

The Symptom Cluster-Based Approach to Individualize Patient-Centered Treatment for Major Depression

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Unipolar major depressive disorder is a common, disabling, and costly disease that is the leading cause of ill health, early death, and suicide in the United States. Primary care doctors, in particular family physicians, are the first responders in this silent epidemic. Although more than a dozen different antidepressants in 7 distinct classes are widely used to treat depression in primary care, there is no evidence that one drug is superior to another. Comparative effectiveness studies have produced mixed results, and no specialty organization has published recommendations on how to choose antidepressants in a rational, evidence-based manner. In this article we present the theory and evidence for an individualized, patient-centered treatment model for major depression designed around a targeted symptom cluster-based approach to antidepressant selection. When using this model for healthy adults with major depressive disorder, the choice of antidepressants should be guided by the presence of 1 of 4 common symptom clusters: anxiety, fatigue, insomnia, and pain. This model was built to foster future research, provide a logical framework for teaching residents how to select antidepressants, and equip primary care doctors with a structured treatment strategy to deliver optimal patient-centered care in the management of a debilitating disease: major depressive disorder. (J Am Board Fam Med 2014;27: 151–159.)

Keywords: Behavioral Sciences, Depression, Evidence-based Medicine, Medical Decision Making, Pharmacotherapy

Unipolar major depressive disorder is a common, debilitating chronic disease that affects 1 in 6 people in the United States during their lifetime.^{1,2} Although as many as 14 million US adults suffer from major depression in a given year,² fewer than half of those affected received any kind of treatment in the previous 12 months.³ Among those who are being treated for major depression, fewer than one-third are receiving at least minimally ad-

equate treatment,³ which is defined by evidence-based practice guidelines as either psychotherapy or appropriate pharmacotherapy.^{4–6} With 5 of 6 depressed US adults left untreated or poorly treated³ and the economic burden of depression surpassing \$83 billion a year,⁷ major depressive disorder is a silent epidemic that warrants a vigorous primary care response.

Primary care doctors, especially family physicians, are the first responders in mental health care in the United States.⁸ Nearly three quarters of Americans who seek care for symptoms of major depression will go to a primary care doctor rather than a mental health specialist.⁸ Driven by changing public attitudes and growing acceptance of mental health treatment over the past 2 decades,⁹ the proportion of the adult population in the US receiving mental health care has increased to more than 20%.¹⁰ Most of this increased mental health care is provided by primary care doctors,³ two thirds of whom have limited or no access to psy-

This article was externally peer reviewed.

Submitted 6 May 2013; revised 23 July 2013; accepted 5 August 2013.

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Funding: none.

Conflict of interest: none declared.

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chotherapy or psychiatry referrals.¹¹ Although pharmacotherapy may not be the first choice for mild to moderate symptoms of depression, without improved access to psychotherapy the use of antidepressants has become the primary choice of treatment for major depressive disorder.¹² Primary care doctors now write more than two thirds of the 233 million annual prescriptions for antidepressants.¹³ In 2005, antidepressants surpassed antihypertensives to become the most commonly prescribed family of medications in the United States.^{14,15}

Antidepressants are a heterogeneous family of medications that are pharmacologically divided into 7 distinct classes (Table 1): selective serotonin reuptake inhibitors (SSRIs),^{16–21} serotonin norepinephrine reuptake inhibitors (SNRIs),^{22–25} norepinephrine dopamine reuptake inhibitors (NDRIs),²⁶ noradrenergic specific serotonergic antidepressants (NaSSAs),^{27,28} serotonin antagonist reuptake inhibitors (SARIs),²⁹ serotonin partial agonist reuptake inhibitors,³⁰ and tricyclic antidepressants (TCAs).^{31,32} There is another class of antidepressants, monoamine oxidase inhibitors, which is rarely used today in primary care but holds particular promise for patients who have failed multiple trials of new-generation medications.³³ All antidepressants act directly on one or more monoamine neurotransmitter pathways, but the exact explanation of how they work is still unknown.³⁴ Furthermore, research efforts to determine which antidepressants are the most effective in treating major depressive disorder have yielded no winners.^{35–41} Although antidepressants are clearly more effective than placebo in treating major depression, with a reasonable number needed to treat of 7,⁴² the question of whether clinically significant differences exist between widely used antidepressants remains the subject of intense debate.

