SELECTING ANTIDEPRESSANT THERAPY FOR PATIENTS WITH MAJOR DEPRESSION

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INTRODUCTION

For several decades, the psychopharmacologic treatment of depression was limited to tricyclic antidepressants (TCAs) (e.g., imipramine, desipramine, doxepin, nortriptyline, and amitriptyline) and monoamine oxidase inhibitors (MAOIs) (i.e., phenelzine and tranylcypromine). The release of fluoxetine, a selective serotonin reuptake inhibitor (SSRI), in the late 1980s ushered in a decade in which there was a fairly dramatic increase in the number and classes of antidepressants. Subsequently released SSRIs included sertraline, paroxetine, fluvoxamine, and citalopram. Other newer antidepressants included bupropion, venlafaxine, nefazodone, and mirtazapine. Currently there are 22 antidepressants available in this country, with another (i.e., reboxetine) on the horizon. Along with this expanded armamentarium to treat depression comes the obvious clinical perplexities of distinguishing the various agents and deciding which to utilize for specific patients. Factors to consider when selecting antidepressant therapy include efficacy, rate of response, tolerability, toxicity/safety, pharmacodynamic and pharmacokinetic drug interactions, dosing schedule and titration, and cost. Evaluation of antidepressants with respect to these factors reveals that each has its distinctive blend of characteristics. The clinician must consider these factors as they relate to the individual patient and select the antidepressant that most ideally meets the patient's needs.

FACTORS TO CONSIDER

The most obvious factor to consider when selecting an antidepressant drug is efficacy(1,2). The likelihood of the patient obtaining an antidepressant response should be of significant concern in the decision making process. Also, the time to onset of response is important as relates to the extent and severity of the patient's symptoms and degree of impairment.

Another factor to consider when selecting an antidepressant drug is adverse effects(1,3,4). Although all drugs have adverse effects, the patient should be able to easily tolerate those of the chosen antidepressant, because this has implications for patient satisfaction as well as compliance. Furthermore, the drug's safety and toxicity must be taken into account(1-4). The patient's concurrent medical illnesses should not be adversely affected by antidepressant therapy. Something else to bear in mind is the possibility and consequences of the patient either accidentally or intentionally overdosing on the drug.

A further factor to consider when selecting an antidepressant drug is drug interactions(1,3,4). The clinician should strive to select an antidepressant drug that would cause neither pharmacodynamic interactions (e.g., additive side effects) nor pharmacokinetic interactions (e.g., increased drug levels) with the patient's concomitant medications. Beyond immediate concerns, there should be contemplation about the overall risk of interactions if additional medications are added or if current medications are switched.

An additional factor to consider when selecting an antidepressant drug is dosing(1). The patient must be willing and able to strictly comply with the recommended dosing schedule of the antidepressant drug. Furthermore, the patient must be willing and able to comply with instructions and/or follow-up visits in order to accomplish upward titration of the antidepressant when the effective dose cannot be started immediately.

A final factor to consider when selecting an antidepressant drug is cost(1-4). The patient should be able to comfortably afford the chosen antidepressant, as this affects both patient satisfaction and compliance.

EVALUATION OF ANTIDEPRESSANTS

Efficacy: Response Rate

It is widely accepted that all antidepressants are roughly equal in efficacy(2,4). Specifically, each antidepressant carries a response rate of approximately 70 percent (4). Whenever
possible, the selection of an antidepressant should be based on the patient's past history of response to antidepressants, as this is the most reliable predictor of response(2-4). To a lesser degree, the past history of response of a family member (e.g., first-degree relative) to antidepressants can be used to increase the probability of choosing the most efficacious agent(2,4). Patients with atypical depression (e.g., mood reactivity, hyperphagia, and hypersomnia) may have a preferential response to MAOIs(2,4,5,6). Although controversial, some believe SSRIs to be less effective and antidepressants with dual neurotransmitter effects (e.g., TCAs, venlafaxine, and mirtazapine) to be more effective for severe depression(1,2,5,7).

Efficacy: Onset of Response

It usually requires 2-4 weeks of therapy before antidepressant effects become apparent(1,2,3,6,8). No antidepressant has been reliably shown to have a clinically relevant faster onset of response compared to other agents. Venlafaxine has been shown to have a faster onset of response if very aggressively dosed (i.e., > 300 mg/d) in the first week of therapy; however, the high incidence of adverse effects limits the clinical utility of this strategy(1,2). Nevertheless, the option remains when a quicker onset of response is highly desirable.

