Primary Care Reports
The Practical CME Journal for Primary Care and Family Physicians
Volume 20, Number 5 / May 2014
www.ahcmedia.com

Authors:

Randy A. Sansone, MD, Professor, Departments of Psychiatry and Internal Medicine, Wright State University School of Medicine, Dayton, OH; Director, Psychiatry Education, Kettering Medical Center, Kettering, OH

Lori A. Sansone, MD, Civilian Family Medicine Physician and Medical Director, Family Health Clinic, Wright-Patterson Air Force Base, Dayton, OH

Peer Reviewer:

Bryan Touchet, MD, Associate Professor and Vice Chair, Psychiatry Residency Training Director, Department of Psychiatry, University of Oklahoma School of Community Medicine, Tulsa

Statement of Financial Disclosure

To reveal any potential bias in this publication, and in accordance with Accreditation Council for Continuing Medical Education guidelines, Dr. L. Sansone (author), Dr. R. Sansone (author), Dr. Touchet (peer reviewer), Dr. Wise (editor), Ms. Coplin (executive editor), and Ms. Kimball (managing editor) report no financial relationships relevant to this field of study.

AHC Media

Psychiatry and Primary Care: The Changing Interface

The views and opinions expressed in this article are those of the authors and do not reflect the official policy or position of the US Air Force, Department of Defense, or U.S. government.

Like other academic disciplines, the field of psychiatry continues to evolve and transform. Many of these changes will potentially influence primary care clinicians as they entail psychiatric diagnosis, psychotropic medications, and treatment concepts. This article will review the new *Diagnostic and Statistical Manual of Mental Disorders*, which debuted in 2013, and discuss the changes that are most relevant to primary care. Then it will discuss the recent introduction into the U.S. antidepressant market of a fifth serotonin norepinephrine reuptake inhibitor (l-milnacipran/Fetzima™), and present this newcomer in the context of similarities and differences with other members of this class of antidepressants. The article will also highlight two new antidepressants, both hybrids of selective serotonin reuptake inhibitors that have been introduced to the U.S. market in recent years (vilazodone/Viibryd™ and vortioxetine/Brintellix™). Next, it will discuss mind-body relationships by reviewing the intriguing theory that some forms of depressive illness may be related to inflammatory processes. Finally, the article presents a perspective of the typical antipsychotics (as opposed to the atypical antipsychotics) as drugs that may harbor potential neurotoxic effects — a perspective couched with a number of caveats. Again, all of these developments represent intriguing evolutions in the field of psychiatry and have potential impacts on primary care clinicians and their practice styles.

Introduction

In this edition of *Primary Care Reports*, we discuss several contemporary

Executive Summary

The recent publication of the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5) and the continuing introduction of new psychoactive drugs create challenges for updated diagnostic and therapeutic choices for primary care patients.

- The new DSM-5 has removed the multi-axial system, virtually eliminated the bereavement precaution in the diagnosis of major depression, has separated panic disorder and agoraphobia into two independent disorders, and has relaxed and broadened the criteria for "somatic symptom disorder."
- While analogous in their actions on serotonin and norepinephrine, the serotonin norpinephrine reuptake inhibitors (SNRIs) are generally structurally different from each other and affect neurotransmitter reuptake in different proportions and degrees.
- Levomilnacipran is the most recent addition to the SNRI family, allows once-daily dosing, is likely to exert simultaneous reuptake inhibition of both serotonin and norepinephrine at all doses, and has not been associated with weight gain.
- New selective serotonin reuptake inhibitors (SSRI) hybrids, vilazodone and vortioxetine, are likely treatment options for patients who do not respond to or cannot tolerate SSRIs or SNRIs.
- Increasing evidence is accumulating that atypical antipsychotics have reduced risk for extrapyramidal side effects and prolactin elevation, are posssibly more effective for the treatment of negative symptoms and social symptoms of schizophrenia, and may exert less neurotoxic features than typical antipsychotics.

topics that either entail a revision in practice approach or offer relatively new interventions or concepts in the primary-care/psychiatry interface. We begin by reviewing several changes in the recently released *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5)[1] — i.e., specifically those changes most relevant to primary care clinicians. Next, we discuss the recent debut of a fifth serotonin norepinephrine reuptake inhibitor (SNRI), and position this novice antidepressant into a clinical context by comparing and contrasting the SNRI antidepressants. Then, we provide an overview of two tenderfoot antidepressants (vilazodone/Viibryd™ and vortioxetine/Brintellix™) that have been recently introduced into the U.S. market, both from a novel class of antidepressants. Then, we examine some new concepts in disease evolution by discussing the role of inflammation in some forms of depressive illness. Finally, we conclude with a discussion of the speculative neurotoxicity of the typical antipsychotics (as opposed to the atypical antipsychotics). We believe that these topics are keenly relevant to primary care clinicians and may temper both the approach to patients as well as practice style.

