REVIEW ARTICLE

First-line pharmacotherapies for depression – what is the best choice?

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KEY WORDS

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ABSTRACT

Major depressive disorder is a significant public health problem and the leading cause of suicide worldwide. Since the discovery of the first effective medications for depression in the late 1950s, a variety of pharmacotherapies have been developed that are useful for treating the full range of depressive disorders. The availability of safer classes of antidepressants, as well as other factors, has resulted in a large increase in the number of depressed individuals who are treated for depression by their primary care providers. This review examines the antidepressants that are currently used as the initial or "first-line" therapies for major depressive disorder (MDD). These newer medications may be grouped into three classes: the selective serotonin reuptake inhibitors, the serotonin and norepinephrine reuptake inhibitors, and the norepinephrine-dopamine reuptake inhibitor. While the modern classes of antidepressants offer superior tolerability and safety over older medications such as the tricyclic antidepressants, there remains no universally effective pharmacologic treatment for MDD, and effective disease management requires careful attention to ongoing assessment of medication response and management of side effects.

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Antidepressants are effective for treating the full spectrum of depressive disorders, from dysthymic disorder and acute major depressive episodes to more classical episodes of melancholia.[1-3] Although once mostly prescribed by psychiatrists, the widespread availability of safer classes of antidepressant medications, as well as changes in health care delivery, have resulted in a large increase in the number of depressed individuals who receive treatment from primary care providers.[2,4] In fact, in the United States, primary care physicians now prescribe about twice the total number of antidepressant medications as psychiatrists. Of course, depressive episodes may also be treated effectively with focused forms of psychotherapy, such as cognitive-behavior therapy or interpersonal psychotherapy. For individuals presenting with a non-psychotic major depressive episode of mild to moderate symptom severity, the initial choice of therapy often depends on the preference of the patient and the discipline of the provider. Psychologists, social workers, and other non-medical professionals are more likely to recommend psychotherapy or counseling before considering a trial of medication. Primary care physicians, on the other hand, are more likely to prescribe antidepressant medication instead of referring out for psychotherapy or counseling. Psychiatrists also will usually prescribe medication, although may combine it with psychotherapy.

The delivery of pharmacotherapy of depression can be viewed as consisting of three strategic phases. The first or "acute" phase, which is the focus of this review, describes the period from the start of treatment until an acceptable response has been obtained. The continuation and maintenance phases are provided to minimize the risks of relapse and recurrence, respectively; the interested reader is referred elsewhere for a concise discussion of preventive treatment strategies.[5] The definition of exactly what constitutes an "acceptable response" has undergone significant change during the past decade. In controlled trials of antidepressants, the traditional definition of response is a 50% improvement compared to baseline score on a depression rating scale[6] (such as the venerable Hamilton Rating

Scale for Depression[7] or the self-report Beck Depression Inventory[8]). In the everyday clinical setting, however, such rating scales are not typically utilized. Conceptually, a response represents a level of improvement such that the patient no longer meets criteria for a major depressive episode; with respect to a global impression of treatment outcome, a responder should be considered much or very much improved. A more exacting outcome, remission, denotes a virtual absence of symptoms, such that the person whose depressive episode has remitted should have no more symptoms than someone who has never been ill.[6,9] The importance of achieving remission as the goal of treatment has become increasingly apparent, and is discussed in more detail elsewhere.[10] Importantly, remission is preferred over response as the goal of acute phase therapy because the former definition is associated with a lower subsequent risk of relapse and superior psychosocial functioning.

Depending on the speed of symptom improvement, acute-phase treatment may extend anywhere from a few weeks to some number of months. Indeed, someone who develops treatment-resistant depression during a series of sequential antidepressant trials may have an indefinite course of acute phase therapy. Patients treated with pharmacotherapy alone are usually seen for biweekly or monthly medication management sessions, which last an average of 15–30 minutes. Most antidepressants currently considered to be first-line therapies are typically started at the minimum therapeutic dose, and clinical judgment is used to determine the speed of upward titration towards the maximally tolerated dose.[11] Some controversy exists regarding both the value of upward titration and the optimal duration of pharmacotherapy necessary before deciding to change treatment options. Specifically, controlled studies have generally not established the benefit of dose increases and, though some experts suggest that up to 12 weeks may be necessary for each treatment trial, others point out that patients who have gained no benefit from as little as 4 weeks of therapy may be better served by changing treatments. This general approach continues until the desired response has been achieved. Whereas this strategy may be viewed by some as "trial and error", in actuality it is an iterative process, in which observations gleaned from each treatment trial help to inform subsequent decisions.