Comparative effectiveness meta-analyses designed to tease out differences in efficacy between antidepressants have produced mixed results.^{35–41} The first comprehensive effort in 2005 concluded that antidepressants do not differ substantially from one another and acknowledged that choosing the most appropriate agent for a given patient is difficult.³⁵ An updated meta-analysis by the same US-based team in 2007 reached the same conclusion.^{36,37} In 2009, researchers based in Europe and Japan created substantial controversy when their data suggested that escitalopram and sertraline were supe-

rior in efficacy and acceptability among commonly prescribed antidepressants.^{38,39} Their studies have been criticized for methodological shortcomings.^{43–48} The newest meta-analysis, which was published in 2011 includes the most up-to-date evidence, again did not detect any clinically important differences in effectiveness among antidepressants.⁴⁰ Reflecting this continuing uncertainty, the latest practice guideline by the Agency for Health care Research and Quality does not recommend one agent over another and suggests only that differences in side effect profiles should be considered when choosing an antidepressant.⁴¹ To date, no specialty organization has offered recommendations on how to choose antidepressants in a rational, evidence-based manner, leaving primary care doctors on the front lines with little guidance.⁴⁹

So how should primary care doctors select which antidepressants to use? In the absence of clear evidence from comparative effectiveness studies, a reasonable way to begin answering this question is to examine how psychiatrists select antidepressants.⁵⁰ An important study in 2004 showed that the most influential factor on which the majority of psychiatrists based their antidepressant choices was the presence of a symptom cluster.⁵⁰ The specific clinical features to which psychiatrists pay the most attention are anxiety, insomnia or hypersomnia, fatigue, anger or irritability, increased or decreased appetite, and melancholic or atypical symptoms.⁵⁰ For example, in a large cohort of depressed patients with accompanying anxiety, psychiatrists were most likely to prescribe paroxetine (an SSRI with sedating properties) and least likely to prescribe fluoxetine (an SSRI with activating properties) or bupropion (an NDRI with activating properties).⁵¹ This suggests that certain “side effects” of antidepressants—for example, sedation or activation—may be capitalized on to treat specific symptoms of depression. A targeted, symptom cluster-based approach to choosing antidepressants reflects the belief of most psychiatrists that not all depression is the same⁵⁰; depression subtypes exist, and those differences may potentially be used to guide drug selection in a logical way.⁵

The symptom cluster-based approach to antidepressant selection is popular among psychiatrists and savvy primary care doctors,^{50–52} but evidence supporting its use is limited.^{53,54} Systemic reviews have compared treatment strategies among de-

Table 1. Commonly Prescribed Antidepressants in Primary Care

Generic Name	US Trade Name	Class*	Dosage Forms	Usual Frequency	Pregnancy Category [†]	Breastfeeding Safety [‡]	Generic Available	Retail Available [§]	Cost
Amitriptyline	Elavil	TCA	Tablet	Once a day	C	NR	Yes	Yes	\$
Bupropion	Wellbutrin	NDRI	Tablet	Three times daily	C	NR	Yes	No	\$\$
	Wellbutrin SR			Twice a day			Yes	No	\$\$
	Wellbutrin XL			Once a day			Yes	No	\$\$\$
Citalopram	Celexa	SSRI	Tablet, solution	Once a day	C	R:B	Yes	Yes	\$
Desvenlafaxine	Pristiq	SNRI	Tablet	Once a day	C	NR	No	No	\$\$\$\$
Duloxetine	Cymbalta	SNRI	Capsule	Once a day	C	NR	No	No	\$\$\$\$
Escitalopram	Lexapro	SSRI	Tablet, solution	Once a day	C	R:B	Yes	No	\$\$\$
Fluoxetine	Prozac	SSRI	Tablet, capsule, solution	Once a day	C	NR	Yes	Yes	\$
	Prozac Weekly		Capsule	Once a week			Yes	No	\$\$\$
Fluvoxamine [¶]	Luvox	SSRI	Tablet	Twice a day	C	R:B	Yes	No	\$\$\$
	Luvox CR		Capsule	Once a day			No	No	\$\$\$\$
Milnacipran [¶]	Savella	SNRI	Tablet	Twice a day	C	NR	No	No	\$\$\$
Mirtazapine	Remeron	NaSSA	Tablet	Once a day	C	R:B	Yes	No	\$
	Remeron SolTab		Oral disintegrating tablet				Yes	No	\$\$
Nefazodone**	Serzone	SARI	Tablet	Twice a day	C	NR	Yes	No	\$\$
Nortriptyline	Pamelor	TCA	Capsule, solution	Once a day	D	NR	Yes	Yes	\$
Paroxetine	Paxil	SSRI	Tablet, solution	Once a day	D	Safe	Yes	Yes	\$
	Paxil CR		Tablet				Yes	No	\$\$\$
Sertraline	Zoloft	SSRI	Tablet, solution	Once a day	C	Safe	Yes	Yes	\$
Trazodone	Desyrel	SARI	Tablet	Three times daily	C	R:B	Yes	Yes	\$
	Oleptro			Once a day			No	No	\$\$\$
Venlafaxine	Effexor	SNRI	Tablet	Twice a day	C	NR	Yes	No	\$\$
	Venlafaxine ER			Once a day			Yes	No	\$\$\$
	Effexor XR		Capsule	Once a day			No	No	\$\$\$\$
Vilazodone ^{††}	Viibryd	SPARI	Tablet	Once a day	C	NR	No	No	\$\$\$\$

