water excretion is impaired in SIADH, as evidenced by urine osmolality levels >100 mOsm/kg.

If hyponatremia occurs with SSRI therapy, it is likely to occur early in course of treatment. One study exploring this association found that the risk of hyponatremia was greatest within the first 2 weeks of treatment, further emphasized in other trials showing median time to onset was 9-11 days. In currently depressed patients with a history of hyponatremia from any cause, who are starting an SSRI, it is suggested to obtain a sodium level at baseline and again 2 weeks after.

In addition to the specific therapies that are aimed at correcting the hyponatremia, therapy should be directed at removing the offending agent. Most cases of hyponatremia resolve with discontinuation of the SSRI and providing supportive care based on the severity of hyponatremia. SIADH-induction cross-sensitivity among SSRI agents has been reported, but published data are scarce. A different SSRI may be initiated, but caution should be used and monitor serum Na+ concentrations at baseline and 1 to 2 weeks after initiation of therapy.

In addition to SSRIs, current evidence suggests a relatively higher risk of hyponatremia with SNRIs and mirtazapine as indicated in the majority of case reports and trials evaluating use in older adults. Bupropion, trazodone, and TCAs were implicated less often.

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Defining Major Depressive Disorder (MDD)

Screening

Who: all adult patients, per United States Preventative Services Task Force (USPSTF)

What: PHQ-9

- Total scores of 5, 10, 15, and 20 represent cut-points for mild, moderate, moderately severe and severe depression, respectively.
- PHQ-9 scores greater than or equal to 10 indicate possible MDD and potential need for pharmacotherapy.

When

The AAFP recommends a pragmatic approach to screening all adults who have not been screened previously and use clinical judgment in consideration of risk factors, comorbid conditions, and life events to determine if additional screening of high-risk patients is warranted.

DSM-5 Criteria for Diagnosis

Any positive screening must be followed up by additional assessment. Further assessment is often performed guided by the mnemonic device SIGECAPS (see below), in which each letter corresponds to one of the diagnostic criteria for MDD in the DSM-5.

To diagnose MDD five or more of the symptoms listed must be present during a 2-week period.

- at least one of the symptoms must be depressed mood or loss of interest or pleasure
- symptoms must not be attributable to another medical condition
- symptoms must represent a change from previous mood, cause significant distress or impair function, and occur daily or almost every day in most cases.
- weight change and suicidality are exceptions to the criteria of daily or near daily occurrence.

Mnemonic	Symptom	Description/Notes
		Depressed mood, empty, hopeless; may manifest as irritability, particularly in children or adolescents
S	Sleep disorder	Insomnia or hypersomnia
I	Interest deficit	Anhedonia
G	Guilt	Worthlessness, hopelessness, regret, excessive guilt; present to a degree that is excessive or delusional
E	Energy deficit	Fatigue or loss of energy
C	Concentration deficit	Indecisiveness or difficulty concentrating; in older adults, may be mistaken for dementia
A	Appetite disorder	Unintended weight loss or weight gain, increased or decreased appetite
P	Psychomotor changes	Slowed or agitated movements observed by others *Less common symptom, but indicative of highly severe disease
S	Suicidality	Recurrent thoughts or plans of death or self-harm; may be passive or active

Differential Diagnosis

Medication-Induced Depression

Numerous medications have been correlated with new-onset or worsening depression, and should be considered when providing a differential diagnosis.

Medication	Description and Notes
anticonvulsants	• Warning included broadly in FDA labeling, but not causally established
antihypertensives β-blockers, CCBs, α2 adrenergic agonists	• β-Blockers and α2-agonists may worsen cardinal symptoms of depression • Cardiovascular disease confounds correlation
hormonal therapies GnRH antagonists, corticosteroids, clomiphene, hormonal contraceptives	• Possible alterations of MAO activity from changes in estrogen and progesterone concentrations
interferon therapies	• Boxed warning for interferon alfa • Careful monitoring required during therapy • Symptoms usually remit quickly on medication discontinuation
isotretinoin	• Linked to depression and other mood disturbances • Recommended monitoring in iPledge
montelukast	• 2020: the FDA added a boxed warning in response to reports of serious adverse effects for mental health (depression, suicidality, other neuropsychiatric adverse events) • FDA recommended seeking alternatives for allergic rhinitis before initiating LTRAs
varenicline (Chantix®)	• 2016: the FDA removed a boxed warning of neuropsychiatric adverse effects (EAGLES study)
vesicular monoamine transporter 2 inhibitors (deu)tetrabenazine, valbenazine	• Boxed warning for deutetrabenazine and tetrabenazine • Observed in the setting of Huntington disease • Caused by depletion of synaptic monoamines
Suicidality	• Recurrent thoughts or plans of death or self-harm; may be passive or active