Adverse Effects: Tolerability

The TCAs, especially those with a tertiary amine structure (e.g., imipramine), have poor overall tolerability owing to their diverse pharmacological actions at α-1 adrenergic receptors (e.g., orthostatic hypotension and dizziness), histamine-1 receptors (e.g., sedation and weight gain), and acetylcholine receptors (e.g., dry mouth and constipation). The overall tolerability of MAOIs is also poor, in part due to food and drug restrictions (see discussion on drug interactions) and in part due to the side effect profile, which includes weight gain, sexual dysfunction, insomnia, and a high incidence of orthostatic hypotension. The newer antidepressants have better overall tolerability compared to traditional antidepressants; however, they too possess problematic adverse effects. The side effect profile of the SSRIs reveals the strong serotonergic effects of these drugs, including sexual dysfunction (e.g., anorgasmia), central nervous system activation (e.g., nervousness and insomnia), and gastrointestinal disturbances (e.g., nausea and diarrhea). Similar adverse effects are characteristic of venlafaxine, although nausea is even more problematic, and hypertension can occur at higher dosages secondary to noradrenergic effects. Bupropion causes insomnia, anxiety, tremor, and seizures. Nefazodone is an α-1 adrenergic receptor blocker, and can consequently cause orthostatic hypotension and dizziness; other adverse effects are sedation and nausea. Mirtazapine is a histamine-1 receptor blocker, and can consequently cause sedation and weight gain; neutropenia is a “black box” warning due to a handful of cases reported during clinical trials, but it is questionable whether this drug has a greater propensity than other antidepressants to cause this adverse effect(1-8).

Adverse Effects: Toxicity/Safety

The TCAs are infamous for being toxic in overdose situations. Potentially fatal cardiac arrhythmias may result from the consumption of as little as 2 g, which is less than a two-week supply for most patients receiving TCA therapy. The MAOIs also possess a narrow therapeutic index, and can be dangerous in overdose situations. Bupropion has a narrow therapeutic index with respect to its ability to cause seizures. The other antidepressants enjoy wide therapeutic indices, although there are safety concerns with venlafaxine (i.e., risk of increased blood pressure) and mirtazapine (i.e., risk of neutropenia)(1,3,4,5,8).

Drug Interactions: Pharmacodynamic

The MAOIs possess potentially life-threatening pharmacodynamic drug interactions, as hypertensive crisis can occur if they are combined with either sympathomimetic agents (e.g., pseudoephedrine) or tyramine-containing foods (e.g., aged cheeses) and serotonin syndrome can occur if they are combined with highly serotonergic agents (e.g., SSRIs). The TCAs possess numerous problematic interactions, as they can produce additive side effects with drugs that cause sedation (e.g., alcohol), hypotension (e.g., prazosin), anticholinergic effects (e.g., diphenhydramine), or cardiotoxicity (e.g., quinidine). Similarly, nefazodone and mirtazapine can cause several significant interactions with drugs that cause hypotension and sedation, respectively. Many of the newer antidepressants, such as the SSRIs, bupropion, and venlafaxine, cause few such interactions because they are relatively devoid of these adverse effects(1,2,4,5,6,8).

Drug Interactions: Pharmacokinetic

Several antidepressants are known to inhibit various cytochrome P450 isoenzymes, including 1A2, 2C9, 2C19, 2D6, and 3A3/4. Plasma concentrations of the drugs metabolized by these isoenzymes may thus be elevated, potentially leading to increased adverse effects or toxicity. Although beyond the scope of this paper, extensive lists of drugs that are substrates for each isoenzyme have been published (see reference 10). Fluvoxamine causes strong inhibition at 1A2 and 2C19 and moderate inhibition at 2C9 and 3A3/4. Fluoxetine causes strong inhibition at 2C9 and 2D6 and moderate inhibition at 2C19 and 3A3/4. Paroxetine causes significant inhibition at 2D6 only. Both sertraline and citalopram possess mild inhibitory effects at several isoenzymes. Of the other newer antidepressants, only nefazodone, which has strong inhibition at 3A3/4, carries a significant risk for cytochrome interactions(1,7,8,9,10).

Most antidepressants are capable of causing drug interactions via protein displacement as a result of their extensive protein binding (i.e., > 90 percent). Several antidepressants, such as fluvoxamine, citalopram, bupropion, and mirtazapine, are approximately 75-85 percent protein bound, and may have a lower propensity for causing such interactions. Notably, venlafaxine is only approximately 30 percent protein bound, and would not be expected to cause such interactions(4,6).