A New Diagnostic Manual: The DSM-5

The DSM-5, the official manual for psychiatric diagnosis in the United States, debuted in May 2013.[1] While there had been an intervening but modest text revision of the manual in 2000 (*Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision; DSM-IV-TR),[2] the DSM-5 represents a major change from the elemental manual of 1994 (*Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition; DSM-IV),[3] which uniquely established five axes for psychiatric diagnosis, including Axis II for the designation of personality disorders.

With the advent of the DSM-5,[1] two major structural changes were manifest. First, unlike previous editions of the manual, the numeral in the title is Arabic (i.e., 5) rather than Roman (i.e., V). Second, while the major psychiatric disorders and personality disorders are still present, the multi-axial system (e.g., Axis I: major psychiatric disorders, Axis II: developmental and personality disorders, Axis III: medical disorders) that was uniquely established in the DSM-IV[3] and continued in DSM-IV-TR[2] was dissolved.[1] (Some of these changes in the DSM may now be reflected in consultation reports by psychiatrists.)

In addition to the preceding structural changes, a number of other reforms were evident among the various clinical diagnoses. However, given that mood, anxiety, and somatoform disorders are the most common psychiatric diagnoses in primary care,[4-6] we will initially focus on the DSM-5 changes relevant to these specific syndromes.

Major Depression. With regard to the diagnosis of major depression, one important change in the DSM-5[1] was the diminished clinical influence of bereavement. In the DSM-IV-TR,[2] depressive symptoms could not be attributed to major depression if they could be better accounted for by bereavement (i.e., bereavement was somewhat of an exclusionary criterion). However, in the DSM-5,[1] the bereavement precaution is virtually eliminated so that the diagnosis of major depression can be readily applied in the context of bereavement.

Anxiety Disorders. As for anxiety disorders, in the DSM-IV-TR,[2] panic disorder was subclassified as "with agoraphobia" or "without agoraphobia." However, in the DSM-5,[1] panic disorder and agoraphobia have been separated into two independent disorders.

Somatoform Disorders. Diagnoses in the DSM-IV[3] and DSM-IV-TR[2] relating to somatoform disorders included somatization disorder, conversion disorder, pain disorder, hypochondriasis, and body dysmorphic disorder. In the new DSM-5,[1] these have been categorized as "somatic symptom and related disorders."

In addition, somatization disorder, present in the DSM-IV-TR,[2] has morphed considerably. Somatization disorder was previously a narrowly defined syndrome that was characterized by the presence of eight symptoms in four different physiological categories (i.e., gastrointestinal, pain, pseudoneurological, and sexual symptoms). However, in the DSM-5, the criteria for this syndrome were relaxed and broadened, and the name was morphed into "somatic symptom disorder."[1] As defined in the DSM-5, somatic symptom disorder consists of one or more somatic symptoms, present for at least 6 months, that result in significant patient distress or impaired functioning.[1] Symptoms do not have to be medically elusive (a significant change), but must result in excessive or disproportionate thoughts, feelings, and/or behaviors by the patient in response to their presence.[1]

New Diagnoses in the DSM-5. In addition to the diagnostic changes for mood, anxiety, and somatoform disorders, the DSM-5 also embraced several new psychiatric diagnoses.[1] Two of these new diagnoses were towed over from the appendix in the back of the previous manual, which was titled, "criteria sets and axes provided for further study." This appendix consists of a collection of diagnoses for which rudimentary criteria have been established but not officially sanctioned through rigorous research. The two transported diagnoses from this appendix into the DSM-5 were premenstrual dysphoric disorder and binge eating disorder. In addition to these two disorders, three other diagnoses potentially relevant to primary care clinicians surfaced in the DSM-5 diagnostic mainstream: 1) excoriation disorder (skin picking), 2) hoarding disorder, and 3) gambling disorder.

