What to Consider When Prescribing Atypical Antipsychotics as Adjunctive Therapy for Major Depressive Disorder (MDD)

np psych navigator

Major Depressive Disorder (MDD) is a prevalent, disabling, and chronic condition. Identifying patients who have not responded to a course of adequate treatment is important as these patients may benefit from adjunctive pharmacotherapy or psychotherapy. The American Psychiatric Association (APA) specifies that 4 to 8 weeks of adequate treatment are needed before concluding treatment nonresponse or partial response.[1] Treatment nonresponse is defined as less than 25% improvement on a standard rating scale. Partial response is defined as equal to or more than 25% but less than 50% improvement on a standard rating scale. Some rating scales used commonly in practice when screening for and assessing symptomatology of MDD include the Patient Health Questionnaire-9 (PHQ-9), the Hamilton Rating Scale for Depression (HAM-D), the Beck Depression Inventory (BDI), and the Zung Self-Rating Depression Scale (SDS).[2-4]

Treatment options in cases of non-or partial response include:

- optimize the dose and/or duration of current therapy
- switch to another antidepressant
- augment treatment (eg, psychotherapy, adjunct medication, electroconvulsive therapy)

Among APA-recommended adjunctive pharmacotherapies for patients with MDD experiencing partial response or treatment nonresponse, atypical antipsychotics have been studied systematically and with a large number of randomized controlled trials.[5] The use of atypical antipsychotic medications as adjunctive therapy to antidepressants has been an area of focus for over 30 years and continues to be a widely recognized and successful treatment option.[6] Augmentation with atypical antipsychotics has been shown to be useful in helping to treat depressive symptoms.[6] There are currently 4 atypical antipsychotics that are FDA approved for adjunctive treatment of MDD.

Important factors to consider when prescribing antipsychotics

Stigma

Patient stigma

Patients prescribed antipsychotics report both self-stigma (eg, low self-esteem, embarrassment) and social stigma (eg, being labeled "crazy").[7] The stigma associated with the use of antipsychotic medications can be compounded by undesired side effects. It is important to understand that antipsychotic medications have been prescribed for a variety of reasons in patients who do not have psychotic symptoms, including depression.[7] In fact, for patients who do not respond to antidepressants, switching to another antidepressant or augmenting with either an additional antidepressant or agent such as an antipsychotic medication are recommended in treatment guidelines.[5,8]

Healthcare provider stigma

Healthcare providers (HCPs), like society at large, can harbor stigmatizing attitudes towards people with mental illness. Although providers may consider themselves to be accepting, it is important to remember that the patient's experience may be quite different.[9] Studies have shown that primary care providers may perceive mental health patients who are prescribed antipsychotics as lacking the insight and capabilities needed to manage their illness.[10] This can hinder formation of a productive and collaborative patient-provider relationship.[10] This relationship can be further hindered if a provider has low expectations for their patient, exhibits a lack of open communication regarding side effects and medication efficacy, or seems uncertain regarding the trajectory of the patient's illness.[10] Providers should aim to communicate realistic goals of therapy, share information with their patients openly, and foster a trusting relationship.[10] Lastly, continuing provider education to better understand both medical diagnoses and updated therapies can improve patient outcomes.[11]

Side effects

Atypical antipsychotics are associated with potential side effects. It is important to be aware of these side effects when considering prescribing these medications. Included below are some of the side effects associated with atypical antipsychotics. This is not an exhaustive list; prior to prescribing any medication, the prescribing information should be consulted. Guidance from the APA recommends that patients treated with antipsychotic medications be monitored for side effects on a regular basis.[12] HCPs should be cognizant that potential side effects can be influenced by a patient's personal and family history as well as current medications. In general, monitoring for specific medication-related side effects is done when starting or titrating antipsychotics or when adding other medications that could contribute to drug-drug interactions.

Metabolic

Atypical antipsychotics can lead to metabolic side effects, including weight gain, hyperlipidemia, hyperglycemia, and type II diabetes, and cardiovascular disease.[12,13] HCPs should assess and follow weight, fasting lipid panel, fasting plasma glucose, hemoglobin A1c and blood pressure in patients starting certain atypical antipsychotics.[14] Antipsychotic-induced weight gain can be addressed using lifestyle interventions, including changes in dietary and exercise habits.[14]

Cardiac

Some atypical antipsychotics have been associated with some prolongation of the QT interval.[12] When considering treatment options, it is essential to evaluate the patient's cardiac history as well as any pertinent family history. A careful medication history should be obtained to ensure that the patient is not taking other medications associated with QT prolongation. An EKG can be obtained prior to prescribing an atypical antipsychotic, when increasing the dose, and if any new cardiac symptoms arise.