Medication management visits also include education about the disorder and its treatment, and patients are made aware of such issues as adherence, side effects, and realistic expectations of benefit. Patients are informed that the initial choice of antidepressant typically has about a 50–60% chance of working, that it may take a number of weeks to see full effects, and that side effects often precede therapeutic effects. As attrition rates due to intolerable side effects typically range between 5–10% in clinical trials of modern antidepressants, it is also helpful to reassure patients with the knowledge that – most of the time – medication side effects are mild-to-moderate in severity and will not greatly interfere with treatment.

The three modern classes of antidepressants that are usually considered "first-line" antidepressants in 2009 are the selective serotonin reuptake inhibitors (SSRIs), the serotonin and norepinephrine reuptake inhibitors (SNRIs), and – at least in the United States and Canada – the norepinephrine-dopamine reuptake inhibitor (NDRI) bupropion. Older standards from the first generation of psychopharmacology, including the tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs), are now generally reserved for patients who do not benefit from several trials of newer medications. With the exception of the TCAs, which were named after the three-ring chemical structure of the first member of the family to be synthesized, the class names reflect the predominant action on monoamine neurotransmitter systems. When reclassified in terms of mechanism of action, most of the tricyclics would be called norepinephrine reuptake inhibitors (NRIs), with clomipramine considered an SNRI. A handful of other antidepressant medications also exist that have little or no effect on monoamine reuptake and do not inhibit the enzyme MAO, including trazodone, nefazodone, mirtazapine, and tianeptine (not available in the United States). These medications influence central nervous system (CNS) neurotransmission by inhibiting various pre- and postsynaptic norepinephrine and serotonin receptors.

The clinical pharmacology of the major classes of antidepressants is briefly reviewed below. The TABLE summarizes the major classes of antidepressants that are frequently used in clinical practice.

Selective serotonin reuptake inhibitors The SSRIs are generally considered the first-line of antidepressant pharmacotherapy and are used widely throughout the industrialized world.[1,2,12] While it is true that some critics argued in the mid-1990s that the success of the SSRIs was primarily the result of pharmaceutical marketing, this criticism has evaporated with the availability of multiple generic SSRIs, and it can now be stated unequivocally that the SSRIs replaced the TCAs as the standard for first-line therapy for four reasons. First, unlike a TCA, an SSRI can usually be started at a therapeutic dose, requiring fewer titrations and making it easier to prescribe. Second, SSRIs cause fewer day-to-day side effects such as dry mouth, blurry vision, constipation, and lightheadedness and, in double blind clinical trials, a lower rate of attrition due to intolerable side effects than the TCAs. Third, the SSRIs have been shown to be comparably effective to TCAs with respect to treatment of depressed outpatients.[1-3,13] Fourth, the SSRIs are much safer in overdose, a point that has profound public