The personality disorders remain unchanged in the DSM-5.[1] However, the next version of the DSM may herald stark changes for the diagnosis of personality disorders. Clearly, this diagnostic manual will continue to evolve, but the next edition of the DSM will not likely emerge for a number of years to come.

Serotonin Norepinephrine Reuptake Inhibitors

Serotonin norepinephrine reuptake inhibitors (SNRIs) are a group or family of antidepressants that are bonded together by their reuptake inhibition of both serotonin and norepinephrine. While analogous in their actions on serotonin and norepinephrine, they are generally structurally different from each other and affect neurotransmitter reuptake inhibition in different proportions or degrees (i.e., the individual SNRIs are similar yet different). At the present time, there are five SNRIs in the U.S. market: venlafaxine immediate- and extended-release (Effexor/Effexor XR™), duloxetine (Cymbalta™), desvenlafaxine (Pristiq™), milnacipran (Savella™), and levomilnacipran (Fetzima™).

Venlafaxine (Effexor/Effexor XR™). Venlafaxine immediate release (Effexor™) was the first SNRI to be introduced into the U.S. market. It was initially approved by the FDA in 1993 for the treatment of major depression.[7] At the outset, venlafaxine immediate-release (dosed twice per day) was plagued with the side effects of nausea and vomiting.[8] In 1997, a micro-encapsulated extended-release formulation (Effexor XR™) was released to market.[7] Taken once daily, the extended-release capsule cannot be breached prior to or during ingestion. Venlafaxine currently has four approved clinical indications through the FDA: 1) major depression, 2) generalized anxiety disorder, 3) panic disorder, and 4) social phobia.[7] Both immediate-release and extended-release venlafaxine are available as brand and generic formulations.

In terms of its chemical structure, venlafaxine is a bicyclic (2 chemical rings).[7] The half-life of immediate-release venlafaxine is 5 hours and the half-life of its active metabolite, o-desmethylvenlafaxine or desvenlafaxine, is 11 hours.[7] For the extended-release formulation, the half-lives for both venlafaxine and desvenlafaxine may be somewhat longer, up to 11 hours and 13-14 hours, respectively.[8] Venlafaxine is primarily metabolized through the liver (P-450 isoenzymes 2D6 and 3A3/4),[7] which indicates a potential for drug interactions.[7] In addition, the 2D6 isoenzyme is metabolically susceptible to genetic polymorphism.

Venlafaxine inhibits the reuptake of both serotonin and norepinephrine in a disproportionate manner. Specifically, venlafaxine demonstrates a 30-fold higher affinity for the reuptake inhibition of serotonin compared to norepinephrine.[9] Moreover, this SNRI inhibits serotonin and norepinephrine reuptake pumps in a sequential manner, with serotonin reuptake inhibition followed by norepinephrine reuptake inhibition.[10] This phenomenon mirrors the general clinical experience with venlafaxine — i.e., that initial side effects are predominantly serotonergic in nature (e.g., headaches, nausea, fatigue, sexual dysfunction) whereas subsequent side effects with higher dosing are both serotonergic and noradrenergic (e.g., the latter side effects being activation effects, dry mouth, and night sweats). At very high doses (e.g., 225 mg per day), venlafaxine appears to exhibit some dopamine reuptake inhibition.[7]

Duloxetine (Cymbalta™). In 2004, duloxetine (Cymbalta™) became the second SNRI to be approved by the FDA.[11] Interestingly, shortly after its approval for the treatment of major depression in August 2004, duloxetine was approved by the FDA for the treatment of diabetic peripheral neuropathy in September 2004. In this latter regard, duloxetine became

the first drug in the United States to be approved for this condition.[11] Since its introduction, duloxetine has received approval through the FDA for several additional syndromes, including: 1) generalized anxiety disorder, 2) fibromyalgia, 3) musculoskeletal pain, and 4) osteoarthritis.[11] With these preceding indications, duloxetine has garnered the most FDA endorsements of any SNRI, including the distinction of clinical indications for various non-psychiatric conditions — each representing a different type of pain syndrome. (Note that while previous antidepressants such as the tricyclics have been broadly utilized in various pain syndromes, official FDA endorsements for pain indications are novel for an antidepressant.) Duloxetine became a candidate for generic formulation at the end of 2013.