CCBs = calcium channel blockers; MAO = monoamine oxidase; leukotriene receptor antagonists = LTRAs

First-Line Pharmacotherapy for MDD

Moderate or severe depression (PHQ-9 scores ≥ 10)

pharmacotherapy is a first-line treatment

Mild depression (PHQ-9 scores <10):

pharmacotherapy may be considered based on:

- patient preference, or
- a lack of response to non-pharmacologic therapy, particularly cognitive-behavioral therapy (CBT)

Selection of pharmacotherapy for the individual patient relies on several factors:

- comorbid conditions
- previous medication trials
- patient preference
- cost
- ease of use
- medication interactions – drug-drug, drug-disease, drug-food, etc.

Comorbidity	Preferred Drug	Non-Preferred Drug or Drugs to Avoid
Cardiac/risk for QT prolongation	Sertraline	Avoid QT-prolonging drugs such as TCAs, doses of citalopram >20 mg/day
Tobacco use	bupropion SR (FDA approved for smoking cessation)	No contraindications
Seizure disorder, risk of seizures		bupropion TCAs
Peripheral neuropathy	• duloxetine (FDA approved for peripheral neuropathy/pain) • high-dose venlafaxine • TCAs	No contraindications
Eating disorder, active or historical		bupropion TCAs
Pregnant	• Mild to moderate depression*: psychotherapy preferred • Severe depression*: SSRIs (eg, sertraline, citalopram, escitalopram)	• paroxetine • MAOIs • vortioxetine (Trintellix®)
Cognitive dysfunction	• vortioxetine (Trintellix®; high level of evidence) • bupropion • duloxetine • SSRIs	Avoid drugs with anticholinergic effects, such as TCAs, paroxetine
Daytime sedation	Dose activating drug in the morning, such as fluoxetine, bupropion, vortioxetine (Trintellix®), duloxetine, or mirtazapine doses >30 mg	Avoid sedating drugs earlier in the day, such as mirtazapine doses <30 mg, paroxetine, or trazodone
Insomnia	Dose sedating drug in the evening/at night, such as mirtazapine doses <30 mg, or paroxetine, trazodone	Avoid activating drugs later in the day, such as fluoxetine, bupropion, vortioxetine (Trintellix®), duloxetine, or mirtazapine doses >30 mg
ADD/ADHD	• Bupropion • dextromethoraphan-bupropion (Avuelity®): newly approved for MDD	No contraindications
Sexual dysfunction	• bupropion • mirtazepine • Vortioxetine (Trintellix®)	• SSRIs (especially paroxetine) • SNRIs (especially venlafaxine)
Weight gain	• SSRIs (except paroxetine) • SNRI	• mirtazepine • paroxetine • TCAs
Polypharmacy	Consider drugs with low potential for CYP interaction, such as citalopram, sertraline, or mirtazapine	Strong CYP-interacting drugs, such as fluoxetine, fluvoxamine, paroxetine, or MAOIs
Suicide risk	Consider drugs low risk in overdose, such as most SSRIs and mirtazapine	• TCAs • MAOIS • Use citalopram cautiously due to risk of QT prolongation

*defined by PHQ-9 Score: 5-9 mild depression; 10-14 moderate depression; 15-19 moderately severe depression; 10-27 severe depression

First-Line Pharmacotherapy for MDD (continued)