TABLE Frequently prescribed antidepressants

Generic name	Usual dose (mg/day)	Prominent side effects	Notes
selective serotonin reuptake inhibitors			
citalopram	20–60	nausea, diarrhea, insomnia, sexual dysfunction, agitation/restlessness, daytime sedation	widely considered first-line antidepressant therapy; also useful for a range of conditions on the clinical boundary of depression (including several DSM-IV anxiety disorders, premenstrual dysphoric disorder, bulimia nervosa)
escitalopram	10–20		
fluoxetine	20–60		
fluvoxamine	100–300		
paroxetine	20–50		
sertraline	50–200		
mixed reuptake inhibitors			
bupropion	300–450	nausea, vomiting, insomnia, headaches, seizures	often a preferred treatment option for patients who cannot tolerate SSRIs
venlafaxine	75–375 (IR) 75–225 (XR)	nausea, diarrhea, nervousness, sweating, dry mouth, muscle jerks, sexual dysfunction; less common: vomiting, insomnia, headaches, tremor, increased blood pressure	relatively small efficacy advantage over the SSRIs, but benefits may be offset by higher cost
desvenlafaxine	50–100	nausea, diarrhea, constipation, dry mouth, sweating, insomnia, dizziness; less common: nervousness, tremor, increased blood pressure	closely related to venlafaxine; recent addition to market
duloxetine	60–120	nausea, diarrhea, vomiting, nervousness, sweating, dry mouth, headaches, insomnia, sexual dysfunction, tremor, elevated liver enzymes	relatively simple dosing schedule
milnacipran	100–200	nausea, nervousness, constipation, dizziness, sweating	not available in the USA
serotonin modulators			
nefazodone	300–600	sedation, perceptual distortions, liver failure (rare)	withdrawn from the market in Europe, Canada, and elsewhere
trazodone	150–600	orthostatic hypotension, sedation, priapism	also used as sedative/hypnotic at lower doses
norepinephrine and serotonin modulator			
mirtazapine	15–60	weight gain, daytime drowsiness	often used in combination with SSRIs and SNRIs

Abbreviations: DSM – Diagnostic and Statistic Manual of Mental Disorders, IR – immediate release, SNRI – serotonin and norepinephrine reuptake inhibitor, SSRI – selective serotonin reuptake inhibitor, XR – extended release

health relevance for treatment of a disorder that is the leading cause of suicide worldwide. To put the difference in overdose lethality in context, the Fatal Toxicity Index (i.e. the number of deaths attributable to overdose per million prescriptions) of the SSRIs is between 1/10 and 1/30 that of the TCAs.[14]

Six SSRIs are available for treatment of depression: fluoxetine, fluvoxamine, sertraline, paroxetine, citalopram, and escitalopram. The SSRIs are grouped as a class because they all selectively inhibit neuronal uptake of serotonin. Selectivity refers to the fact that, unlike TCAs, the SSRIs do not have strong effects on acetylcholine, histamine, or α- and β-adrenergic receptors. With one exception (i.e. citalopram and escitalopram), the SSRIs are distinctly different chemicals and, for particular patients, there are important pharmacologic differences among members of the class. These differences include: elimination half-life, effects on liver enzyme systems (i.e. CYP450 isoenzymes) involved in drug metabolism, magnitude of effects on other monoamine receptors, and the antidepressant activity of drug metabolites.[5,15,16] Because of these differences, the SSRIs should not be thought of as interchangeable drugs, and substituting a prescription for one SSRI with another in the midst of therapy can be problematic.

Escitalopram, the newest drug within the class and the only one still under patent protection in the United States, is the most selective SSRI, has the simplest dosing requirements, and may have stronger antidepressant activity than proportional doses of its parent drug, citalopram.[5,17] Whether these features justify its preferential use over generically available (and less expensive) SSRIs provokes strong views from different experts, and it is not uncommon for some health systems to recommend use of another drug ahead of escitalopram. For example, although escitalopram was found to be among the most effective of the modern antidepressants in the recent meta-analysis of Cipriani et al.[18], the authors concluded that sertraline may be preferred because of differences in cost.

While the SSRIs demonstrate a substantially lower incidence of nuisance side effects than the TCAs, about 5–10% of people who begin treatment with SSRIs in double-blind randomized controlled trials (RCTs) will discontinue therapy because of side effects. The side effects that most often interfere with SSRI therapy result from the gastrointestinal and CNS effects of inhibiting serotonin uptake. Particularly common side effects include nausea and diarrhea, as well as headache, tremor, nervousness, insomnia, and sexual side effects like diminished libido or difficulty having an orgasm. An increased risk of falls and fractures in the geriatric population has also been reported recently[19,20], and may reflect more subtle, age-dependent effects of SSRI therapy on balance and bone strength.