Duloxetine has three rings in its chemical structure, two of which are adjacent to each other.[11] The half-life of duloxetine is approximately 12 hours.[11] The metabolism of duloxetine culminates in a number of metabolites, which are either fleeting or lack meaningful biological activity.[12,13] Duloxetine is metabolized mainly through the hepatic P-450 isoenzyme system (2D6, 1A2 isoenzymes), which indicates a potential risk for drug interactions.[11] Because of the presence of 2D6 metabolism, patients may have varying abilities to metabolize the drug due to genetic polymorphism.[11] The dosing of duloxetine is once per day.

Like venlafaxine, duloxetine displays a dominant serotonergic influence in comparison to its noradrenergic influence. However, this SNRI demonstrates only a 10-fold higher selectivity for serotonin reuptake inhibition compared with norepinephrine reuptake inhibition.[14] Like venlafaxine, the invocation of reuptake inhibition is sequential, with an initial influence on serotonin followed by a subsequent influence on norepinephrine.[15]

Desvenlafaxine (Pristiq™). In 2008, desvenlafaxine (Pristique™) became the third SNRI to receive approval from the FDA for use in the United States.[16] Desvenlafaxine is the active metabolite of venlafaxine. Therefore, desvenlafaxine has some pharmacological similarities to venlafaxine. This SNRI is solely manufactured as an extended-release tablet and is clinically approved by the FDA for the treatment of major depression.[16] Desvenlafaxine is not yet available in a generic formulation.

Desvenlafaxine consists of two chemical rings that are not adjacent to each other.[17] The elimination half-life of desvenlafaxine is approximately 11 hours[16] and the drug can be dosed once per day. Desvenlafaxine is partially metabolized through the P-450 isoenzyme system (3A4) and partially metabolized through hepatic conjugation.[16] Because of its metabolism through the 3A4 isoenzyme, desvenlafaxine is not subject to genetic polymorphism, as is the case with drugs that are metabolized through the 2D6 isoenzyme. Nearly 50% of desvenlafaxine is excreted unchanged in the urine,[17,18] which suggests that desvenlafaxine undergoes less extensive metabolism through the P-450 isoenzyme system than most other drugs.[18,19] Because of its reduced interface with the P-450 isoenzyme system, desvenlafaxine should have a reduced risk for potential drug interactions in comparison with the preceding SNRIs.[20] Desvenlafaxine does not have any active metabolites.[21]

Like duloxetine, desvenlafaxine demonstrates a 10-fold higher selectivity for serotonin reuptake inhibition compared with norepinephrine reuptake inhibition.[22,23] As for the temporal effects of desvenlafaxine on serotonin and norepinephrine reuptake inhibition — either sequential or simultaneous — we were unable to locate any empirical data in this regard.

Milnacipran (Savella™). In 2009, milnacipran (Savella™) became the fourth SNRI to be introduced into the United States.[24] While marketed in France since 1997 for the treatment of major depression,[25] milnacipran is presently only indicated by the FDA for the treatment of fibromyalgia. Milnacipran is not available in a generic formulation and the expiration of the patent is not imminent.

Milnacipran contains one chemical ring[26] and is a racemic mixture that is composed of d-milnacipran and l-milnacipran.[24] D-milnacipran has a half-life of 8-10 hours whereas l-milnacipran has a half-life of 4-6 hours.[24] Unlike the other SNRIs, which entail once-daily dosing, milnacipran is dosed twice-per-day. Milnacipran undergoes conjugation in the liver and it is devoid of any significant interactions with the P-450 isoenzymes, suggesting few if any drug interactions and no susceptibility to genetic polymorphism.[23] Milnacipran has no significant active metabolites[23] and most of the administered drug is excreted in the urine,[23] either as the parent compound (55%) or as several inactive metabolites.[24]

Milnacipran is the most balanced reuptake inhibitor among the SNRIs, with nearly equipotent reuptake inhibition of serotonin and norepinephrine.[25] Rather than the sequential effect on serotonin and norepinephrine that is observed with venlafaxine and duloxetine, milnacipran exerts at all doses a simultaneous effect on the reuptake inhibition of both serotonin and norepinephrine.[23]

Levomilnacipran (Fetzima™). Levomilnacipran (Fetzima™) is the most recent addition to the SNRI line and was approved by the FDA in 2013 for the treatment of major depression.[27] It is the more active l-enantiomer of milnacipran.[28] Levomilnacipran was developed at the outset as a sustained-release formulation (once per day dosing),[28,29] a pharmacological maneuver that will likely improve patient compliance as well as enhance marketability. The patent expiration for levomilnacipran is presently projected at 2023.