Dosing: Schedule

The TCAs and mirtazapine can be given on a once-daily dosing schedule. The SSRIs can also be given on a once-daily dosing schedule, except for fluvoxamine, which is usually given on a twice-daily dosing schedule when medium-range dosages are attained. The MAOIs and nefazodone are given on a twice-daily dosing schedule. Venlafaxine is usually given on a twice-daily dosing schedule; however, the extended release formulation allows for once-daily dosing. Since individual doses of bupropion cannot exceed 150 mg, it is given on a twice-daily or thrice-daily schedule, depending upon the total daily dosage; the sustained release formulation allows for twice-daily dosing, even at higher dosages(1,4,5,6,8).
The starting dose is the usual therapeutic dose for mirtazapine (15 mg/d). The necessity for dosage titration varies between the individual SSRIs, such that fluoxetine and paroxetine rarely require dosage titration (i.e., 20 mg/d is sufficient), sertraline and citalopram sometimes require dosage titration (from 50 mg/d to ≥ 75 mg/d and from 20 mg/d to ≥ 30 mg/d, respectively), and fluvoxamine usually requires dosage titration (from 50 mg/d to > 100 mg/d). Both nefazodone and bupropion are initiated at 200 mg/d and generally require titration to at least 300 mg/d. The starting dose of venlafaxine is 75 mg/d, whereas the usual therapeutic dose is approximately 150-225 mg/d. The standard for dosing TCAs is to meticulously increase the dosage in incremental fashion from a small starting dose to a wide usual therapeutic dosage range (e.g., from 50 mg/d to 150-300 mg/d for imipramine, desipramine, and amitriptyline; from 25 mg/d to 75-150 mg/d for nortriptyline). MAOIs also typically require dosage titration (e.g., from 15 mg/d to ≥ 30 mg/d for phenelzine)(1-6,8).

Cost

For purposes of the following discussion, costs are based on a one-month supply of the stated dosage at average wholesale price(11). Unquestionably the least expensive antidepressant drugs are the MAOIs such as phenelzine ($28.20; 30 mg/d). The TCAs are available as generic products and are relatively inexpensive drugs, although secondary amine agents such as nortriptyline ($70.80; 75 mg/d) cost more than tertiary amine agents such as imipramine ($62.10; 150 mg/d). In general, the newer antidepressant drugs are relatively expensive, although they certainly range in their costs. The least expensive SSRI is citalopram ($63.00; 40 mg/d), whereas the most expensive SSRI is fluvoxamine ($84.60; 100 mg/d). As concerns the other SSRIs, fluoxetine ($79.20; 20 mg/d) is more expensive than paroxetine ($72.00; 30 mg/d) and sertraline ($72.30; 100 mg/d). Several of the newer antidepressants have costs that are similar to those of the SSRIs, including venlafaxine ($75.90; 150 mg/d of extended release dosage form), nefazodone ($74.40; 300 mg/d), and mirtazapine ($71.70; 30 mg/d). The cost of bupropion ($91.80; 300 mg/d of sustained release dosage form) exceeds that of even the newer antidepressants. Generic bupropion has costs comparable to the proprietary product. Generic fluvoxamine recently became available. Generic fluoxetine will soon become available.

The characteristics of each antidepressant drug/class as relates to the various factors are summarized in Tables I-VII.
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CONCLUSIONS

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It would behoove the clinician to involve the patient in the decision making process instead of making general assumptions and unilateral decisions. Each patient must be appreciated as a unique individual with unique concerns. First, patients will vary with respect to how they view facets of an important
factor. For instance, concern over potential adverse effects may be important for two patients, but the one who is a student may be wary of sedation, whereas the one who enjoys an active sex life may be concerned with anorgasmia. Finally, patients will vary with respect to the emphasis that they place on the various factors, such that some are paramount and others are marginal. For example, two patients may be concerned over both cost and safety, but one may request the least expensive drug because cost is the overriding matter, whereas the other may request the safer drug because concern over toxicity is supreme. Of course, notwithstanding the concerns of patients, the clinician also has a unique perspective with respect to interpretation of the various factors. For instance, the clinician may have a different level of concern over such things as potential drug interactions and effects of drugs on existing medical conditions than does the patient owing to differences in knowledge and understanding. Thus, both patients and clinicians have concerns that must be thoroughly shared with each other so that a consensus is reached on the selection of the most ideal antidepressant.

In summary, it is vital for the clinician to do the following when selecting patient-specific pharmacotherapy for depression: allow the patient to participate in the decision making process; discuss the various antidepressants within the context of the aforementioned factors as they relate to the patient; and arrive at a consensus as to which antidepressant best meets the patient’s needs.

References