*TCA, tricyclic antidepressant; NDRI, norepinephrine dopamine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin norepinephrine reuptake inhibitor; NaSSA, noradrenergic specific serotonergic antidepressant; SARI, serotonin antagonist reuptake inhibitor; SPARI, serotonin partial agonist reuptake inhibitor.

[†]C, no adequate or well-controlled studies in humans; D, positive evidence of human fetal risk based on adverse reaction data or studies in humans.

[‡]NR, not recommended; R:B, weigh risk-benefit; safe, safe for nursing; based on Lexicomp Online Clinical Databases (<http://online.lexi.com>).

[§]Available for a low monthly cost through programs offered by large chain stores (e.g., Walmart, Kroger, Sam's Club, Target, Costco, CVS, Kmart, Walgreens).⁶⁸

^{||}\$ = <\$50 per month; \$\$ = \$50 to \$100 per month; \$\$\$ = \$100 to \$150 per month; \$\$\$\$ = >\$150 per month; based on 2011 Consumer Reports Health Best Buy Drugs.⁶⁸

[¶]In the United States, fluvoxamine is approved only for obsessive-compulsive disorder; milnacipran is approved only for fibromyalgia; both agents are used off-label to treat depression.^{19,24}

**Serzone, the brand name form of nefazodone, was discontinued in 2004 because of hepatotoxicity; generic nefazodone is available with a black box warning for liver failure.⁵⁷

^{††}Approved in 2011, vilazodone is the newest antidepressant in a novel therapeutic class; given that data is limited, it is not discussed in this article.

pressed patients with accompanying symptoms of anxiety, insomnia, pain, loss of energy, and atypical features.^{53,54} Although these studies were unable to

draw reliable conclusions about the superiority of any antidepressant for a specific symptom cluster, the authors cautioned that very few trials in their

analyses were correctly designed or adequately powered to test this approach.^{53,54} Since most of the available data are from analyzing subgroups in large studies that did not intentionally enroll patients with significant accompanying symptoms, the quality of actual head-to-head evidence is very low.^{53,54} Investigators have called for high-quality, prospectively designed, randomized head-to-head trials of commonly prescribed antidepressants in well-defined populations of patients with prominent symptom clusters.^{53,54} Such research has the promise of finally producing direct evidence for a more individualized, patient-centered method of choosing antidepressants to treat major depression in primary care.