Like milnacipran, levomilnacipran has one ring in its chemical structure.[26] The half-life of levomilnacipran is approximately 12 hours.[30] Levomilnacipran undergoes desethylation, which occurs primarily through the 3A4 isoenzyme, as well as hydroxylation.[30] The resulting

Table 1: Comparison of Serotonin Norepinephrine Reuptake Inhibitors

Feature	Venlafaxine	Duloxetine	Desvenlafaxine	Milnacipran	Levomilnacipran
Year of FDA Approval	1993: IR 1997: XR	2004	2008	2009	2013
Generic	Yes	Yes	No	No	No
FDA Indications	Major depression Generalized anxiety disorder Panic disorder Social phobia	Major depression Generalized anxiety disorder Diabetic peripheral neuropathy Fibromyalgia Musculoskeletal pain Osteoarthritis	Major depression	Fibromyalgia	Major depression
Half-life (hours)	Venlafaxine IR: 5 Desvenlafaxine IR: 11 Venlafaxine XR: 11 (?) Desvenlafaxine XR: 13-14 (?)	12	11	d-enantiomer: 8-10 l-enantiomer: 4-6	12
Metabolism/ Excretion	Mainly hepatic (P-450)	Mainly hepatic (P-450)	Partially hepatic, but not via P-450	Primarily renal	Primarily renal
Active Metabolites	Desvenlafaxine (o-desmethly-venlafaxine)	None	None	None	None
Dosing	Venlafaxine IR: twice per day Venlafaxine XR: once per day	Once per day	Once per day	Twice per day	Once per day
5HT: NE Reuptake Inhibition Ratio	30:1	10:1	10:1	1:1	1:2
5HT/NE Inhibition Process	Sequential (5HT then NE)	Sequential (5HT then NE)	?	Simultaneous	Simultaneous (?)

Note: IR = immediate release; XR = extended release; all serotonin norepinephrine reuptake inhibitors can cause elevations in blood pressure, serotonergic and noradrenergic side effects, discontinuation syndromes, and suicidal ideation at initiation

metabolites are inactive.[27] Nearly 60% of levomilnacipran is excreted unchanged in the urine.[30] Strong 3A4 isoenzyme inhibitors such as ketoconazole may increase the levels of levomilnacipran.[30]

Unlike the serotonergic predominance of most SNRIs, levomilnacipran demonstrates a two-fold greater potency for norepinephrine reuptake inhibition in comparison to serotonin reuptake inhibition.[28] Like milnacipran, levomilnacipran is likely to exert a simultaneous reuptake inhibition effect on both serotonin and norepinephrine at all doses, although this remains an assumption.

Because levomilnacipran is relatively new, we will review dosing, side effects, and possible clinical

niches. Levomilnacipran is formulated in 20, 40, 80, and 120 mg capsules. The initial dose is 20 mg per day, which is maintained for several days and then followed with a suggested increase to 40 mg per day. The dosage range of levomilnacipran is 40-120 mg per day. Gastrointestinal (e.g., nausea, constipation, vomiting) and cardiac (e.g., elevated heart rate, tachycardia, palpitations) side effects are most common as well as hyperhidrosis and erectile dysfunction.[27] In a 48-week study, levomilnacipran did not result in any mean changes in body weight.[31] While the clinical role of levomilnacipran remains unclear, it may be useful for patients who are refractory to other antidepressants, subpopulations of patients whose symptoms are believed to be related to a deficiency of norepinephrine, or patients who are sensitive to SSRI-induced weight gain.

A Clinical Comparison of the SNRIs. Table 1 provides a comparison of the SNRIs, both their similarities and differences. Of the available SNRIs, only venlafaxine and duloxetine are available in generic formulations, suggesting a potential cost advantage. In terms of indications by the FDA, duloxetine has the most (six indications), followed by venlafaxine (four indications), and desvenlafaxine, milnacipran, and levomilnacipran (one indication each).