With regard to their use during pregnancy, it has been widely assumed that SSRIs pose a small and nonspecific risk for the fetus, with untreated depression conveying a larger, known risk for both the mother and fetus.[21] This notion was supported by the recent findings of a study by Cohen et al.[22], which showed that pregnant women who chose to discontinue antidepressants were at significantly higher risk of depressive relapse than those who continued with treatment throughout the pregnancy. The benefit of antidepressant use during pregnancy must be balanced against known risks, however, and data are accumulating which suggest that several specific risks may need to be taken into account. For example, an SSRI discontinuation syndrome, which usually runs a benign course, has been associated with seizures in newborns.[23] The SSRIs have also been linked to the development of pulmonary hypertension in the third trimester of pregnancy[24], and evidence of rarer cardiac teratogenic effects have been specifically implicated with paroxetine use[25-27]. Before initiating a trial of an antidepressant medication during pregnancy, the value of an alternative intervention with lower risks to the fetus – such as cognitive behavior therapy – should be considered.

One particular area of controversy surrounding SSRI use concerns the risk of iatrogenic behavioral toxicities. As is the case with other antidepressants, the initiation of therapy with an SSRI sometimes provokes an uncomfortable state of behavioral activation, which may manifest as agitation or akathisia (i.e. motor restlessness and a subjective feeling of "crawling out of one's skin"). This uncomfortable state may help explain reports of treatment-emergent onset of worsening suicidal ideation and behavior, especially when this uncomfortable motor activation is coupled with the dysphoric affective state and hopelessness often associated with more severe depression. Induction of mania and, with respect to treatment-emergent suicidality, dysphoric mixed states also occur on the order of about 1 or 2 cases per 100 patients treated.

The association between an increase in suicidal behavior and the use of antidepressants in general – and SSRIs in particular – has been extensively debated over the past 18 years.[28-30] Most recently, this controversy has resurfaced as part of a broader concern about the increasing use of antidepressants in children and adolescents.[31-36] To address this issue, the Food and Drug Administration (FDA) reviewed data from 24 double-blind, placebo-controlled RCTs and determined that the risk of suicidal behavior, broadly defined, was approximately 4 per 100 children and teenagers treated with antidepressants, which was about twice the incidence observed on placebo.[37] It is noteworthy that there were no completed suicides among the more than 4200 children and adolescents who participated in these RCTs. A subsequent FDA review of an even more extensive dataset from RCTs of adults revealed that there was also a slight increase in suicidal behavior among 18–24 year olds (~1% greater than placebo), but not among older age groups. In fact, there was a significant decrease in suicidal behaviors among older patients treated with active medications compared to those treated with placebo. This strongly suggests that treatment-emergent suicidal ideation is an age-dependent phenomenon. Expert opinion differs, however, as to whether this trend reflects a neurodevelopmental phenomenon or is a consequence of the induction of mixed states in youths who have not yet been recognized to have bipolar disorder.[34,38,39]

Regardless of the etiology, it is also noteworthy that recent regulatory warnings stemming from this debate have been proximally linked to decreases in the prescription of antidepressants to depressed youths.[40,41] Given the observed decline in the rate of suicide in children and teenagers during the two decades prior to this regulatory action[42,43], concerns have been raised about the potential hazards of under-treating depression in childhood and adolescence.

Serotonin-norepinephrine reuptake inhibitors

The SNRIs' effects on both serotonin and norepinephrine neurotransmission pathways were initially viewed as having potential for broader antidepressant activity than the more selective SSRIs. The SNRI class includes venlafaxine, duloxetine, milnacipran (which is not approved for treatment of depression in the United States), and desvenlafaxine (which is not available in Europe).

Venlafaxine is the most extensively studied of the SNRIs for treatment of major depressive disorder (MDD). Results of a meta-analysis of patient data from the first eight comparative RCTs of venlafaxine found a 10% advantage in remission rates for the SNRI over the SSRI studied (45% vs. 35%), which is consistent with the predicted "dual-reuptake inhibitor hypothesis".[44] A statistically significant advantage for venlafaxine was also confirmed by several subsequent meta-analyses of larger sets of studies, although the magnitude of the advantage was smaller than originally believed[45-47] and may be heavily dependent on comparisons with fluoxetine.[48]