Any primary care model for a symptom cluster-based approach to antidepressant selection must be centered on a set of commonly occurring symptoms, each of which may effectively be treated by a pharmacologically appropriate class or classes of antidepressants. Based on available evidence and expert consensus, the most common and clinically relevant symptoms accompanying depression are anxiety, fatigue, insomnia, and pain.^{49–54} Thus, these four symptoms are a logical starting point to conceive a treatment model. Each of these 4 symptoms is physiologically mediated by one or more monoamine neurotransmitter pathways.³⁴ Anxiety is primarily regulated by serotonergic neurons projecting from the dorsal raphe nucleus in the brainstem to the limbic system that controls fear.³⁴ Fatigue is mediated through actions on the limbic cortex as well, but by norepinephrine pathways from the locus coeruleus, part of the reticular activating system that projects to the frontal cortex to control attention and concentration.³⁴ Insomnia is caused by dysregulation in the brainstem sleep centers, which involve serotonin 2A (5HT_{2A}) receptors.³⁴ Pain is thought to be mediated by both the serotonin and norepinephrine pathways acting directly to potentiate the pain-killing effects of the endogenous opioid system.⁵⁵ Understanding how these core symptoms are related to deficiencies in specific neurotransmitters is the first step to choosing the most appropriate types of antidepressants for each symptom cluster.

Anxiety is the first symptom to consider in the current effort to build a rational treatment model for depression in primary care (Table 2). As noted above, it is regulated by serotonergic neurons acting on the limbic system that controls fear.³⁴ It is

Table 2. Recommended Treatment for Depression with Anxiety

Symptom Cluster	Recommended Classes	Classes to Avoid	First-line Antidepressants
Anxiety	SSRI	NDRI	Citalopram
Tearfulness		SNRI	Escitalopram
Obsessive-compulsiveness			Fluvoxamine Sertraline

NDRI, norepinephrine dopamine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin norepinephrine reuptake inhibitor.

important to note that the same neurons arising from the brainstem that mediate anxiety also project to the frontal cortex to control mood and to the basal ganglia to influence obsessions and compulsions.³⁴ The triad of anxiety, tearfulness, and obsessive-compulsive behaviors is part of the “serotonin deficiency syndrome,”³⁴ a common symptom cluster encountered in a subpopulation of patients with major depressive disorder. Individuals with this symptom cluster may benefit most from an SSRI (Table 2). Supporting the superiority of SSRIs in this clinical setting is evidence that, in contrast to other antidepressant classes, most SSRIs are also approved by the US Food and Drug Administration (FDA) to treat generalized anxiety disorder and panic disorder, and only SSRIs are approved to treat obsessive-compulsive disorder.^{40,41} Although some SNRIs also are approved to treat anxiety disorder, patients with this symptom cluster may be less likely to benefit from them because of sympathetic (fight or flight) effects of norepinephrine on the cardiovascular and nervous systems, which can provoke anxiety.³⁴ Patients with this symptom cluster are also least likely to benefit from an NDRI, given its lack of serotonin activity and more activating properties.⁵¹ Under the current proposal, the best antidepressant to treat a depressed patient with anxiety, tearfulness, and obsessive-compulsive behavior is an SSRI such as citalopram, escitalopram, fluvoxamine, or sertraline (Table 2). Two other SSRIs with important activating (fluoxetine) and sedating (paroxetine) action will be examined later in the context of other symptom clusters.

Fatigue is the second symptom under consideration (Table 3). Energy, attention, concentration, and related cognitive functions are mediated by norepinephrine.³⁴ In contrast to the anxious and tearful patient described earlier, those with fatigue-

Table 3. Recommended Treatment for Depression with Fatigue

Symptom Cluster	Recommended Classes	Classes to Avoid	First-line Antidepressants
Fatigue	NDRI	NaSSA	Bupropion
Anhedonia	SNRI	SARI	Desvenlafaxine
Weight gain	Activating SSRI		Fluoxetine Venlafaxine

NaSSA, noradrenergic specific serotonergic antidepressant; NDRI, norepinephrine dopamine reuptake inhibitor; SARI, serotonin antagonist reuptake inhibitor; SNRI, serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

dominant depression often present with blunted affect, emotional withdrawal, weight gain, or anhedonia (loss of pleasure).⁵ These so-called atypical symptoms of depression are regulated by dopaminergic neurons projecting from the ventral tegmental area of the brainstem to the cerebral cortex.³⁴ Since deficiencies of norepinephrine and dopamine are thought to be the cause of atypical depression, recommending an SNRI (to increase norepinephrine) or NDRI (to boost both norepinephrine and dopamine) is the logical choice. Fluoxetine, an unusual SSRI with some norepinephrine reuptake inhibition,³⁴ is the most activating SSRI available and is preferred by most psychiatrists to treat depression with fatigue.⁵² Under the current proposal, the best antidepressants for treating the symptom cluster of fatigue, weight gain, and anhedonia should be bupropion (NDRI), venlafaxine or desvenlafaxine (SNRIs), and fluoxetine (SSRI) (Table 3). Two other SNRIs, duloxetine and milnacipran, with FDA indications to treat chronic pain, will be discussed later in the context of another symptom cluster. Fatigued patients are least likely to benefit from sedating antidepressants like NaSSAs and SARIs, which are better reserved for treating insomnia.²⁹