Specifier and Criteria	Notes	First-Line Pharmacotherapy
With anxious features • Feeling "keyed up" or tense • Feeling often restless • Difficulty concentrating because of worry • Fear that something awful may happen • Feeling of losing control	• Prominent feature of both bipolar affective disorder and MDD • High anxiety levels are associated with higher suicide risk, longer duration of illness, and greater likelihood of treatment nonresponse	• SSRIs • SNRIs
With mixed features • Elevated, expansive mood • Inflated self-esteem or grandiosity • More talkative than usual or pressure to keep talking • Flight of ideas or racing thoughts • Increase in energy or activity, decreased need for sleep • Risky behavior	• Mixed features associated with a major depressive episode are a significant risk factor for development of bipolar I or bipolar II disorder	• Limited data; lurasidone (Latuda®) and ziprasidone (Geodon®) have demonstrated positive effects
With melancholic features • Loss of pleasure in all, or almost all, activities • Lack of response to good things happening • Depression that is regularly worse in the morning • Early morning awakening • Psychomotor changes • Significant anorexia or weight loss • Excessive or inappropriate guilt	• Psychomotor changes are almost always present and are observable by others • More common in more severe episodes • More likely to occur in patients with psychotic features	• No superiority data; SNRIs and TCAs have positive data
With atypical features • Significant weight gain or increase in appetite • Hypersomnia • Leaden paralysis • Long-standing pattern of interpersonal rejection sensitivity	• Hypersomnia: sleep > 10 hr/day (or an increase of ≥ 2 hr/day than when not depressed) • Leaden paralysis: feeling heavy, leaden, or weighted down, usually in arms or legs	• No superiority data overall; MAOIs superior to TCAs
With psychotic features • Delusions • Hallucinations	• Presence of either or both criteria merits specifier	• Second-generation antipsychotic in combination with antidepressant
With catatonia • Catalepsy, negativism • Waxy flexibility, posturing • Stupor, agitation • Mutism, echolalia, echopraxia • Mannerisms, stereotypies, grimacing	• Immobility and mutism are common • ≥3 symptoms required for diagnosis	• Benzodiazepines
With peripartum onset • During pregnancy, or • Within 4 weeks postpartum	• Consider wellbeing of maternal/fetal dyad in therapy selection	• No superiority data
With seasonal pattern • Regular temporal relationship between the major depressive episodes and a particular time of the year which • Remission in other times of the year	In most cases, episodes begin in fall or winter and remit in spring Often characterized by: • Prominent changes in energy • Hypersomnia • Overeating • Weight gain • Craving for carbohydrates	• SSRIs and bupropion have been studied, with no superiority data; bupropion has FDA approval

Antidepressant Drug Interactions

SSRIs

Medication	Significant Pharmacokinetic Interactions*	Significant Pharmacodynamic Interactions
Fluvoxamine a potent inhibitor of CYP 1A2, 2C19 and weak inhibitor of 3A4 and 2C9	agomelatine clozapine duloxetine phenytoin theophylline tricyclic antidepressants warfarin	Potential serotonin syndrome when combined with other serotonin-enhancing antidepressants, including: • tramadol • fentanyl • buspirone • St John's Wort • lithium • ondansetron • linezolid Increased risk of bleeding (particularly upper GI bleed) with: • NSAIDs, including aspirin • warfarin and other anticoagulants • Antiplatelets Other pharmacodynamic interactions to consider: • Other drugs which can also cause sexual dysfunction (antipsychotics) • GI effects (acetylcholinesterase inhibitors) • Hyponatraemia (thiazide diuretics) • Lower seizure threshold (antiepileptics; unlikely if epilepsy well-controlled)
Fluoxetine Paroxetine potent inhibitor of CYP 2D6	tricyclic antidepressants	
Sertraline	Unlikely to cause clinically significant pharmacokinetic drug interactions	
Citalopram Escitalopram	Contraindicated with other drugs which can prolong QT interval – see QT prolongation chart Unlikely to cause other clinically significant pharmacokinetic drug interactions.	

TCAs

Medication	Significant Pharmacokinetic Interactions *	Significant Pharmacodynamic Interactions
All	cimetidine cinacalcet fluoxetine fluconazole Fluvoxamine mirabegron paroxetine propafenone terbinafine ritonavir (at higher doses only) May reduce the plasma levels of TCAs: carbamazepine	Potential serotonin syndrome when combined with other serotonin-enhancing antidepressants; same as SSRIs above. Caution: • in pre-existing cardiac disease or with other drugs which effect cardiac function (antiarrhythmics) • in epilepsy and with other drugs which lower the seizure threshold (eg antipsychotics. bupropion) • with other drugs with sedative or anticholinergic properties (eg constipation, blurred vision, confusion)

*warrants avoiding medication use; increases plasma levels and potential adverse effects

Antidepressant QT Prolongation Comparison

Risk evaluation when used at therapeutic doses and without other risk factors present.