While better tolerated than the TCAs, venlafaxine tends to cause a broader array of side effects than the SSRIs, including signs of noradrenergic activity such as dry mouth, constipation, and increased pulse.[49] The most clinically worrisome side effect to emerge involves an increase in blood pressure, with rates ranging from about 2% above placebo at lower therapeutic doses (i.e. 75–150 mg/day) to as high as 10% at doses of 300 mg/day or higher of the immediate release formulation.[50] The incidence of treatment-emergent hypertension was highest in older male inpatients with severe depressive symptoms, suggesting that the specific risk may be greatest in those already at increased risk of developing hypertension.[50] Clinical experience suggests that treatment-emergent high blood pressure is reversible with cessation of venlafaxine therapy. Venlafaxine is also among the most difficult of the newer antidepressants to abruptly discontinue after an extended course of treatment because of the occurrence of discontinuation-emergent symptoms such as nausea, chills, insomnia, irritability, and paresthesias.[51] There have also been concerns that an overdose of venlafaxine may be more dangerous than one with SSRIs (but still less dangerous than an overdose with TCAs).[14] However, it is unclear if the higher Fatal Toxicity Index score merely reflects the fact that venlafaxine is often prescribed by psychiatrists for difficult-to-treat patients (who are at greater risk of suicide), or if the noradrenergic effects at higher doses cause an increased risk of cardiac arrhythmias.

As the extended-release formulation of venlafaxine is still patent protected in most countries (and, as a result, can cost about 5 × more than a generic SSRI), its relatively small (i.e. 6–10%) advantage in efficacy observed in RCTs has not generally been viewed as sufficient justification to warrant first-line use. However, this form of venlafaxine is one of the better-studied alternatives for patients who do not benefit from SSRIs and must be switched to another agent.[44] Two recent studies have demonstrated an almost identical numerical advantage for venlafaxine extended release (XR) as compared to a second trial within the SSRI class, supporting its use as a second-line therapy. This advantage was statistically significant in a large study conducted in Spain[52] but did not meet significance in a smaller study conducted as part of the STAR*D project[53]. Use of higher doses of venlafaxine may also improve response in more difficult-to-treat depression.[54]

For people with normal hepatic metabolism, venlafaxine is primarily metabolized to O-desmethylvenlafaxine (ODV) by the enzyme CYP450 2D6, and ODV plasma levels are normally two to three times higher than those of the parent drug. As a result, with the exception of patients who are "poor metabolizers" through the CYP450 2D6 system, patients who have been treated with venlafaxine have been treated (primarily) with desvenlafaxine. On its own, desvenlafaxine may offer some advantages over venlafaxine, including lower minimum therapeutic dose (50 mg vs. 75 mg), narrower dosing range (50–100 mg/day vs. 75–375 mg/day), greater bioavailability (80% vs. 49%), and greater potency for inhibiting norepinephrine reuptake.[55,56] Desvenlafaxine may also have particular advantages for CYP450 2D6 slow metabolizers, who may have unusually high concentrations of the parent drug, although – as of yet– there are no data from prospective trials to support this hypothesis. As such, there is not yet sufficient clinical experience to weigh the relative merits and limitations of this compound against those of venlafaxine. The same is true for comparisons of desvenlafaxine and the SSRIs.

Duloxetine was introduced in the United States in 2004 and differs from venlafaxine in several respects. Its comparative advantages include a simpler dosing schedule, stronger in vitro effects on inhibiting norepinephrine uptake, lower risk of treatment-emergent high blood pressure, and fewer discontinuation symptoms when treatment is terminated.[57-59] Initiating duloxetine therapy at the usual starting dose (60 mg/day), however, may be associated with more bothersome side effects than initiating therapy with venlafaxine XR at 75 mg per day.[59] One meta-analysis of six early studies comparing minimum-dose therapy with fluoxetine or paroxetine found an advantage for duloxetine (40–120 mg/day) among more patients with more severe depression, but not among patients with milder depression.[60] However, no significant difference was observed in three subsequent studies comparing duloxetine with escitalopram.[61-63] In addition, because some patients experience elevations of liver enzymes early in therapy, the package insert for duloxetine warns about its use in patients with alcoholism or liver disease.[57,58]

Other modern antidepressants Bupropion was the first of the newer antidepressants to be approved for use in the United States and is second only to fluoxetine in terms of years of clinical longevity.[64] Bupropion is the only medication to be classified as an NDRI and the only modern antidepressant that has no direct effects on serotonergic neurotransmission.[65,66] This unique profile likely accounts for its different side effect profile from the SSRIs, which includes a virtual absence of sexual side effects.[67] In fact, in the United States bupropion is one of the preferred treatment options for patients who cannot tolerate SSRIs or SNRIs, and it is often used in combination with SSRIs to enhance efficacy or reduce sexual side effects.[64] Despite the long track-record of use in the United States, bupropion has only recently been introduced in Europe.