Insomnia is the third symptom under consideration (Table 4). As discussed earlier, insomnia is regulated by sleep centers in the brainstem, which involve 5HT_{2A} receptors.³⁴ Antidepressant classes with powerful 5HT_{2A} blocking activity, such as NaSSAs (mirtazapine) and SARIs (nefazodone and trazodone), should be particularly effective at alleviating insomnia and improving sleep architecture.²⁹ Studies have shown that mirtazapine significantly shortens time to sleep onset, increases total sleep duration, and improves sleep efficiency.²⁹ Psychiatrists prefer SARIs such as nefazodone and

trazodone over other agents for treating depression with insomnia, whereas primary care doctors tend to choose paroxetine, a unique SSRI with prominent anticholinergic action and sedating properties.⁵² Depressed patients with insomnia also occasionally present with clinical indications of weight loss and hyperarousal, especially if their depression is complicated by posttraumatic stress disorder.⁵⁶ Paroxetine and mirtazapine are recommended as first-line treatments for posttraumatic stress disorder by the National Institute for Clinical Excellence⁵⁶ and are likely the best choices for patients with insomnia plus hyperarousal. Mirtazapine is a good choice for restoring body weight when weight loss is a concern.^{27,28} In contrast to the fatigued patient discussed earlier, antidepressants like SNRIs and NDRIs are least likely to benefit patients with insomnia since they may be too activating. Under the current proposal, the best antidepressants for treating insomnia, hyperarousal, and weight loss are mirtazapine, paroxetine, trazodone, and nefazodone (Table 4). Physicians should be aware that Serzone (Bristol-Myers Squibb Co, New York, NY), one of the brand names of nefazodone, was discontinued in the United States in 2004 because of hepatotoxicity.⁵⁷ Generic nefazodone remains available, but it is rarely used because of a black box warning for fulminant liver failure.⁵⁷

Pain is the last symptom to consider in the current effort to build a rational treatment model for depression (Table 5). Pain is thought to be mediated by both serotonin and norepinephrine acting directly to potentiate the analgesic effects of the endogenous opioid system.⁵⁵ Since deficiencies of both serotonin and norepinephrine are present, it is logical to recommend an SNRI. Duloxetine is

Table 4. Recommended Treatment for Depression with Insomnia

Symptom Cluster	Recommended Classes	Classes to Avoid	First-line Antidepressants
Insomnia	NaSSA	NDRI	Mirtazapine
Hyperarousal	SARI	SNRI	Nefazodone
Weight loss	Sedating SSRI		Paroxetine Trazodone

NaSSA, noradrenergic specific serotonergic antidepressant; NDRI, norepinephrine dopamine reuptake inhibitor; SARI, serotonin antagonist reuptake inhibitor; SNRI, serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

Table 5. Recommended Treatment for Depression with Pain

Symptom Cluster	Recommended Classes	Classes to Avoid	First-line Antidepressants
Chronic pain	TCA	None	Amitriptyline
Headache	SNRI		Duloxetine
Somatization			Milnacipran Nortriptyline

SNRI, serotonin norepinephrine reuptake inhibitor; TCA, tricyclic antidepressant.

