Considerations in Choosing an Antidepressant

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The number of antidepressants available to clinicians has steadily increased, and others may soon be approved and released. Some antidepressants, such as mirtazapine and bupropion, differ in their pharmacologic actions from those whose actions involve serotonin or norepinephrine reuptake. However, with the possible exceptions of mirtazapine and venlafaxine, there is little evidence for the differential effectiveness of different antidepressants for a major depressive episode.

The choice of antidepressant can be a difficult one. The clinician must consider the various subtypes of depression—secondary depression, atypical depression, psychotic depression, bipolar depression, and seasonal affective disorder—which may respond differently to different medications. However, even for an episode of major depression, the choices may appear daunting, leaving some practitioners to fall back on habit without thinking through their decisions.

In this column we review basic considerations in the choice of an antidepressant. Differences among SSRIs that may influence the choice are discussed, as are augmentation strategies to improve partial response.

Basic considerations

Under the best circumstances, a clinician might know which medication the patient has responded to in the past, or perhaps which medication has been used to successfully treat a relative of the patient. However, usually a medication must be selected without this knowledge. In addition to taking a personal and family history of mental illness, the clinician should also determine the patient's general health status and any other medications the patient is taking. Prescribed and over-the-counter medications, herbal remedies, and alcohol and recreational drugs may interact with some antidepressants.

Other considerations should influence the clinician's choice. First is ease of use. Some medications, such as bupropion, must be taken several times a day when used at higher dosages. The dosage of others, such as nefazodone, may need to be slowly increased over several days or weeks. In both instances, patients' compliance may be affected; patients may forget a dose or become confused and skip a dose.

A second consideration is safety. Some depressed patients may attempt suicide by taking an overdose of prescribed medications. The newer antidepressants appear relatively safe when patients overdose with them, but the older medications, such as the tricyclics, may present problems.

A third consideration is tolerability, which is related to the side effects of the medication. All medications have some side effects, many of which are of little consequence. However, some side effects, such as orthostatic hypotension, are more serious. Others, such as sedation or appetite stimulation, may be useful early in treatment but cause problems later in treatment when the patient has recovered. Still other side effects, such as sexual dysfunction, may be of little consequence for a depressed patient but may interfere with functioning after recovery. Planning for these side effects and discussing options with patients may increase compliance for both the short and long term.

A fourth consideration when choosing an antidepressant is possible drug interactions. Depressed patients, especially elderly persons, may be taking several medications prescribed by other physicians. Some antidepressants can induce or inhibit liver enzymes necessary for the metabolism of many medications, thereby lowering or raising the blood levels of these medications to subtherapeutic or dangerous levels. It is often possible to plan for these interactions and to monitor medication levels. However, a new physician adding another medication may not have accurate knowledge of the patient's other medications.

A final consideration is cost. Medications are often expensive, and some are not covered by some insurance plans. The older antidepressants and fluoxetine are available in less expensive generic forms.

Choosing an SSRI

Although no antidepressant is ideal, many clinicians begin with one of the SSRIs because of their ease of use, safety in overdose, and generally high tolerability. SSRIs are also effective in the treatment of anxiety disorders, which often co-occur with depression. However, because of the important differences between the SSRIs, further considerations come into play.

All of the SSRIs are easy to use and can be started at a therapeutic dosage with once-a-day administration, although the dosage is often increased

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over time for patients who do not fully respond. As noted, the SSRIs also share an excellent safety profile. However, their side effects differ. For example, paroxetine is the SSRI most associated with sedation and weight gain. In addition, discontinuation of paroxetine has been associated with effects more severe than those of discontinuing sertraline and fluoxetine (1). However, fluvoxamine, with its shorter half-life, may also have more severe discontinuation effects than other SSRIs. Among males paroxetine may cause greater sexual dysfunction than sertraline (2).

Furthermore, fluoxetine, fluvoxamine, and paroxetine lead to significant inhibition of various cytochrome P-450 enzymes, whereas citalopram and sertraline have minimal effects and cause fewer drug interactions.

Inadequate treatment response

On the basis of these considerations, clinicians can make better choices not only among the SSRIs but also among other antidepressants. However, a sizable minority of patients fail to respond adequately to any antidepressant, even when the diagnosis is correct and the medication is given at an optimal dosage for an adequate amount of time. It should be noted that although six weeks is often regarded as adequate, some patients may need up to three months.

For convenience, patients who have an inadequate response may be divided into two groups—those who show a partial response and those who show a minimal response or no response. Patients who have an adequate response but whose symptoms recur are generally regarded as partial responders.

For patients who have no response or a minimal one, we recommend switching to a different antidepressant. Augmenting a medication to which a patient has failed to respond has little research support and seems to be of questionable logic. Furthermore, we recommend that the clinician choose an antidepressant with a different or an additional action rather than a drug from the same class. Although there is evidence that some patients may respond to one SSRI after failing to respond to another, success is more likely with a medication from another class. Therefore, a preferable second step would be to switch to a medication such as bupropion, which does not directly affect serotonin, or venlafaxine, which blocks norepinephrine reuptake as well as serotonin reuptake.

It should also be noted that monoamine oxidase inhibitors and electroconvulsive therapy have been shown to be effective with treatment-resistant depression and are typically underused, as are various psychotherapies such as cognitive-behavioral, behavioral, and interpersonal therapies.

Many strategies can be used in augmenting an antidepressant to which a patient has had a partial response, although relatively few are supported by rigorous evidence from double-blind trials. In many clinical reports of the combined use of two antidepressants, no attempt was made to withdraw the first antidepressant, and it is therefore unclear whether the second augmented the first or succeeded after the first did not. Generally a drug should be withdrawn when it has been given at an adequate dosage for a sufficient duration without producing any objective signs of improvement.

In the case of partial response to an antidepressant, the addition of a therapeutic level of lithium is the best-validated augmentation strategy. This strategy appears effective for a variety of antidepressants. Use of thyroid supplementation is less validated but appears more successful with female patients.

The possibility of drug interactions must always be considered when combining a second antidepressant, an anticonvulsant, or an antipsychotic with an antidepressant. Some strategies, such as combining an SSRI and desipramine, which has a strong norepinephrine action, have some research support and seem logical, although one might ask if venlafaxine alone would have the same action. Similarly, adding venlafaxine to an SSRI has some support, but it seems unnecessary because it duplicates the serotonin reuptake effect. Clinicians who try this combination should always attempt to discontinue the SSRI. ♦

References

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