Akathisia

Akathisia is restlessness, often with excessive leg movements, pacing, and inability to sit or stand still, that can develop within weeks of starting or increasing the dosage of an antipsychotic.[12,15] Patients should be asked about restlessness, slow movements, shaking, and rigidity at the time of medication initiation and dose increases. There are scales that can be used to assess these side effects. Two commonly used scales include the Abnormal Involuntary Movement Scale (AIMS) and the Barnes Akathisia Rating Scale (BARS).[16] These scales are widely used for the measurement of akathisia symptoms.

Tardive dyskinesia (TD)

Tardive syndromes are persistent involuntary movement disorders and can include choreiform movements of the mouth, tongue, face, extremities, and trunk. TD has been reported after exposure to any of the currently available antipsychotic medications.[12] Loughlin et al estimate a 0.8% to 1.9% average annual prevalence of TD in patients taking antipsychotics.[17] It is important to consider such side effects when monitoring a patient during their course of treatment. There are currently 2 vesicular monoamine transporter 2 (VMAT2) inhibitors that are FDA-approved for the treatment of TD.[17]

Use in Elderly Patients

Atypical antipsychotics have been used as off-label treatments for dementia-related psychosis in elderly patients. In 2004, the FDA updated labeling with a boxed warning for all atypical antipsychotic medications - stating that elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death.[18]

Neuroleptic malignant syndrome (NMS)

NMS presents with the classic triad of rigidity, hyperthermia (> 100.4°F on at least 2 occasions), and sympathetic nervous system lability (hypertension, tachycardia) in the context of exposure to a dopamine antagonist.[12] It has been reported following the withdrawal of a dopamine agonist.[12] The differential diagnosis for NMS in patients also taking serotonergic medications includes serotonin syndrome.[12] Serotonin syndrome can present with similar symptoms, including tachycardia, diaphoresis, restlessness, confusion, delirium, and clonus.[19] If either of these conditions is suspected in a patient taking an atypical antipsychotic, the medication needs to be discontinued immediately and supportive care given. If misdiagnosed or mistreated, both NMS and serotonin syndrome can be fatal.

It is important for HCPs to be knowledgeable and comfortable when prescribing atypical antipsychotics as adjunctive therapy for MDD. An understanding of the indication, mechanism of action, expected onset of action, and side effect profiles of these medications is important when communicating with patients regarding their mental health treatment plan. Additionally, having an awareness of the stigma that some patients may be dealing with and normalizing the use of atypical antipsychotic medications for MDD can help. Patients taking atypical antipsychotics as adjunctive therapy for MDD should be monitored for side effects and treated when appropriate. HCPs should also keep in mind the possibility of nonadherence to medication during follow-up visits. Consider using the checklist on the next page when initially prescribing medications for adjunct treatment of MDD. This may help in improving patient-provider communication, patient engagement in their own care, treatment adherence, and patient outcomes.

Promoting adherence to adjunctive atypical antipsychotic therapy for MDD

Poor adherence to medications prescribed for depression is common.[20] Patients cite factors including concerns about side effects, fear of addiction, lack of confidence in efficacy, difficult or transient living situation, economic stressors or inability to purchase medications, inadequate medical supervision, lack of family or community involvement, and the depressive episodes themselves.[1,21] HCPs can inadvertently promote nonadherence through insufficient patient education and poor follow-up. The quality and accessibility of information provided during the first prescription visit can make a difference in treatment adherence.[21,22] HCPs can help patients to optimize treatment adherence using these techniques.[21]

- ☐ Confirm that MDD with inadequate treatment response is biologically based and that adjunctive treatment options exist.
- ☐ Discuss pharmacologic therapies available and the patient's expectations.
- ☐ Focus on specific medication options available based on the severity of illness, prior and current medications, and medical comorbidities.
- ☐ Discuss the medication's mechanism of action.
- ☐ Educate on the stigma of the condition and the medication being prescribed.
- ☐ Review possible side effects and safety issues as well as how baseline and follow-up testing will help to ensure patient safety in the long term.
- ☐ Review the latency of action to avoid frustration with delayed onset of symptom relief.
- ☐ Review expected treatment duration.
- ☐ Review dosages and titration schedule if appropriate.
- ☐ Make a short-term monitoring plan with the patient to evaluate tolerability within 3 weeks.
- ☐ Make a longer-term treatment plan with the patient to evaluate efficacy and continued tolerability.
- ☐ Continue to monitor metabolic and other side effects in the long term.
- ☐ Consider other adherence boosters, including:
  - Family member involvement with the treatment plan
  - Links to other HCPs, dieticians, therapists, and counselors
  - Assure the patient of your availability in case of necessity (clinic phone number, patient portal messages, etc.)

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