a SNRI that is FDA approved to treat major depression as well as painful diabetic peripheral neuropathy, fibromyalgia, and chronic musculoskeletal pain.²³ Milnacipran is an SNRI that is approved in the United States only for the treatment of fibromyalgia, but it is popular in other countries for treatment of depression.²⁴ There are only a few studies that directly compare an SNRI with other antidepressants for treating depression with pain, and all these studies are flawed and underpowered.⁵³ It is hoped that future research will elucidate the exact role of SNRIs in the treatment of painful depression. What has been used for decades as effective treatment for a number of chronic pain conditions—including idiopathic neuropathy,⁵⁸ fibromyalgia,⁵⁹ painful diabetic neuropathy,⁶⁰ prophylaxis of episodic migraine,⁶¹ and chronic musculoskeletal pain⁶²—are TCAs such as amitriptyline and nortriptyline. Although TCAs are older and in general less well-tolerated than newer antidepressants, they have a similar if not better efficacy in treating depression.⁶³ TCAs also have the added advantage of >50 years of experience in the hands of psychiatrists and primary care doctors.⁶³ Therefore, under the current proposal, the best antidepressants to treat depression with chronic pain are duloxetine, milnacipran, amitriptyline, and nortriptyline (Table 5).

An individualized, patient-centered treatment model for depression, created around a targeted symptom cluster-based approach to antidepressant selection, is described herein (Tables 2 to 5). In healthy adults with unipolar major depressive disorder, the choice of antidepressants should be guided primarily by the patient's dominant symptom cluster. Patients do not need to have all the symptoms in a symptom cluster to warrant treatment. Further distinction between medications in the same cluster may be guided by comorbid medical or psychiatric conditions, previous response (or

lack thereof) to a particular agent, preexisting renal or hepatic dysfunction, drug-drug interactions, frequency of dosing, and other factors. Pregnancy raises special concerns, especially with regard to teratogenicity and safety during breastfeeding. Sertraline has the best safety record in pregnant patients, whereas paroxetine should be avoided if possible.^{64,65} Age is also an important determinant. Fluoxetine has the best evidence in children and adolescents and is generally considered first-line treatment in this population.^{66,67} Lastly, the cost of medications has a significant impact on patients and the health care system. Antidepressants range from \$4 per month for older generics to >\$500 per month for newer brand name drugs.⁶⁸ One study comparing depression remission rates with costs of treatment for different medications suggested that escitalopram is the most cost-effective antidepressant in the primary care setting, at least in Europe.⁶⁹ These European estimates may differ from the US experience because of significant differences in price for some medications.

This proposed symptom cluster-based treatment model is based on the highest-quality evidence available, plausible neurobiological mechanisms, and years of practical experience. Veteran primary care doctors may find these recommendations comparable to their current practices, which were developed through trial and error. Nevertheless, direct evidence to support the use of a symptom cluster-based approach is very limited and complicated by studies with flawed designs and inadequate power.^{53,54} This model should be vigorously tested with high-quality, prospectively designed, randomized head-to-head trials of commonly prescribed antidepressants in populations of patients with well-defined symptom clusters. Future research should also strive to elucidate the complete mechanism of action for antidepressants, which may lead to the discovery of new biological targets for rational drug design. Lastly, primary care doctors need to know what to do after an initial antidepressant fails. No strategy—whether by augmentation with a second antidepressant or switching antidepressants within or between classes—has been proven superior.^{70–72}

Conclusion

Unipolar major depressive disorder is a common, disabling, and costly disease that is the leading

cause of ill health, early death, and suicide in the United States. Primary care doctors, particularly family physicians, are the first responders in this silent epidemic. While there are more than a dozen different antidepressants in 7 distinct classes that are widely used to treat depression in primary care, there is no evidence that one drug is superior to another. Comparative effectiveness studies have produced mixed results, and no specialty organization has published recommendations on how to choose antidepressants in a rational, evidence-based manner. In this article we presented the theory and evidence for an individualized, patient-centered treatment model for major depression that is designed around a targeted symptom cluster-based approach to antidepressant selection. Using this model in healthy adults with major depressive disorder, the choice of antidepressants should be guided by the presence of 1 of 4 common symptom clusters: anxiety, fatigue, insomnia, and pain—each of which may be effectively treated by an appropriate class or classes of antidepressants. This model was created to act as a practical construct to foster the design of future prospective, randomized trials that will put the symptom cluster-based approach to the test. In addition, this model provides a logical framework for teaching residents how to choose antidepressants that goes beyond arbitrary trial and error. Finally, the ultimate goal of the model is to equip primary care doctors with a structured treatment strategy to deliver optimal patient-centered care in the battle against depression.

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