SSRIs

Drug	Risk
citalopram (>20 mg/day)	High
escitalopram	Medium
fluoxetine, paroxetine, sertraline, fluvoxamine	Low

SNRIs

Drug	Risk
Venlafaxine	Medium
desvenlafaxine, duloxetine	Low

TCAs

Drug	Risk
amitriptyline	High
clomipramine, imipramine, nortriptyline, desipramine	Medium
doxepin	Low

Novel Antidepressants

Drug	Risk
mirtazapine	Medium
buspirone, bupropion, vortioxetine, vilazodone, trazodone	Low
Vilazodone	Inconclusive

Atypical Antipsychotics

Drug	Risk
ziprasidone, iloperidone, quetiapine	High
olanzepine, risperidone, peliperidone, aripiprazole, asenapine, clozapine, brexpiprazole, lurasidone	Medium

Treatment Goals & Monitoring

Therapeutic Endpoints for MDD

Although disease remission is the priority, a response to treatment is the minimal standard clinical goal for the acute treatment phase of depression. Treatment must be tailored based on the patient's expectations and goals of treatment, pragmatically taking in account both the benefits and limitations that antidepressant therapy can provide.

Psychometrics can be used as an objective tool at baseline and subsequent follow up to assess the outcomes of pharmacotherapy and track if clinical goals for efficacy are met.

Monitoring and Management in Special Populations to be reviewed in Part II (February 2023)

Partial Response

25%-49% reduction in symptoms based on psychometrics

Partial response to treatment often indicates a need to further adjust treatment through strategies as detailed on pages 7-8:

- dose optimization/titration
- therapy augmentation
- combining antidepressant therapies
- switching antidepressant therapies

Response

50% or greater reduction in symptoms based on psychometrics after a 4- to 8-week trial of therapy

Patients who achieve a response to therapy:

- are encouraged to continue treatment for 4–9 months
- have a goal of maintaining therapeutic gains
- preventing relapse
- improving the trajectory toward remission

Remission

Complete resolution of depressive symptoms; psychometric thresholds vary based on the scale

After 6 months of treatment without recurrence, more than 50% of patients will achieve a remission of depression. Risk for depressive relapse is cumulative with additional episodes; therefore, patients with a relapse of depression should continue treatment for a minimum of 1 year and individuals with 3 or more depressive episodes should consider lifelong treatment.

Quality Metrics

Antidepressant Quality Metrics for 2023

Antidepressant Medication Management Effectiveness Acute Phase Treatment (Fidelis)

Assesses adult patients 18 years of age and older with a diagnosis of major depression, who were newly treated with antidepressant medication, and remained on an antidepressant medication for at least 84 days (12 weeks).

What patients are excluded from this quality metric?

- Members who did NOT have an encounter with a diagnosis of major depression during the period from 60 days prior to the initial fill of an antidepressant and for 60 days after (121-days total review).
- Members in hospice or using hospice services anytime during the measurement year.

GLIN Pharmacy Assistance in Quality Metrics for 2023

With the expansion of the GLIN Pharmacy Team in 2023, our pharmacists will be available to assist in improving these outlined quality metrics. Our pharmacists will provide payer quality reports as done in previous years OR provide patient specific messages within your electronic medical record with recommendations AND patient follow-up if agreeable by your providers.

Best Practices to Improve Adherence to Antidepressant Therapy

Risk factors for treatment failure include patient nonadherence, which occurs in the first month of treatment in approximately 40% of adults who discontinue antidepressant medication.

- Patients who concurrently receive psychotherapy are more likely to continue antidepressant therapy.
- Continued contact with the treating physician benefits some patients after recovery.
- Educate patients sufficiently on expected timeframe to effect (2-6 weeks), plan for optimization and augmentation if needed, potential transient adverse drug reactions with start of therapy to set realistic patient expectations of treatment course, plan, and goals
- Dispense 90-day supplies on generic medications whenever possible to prevent missed monthly refills
- Suggest use of medication reminder applications or alarms to improve adherence
- Send cancelation requests to pharmacy with any changes in medications or dose to ensure outdated scripts are not refilled accidentally
- Utilize medication adherence reports from payers to identify non-adherent patients
- Medent Users – Use the “Import RX History” feature to review prescription fill history for your patients during appointments to encourage compliance

For additional questions, please reach out to your assigned Clinical Transformation Consultant.

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