Initially, use of bupropion was limited by concerns of an increased risk of seizures (which is reflected by a seizure risk at doses >450 mg/day that is higher than the risk for all other newer antidepressants) and its rather cumbersome

three-times-a-day dosing regimen. The introduction of sustained release (twice daily) and extended release (once daily) formulations have enhanced ease of use, and additional clinical experience suggests that the drug is helpful for anxiety associated with depression.[68] Unlike most of the SSRIs and the SNRIs venlafaxine and duloxetine, bupropion is not approved for treatment of any of the anxiety disorders, and many clinicians believe that it is less useful than the other first-line medications for management of conditions such as social anxiety disorder, panic disorder, and obsessive compulsive disorder. Anxiolytic effects have been demonstrated in studies of patients with depression[69], however, and it is fairer to say that bupropion is not adequately studied in primary anxiety disorders than it is ineffective. Several meta-analyses have confirmed comparable efficacy with the SSRIs across the broad grouping of MDD[67,70], with perhaps a small advantage of SSRIs for relief of anxiety and bupropion for reducing fatigue and sleepiness.[71] In the two published studies that directly compare venlafaxine XR with bupropion for MDD, few significant differences in efficacy were identified[53,67], although bupropion did show the expected significant advantage on measures of sexual functioning in the one study that specifically measured these side effects[72].

Mirtazapine, considered a "tetracyclic" antidepressant due to its four-ringed chemical structure, has antidepressant effects that are likely attributed to the interplay between serotonin-2 and noradrenergic α_2 receptor blockade, with additional antagonism of histamine receptors.[73] This unique neurochemical profile helps to explain why mirtazapine is the most sedating of the modern antidepressants and the only one implicated in weight gain during acute-phase treatment. While these effects can be beneficial for more severely depressed patients, especially those at midlife and older, many younger patients view these qualities as bothersome, which may explain mirtazapine's relatively poor penetration into the US market. Mirtazapine nevertheless has utility for selected patient subgroups, and its side effect profile is still somewhat more favorable than that of a TCA. When compared with the SSRIs and venlafaxine, mirtazapine therapy typically produces a more rapid onset of symptom relief.[74-76] The neurochemical and clinical effects of mirtazapine may also complement those of a reuptake inhibitor, and today it is used as much in combination with SSRIs and SNRIs as a monotherapy. In one of the STAR*D sub-studies, mirtazapine and the TCA nortriptyline did not significantly differ in efficacy.[77] In another, the combination of mirtazapine and venlafaxine XR was significantly better tolerated than the MAOI tranylcypromine, although a numeric advantage in remission rates was not statistically significant.[78] For these and other reasons, mirtazapine continues to have a use, primarily in the management of more difficult-to-treat depression.

Recent developments The results of the recent meta-analysis by Cipriani et al.[18] should be evaluated in the context of the above discussion of depression pharmacotherapy. They employed a multiple-treatments meta-analysis, using both direct and indirect comparisons, to assess the efficacy and acceptability of 12 newer antidepressants for treatment of major depression in the acute phase. The results suggested that four antidepressants: mirtazapine, escitalopram, venlafaxine, and sertraline were generally more effective than comparators; and four antidepressants: duloxetine, fluoxetine, fluvoxamine, and reboxetine were generally less effective than comparators. As escitalopram and sertraline also demonstrated the best acceptability profiles, the authors recommended these drugs for first-line therapy, with the advantage going to sertraline in countries in which escitalopram is still patent-protected.[18]

The analysis was carried out using data from 117 trials that included nearly 26,000 individuals randomly assigned to various antidepressant regimens. The statistical method used in the study, sometimes known as "mixed-treatment comparisons meta-analysis", integrated data from direct and indirect comparisons among the drugs to assess their overall efficacy and acceptability. While a far-reaching comparison of pharmacologic treatments for depression such as this may be important to guide clinical practice, the methods that enabled these comparisons also limit the interpretation and clinical applicability of the results. Specifically, difficulties arise from use of the mixed-treatments approach, which permits researchers to draw conclusions about the efficacy relationship between hypothetical drugs A and C based on their individual comparisons to drug B (the common comparator). With this method, the results of direct comparisons will significantly shape the results of the indirect comparisons. This can be a concern, as the biases of primary trials tend to become amplified when indirect relationships are extrapolated. In the current analysis, the escitalopram-citalopram and sertraline-fluoxetine matchups suffer from this phenomenon, and tend to inflate the overall standing of the victor of each comparison.

Limitations in study design can hinder interpretation of the results in other ways as well, as is suggested by the relatively poor showing of fluoxetine in the overall comparisons. From a pharmacologic perspective, fluoxetine's long half-life (which affords it certain clinical benefits, such as a virtual absence of discontinuation emergent symptoms) causes it to perform less favorably in shorter studies such as the ones included in the current analysis. Fluoxetine reaches steady-state levels over a period of 4–6 weeks, placing the drug at a short-term disadvantage in eight-week trials that favor drugs which are quicker to demonstrate their antidepressant effects. Issues with drug dosing are also influential, and likely contributed to duloxetine's relatively

poor standing in the overall comparisons. These shortcomings suggest that the multiple-treatments approach is limited by the challenges of standard meta-analyses, but may also have the additional burden of the limitations introduced by indirect comparisons. Overall, we find traditional meta-analyses (which employ only direct comparisons) to be more useful for aggregating data from clinical trials and ultimately informing clinical practice.

Conclusions The availability of generic formulations of SSRIs has removed the one real barrier against first-line use, namely cost. This class of medications is not without some problems, most notably that approximately one half of patients do not respond and, during longer term therapy, a significant minority, if not a majority, of individuals report sexual dysfunction as a side effect. Nevertheless, the significant safety and tolerability advantages compared to the TCAs, and modest but real tolerability advantages compared to the SNRIs, justify considering this class of medications first when selecting an antidepressant for a mild-to-moderately severe episode of major depressive disorder. For patients for whom an alternate approach may be clinically indicated, the SNRIs and, at least in the United States, bupropion represent valuable additional first-line options.

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ARTYKUŁ POGLĄDOWY

Leki pierwszego wyboru w terapii depresji – który jest najlepszy?

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SŁOWA KLUCZOWE

leki przeciwdepresyjne, bupropion, depresja, inhibitory wychwytu zwrotnego serotoniny i noradrenaliny (SNRI), wybiórcze inhibitory wychwytu zwrotnego serotoniny (SSRI)

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STRESZCZENIE

Depresja duża jest poważnym problemem zdrowia publicznego i główną przyczyną samobójstw na świecie. Od czasu odkrycia pierwszych skutecznych leków przeciwdepresyjnych (a więc od lat 50. XX wieku) pojawiło się bardzo wiele rodzajów farmakoterapii, które pozwalają skutecznie leczyć pełne spektrum zaburzeń depresyjnych. Dostępność bezpieczniejszych grup leków przeciwdepresyjnych (LPD), jak również inne czynniki, przyczyniły się do znacznego wzrostu liczby chorych na depresję, których terapię prowadzą lekarze pierwszego kontaktu. Tematem niniejszego artykułu przeglądowego są współcześnie dostępne LPD stosowane jako leki pierwszego wyboru w leczeniu depresji dużej (*major depressive disorder* – MDD). Wśród tych nowszych substancji można wyróżnić trzy grupy: wybiórcze inhibitory wychwytu zwrotnego serotoniny, inhibitory wychwytu zwrotnego serotoniny i noradrenaliny oraz inhibitory wychwytu zwrotnego noradrenaliny i dopaminy. Wprawdzie LPD należące do nowych klas cechują się lepszą tolerancją i bezpieczeństwem w porównaniu ze starszymi grupami leków (takimi jak trójpierścieniowe leki przeciwdepresyjne), to jak dotąd nie opracowano uniwersalnej terapii farmakologicznej, która byłaby skuteczna u każdego chorego z MDD. Skuteczne postępowanie lecznicze wymaga uważnej, ciągłej analizy odpowiedzi na zastosowaną terapię oraz właściwego reagowania na pojawienie się działań niepożądanych.