In comparison with other families of antidepressants, such as the selective serotonin reuptake inhibitors (SSRIs) or tricyclic antidepressants, the SNRIs have relatively short half-lives (8-12 hours) and few-to-no active metabolites (i.e., an overall simpler pharmacology). Being primarily metabolized through the P-450 isoenzyme system, venlafaxine and duloxetine are more likely to have potential drug interactions. In addition, both of the preceding SNRIs entail partial metabolism through the 2D6 isoenzyme, indicating a susceptibility to genetic polymorphism. In contrast, desvenlafaxine, milnacipran, and levomilnacipran largely bypass the P-450 isoenzyme system and are therefore less likely to precipitate drug interactions. Of the five available SNRIs, only venlafaxine has an active metabolite (desvenlafaxine). As for dosing, venlafaxine immediate release and milnacipran are dosed twice per day whereas the remaining SNRIs are dosed once-per-day.

While all SNRIs are serotonin/norepinephrine reuptake inhibitors, each demonstrates a different influence or proportionate effect on reuptake inhibition. Venlafaxine is the most serotonergic SNRI, followed by duloxetine and desvenlafaxine. In contrast, milnacipran exerts a relatively equal influence on serotonin and norepinephrine reuptake inhibition whereas levomilnacipran demonstrates greater norepinephrine reuptake inhibition than serotonin reuptake inhibition. Whether these disproportionate influences on reuptake inhibition among the SNRIs will yield any meaningful clinical differences beyond their manifestations as potential side effects is yet to be determined. However, such differences indicate that these drugs are clearly dissimilar from one another. Finally, both venlafaxine and duloxetine exhibit dose-related sequential effects on reuptake inhibition. In contrast, while desvenlafaxine is unclear in this regard, milnacipran and likely levomilnacipran act simultaneously on serotonin and norepinephrine reuptake inhibition.

SNRIs will remain a fertile area for scientific investigation over the next few years. Given their disproportionate effects on serotonin and norepinephrine, one wonders whether these differences will translate into significant clinical differences. For example, does a specific profile in this regard confer greater benefits with pain management in general, or with specific types of pain? Will these profiles predict better responses to depression in subpopulations of mood-disordered patients? The answers await us!

The New SSRI Hybrids

Without a doubt, the SSRIs have enjoyed longstanding success in the treatment of various psychiatric disorders. Not only do these antidepressants demonstrate a broad range of clinical efficacy, but they have relatively few long-term side effects, with the exceptions of possible sexual dysfunction and weight gain, which vary among the drugs. Over the past few years, SSRI hybrids (i.e., a basic SSRI function with additional neurotransmitter effects) have been developed. Two are now available in the United States — vilazodone (Viibryd™) and vortioxetine (Brintellix™).

Vilazodone (Viibryd™). Vilazodone (Viibryd™) was approved by the FDA in 2011 for the treatment of major depression.[32] Vilazodone is an SSRI-type antidepressant with partial agonist function at the $5HT_{1A}$ receptor site — i.e., it demonstrates SSRI activity plus $5HT_{1A}$ activity (dual action).[32] Being new to the market, vilazodone is not available in a generic formulation.

Vilazodone has a 5-ring chemical structure.[33] The drug is metabolized through the P-450 isoenzyme system, predominantly through the 3A4 isoenzyme and to a lesser degree through the 2D6 and 2C19 isoenzymes.[32,33] This metabolic profile indicates the possibility of drug interactions, particularly with those drugs that inhibit or induce the 3A4 isoenzyme (i.e., lower doses of vilazodone are recommended when co-administered with potentially inhibiting drugs such as erythromycin, amiodarone, protease inhibitors, and ketoconazole[34]). Because of modest effects at the 2D6 isoenzyme, the risk of influences from genetic variability with vilazodone is modest. The half-life of vilazodone is approximately 25 hours[32,33] and the drug does not appear to have any active metabolites.[34]

Vilazodone is formulated in 10 mg, 20 mg, and 40 mg unscored tablets.[32] The initial or starting dose is 10 mg per day, with gradual titration to a recommended daily dose of 40 mg per day. However, in contrast to inpatients, outpatients will likely benefit from lower maintenance doses. The most common side effects of vilazodone are gastrointestinal in

nature (e.g., diarrhea, nausea, vomiting) as well as insomnia.[35] The risk of weight gain appears to be marginal and rates of sexual dysfunction are only 1-2% higher than placebo.[34] Unlike SNRIs, vilazodone does not appear to increase blood pressure.[36]

The explicit role of vilazodone in clinical practice remains unclear. At the outset, vilazodone will likely be used for patients who are unresponsive to more traditional antidepressants. In addition, vilazodone may be useful in patients with predilections to antidepressant-induced weight gain or sexual dysfunction (SSRIs, SNRIs), or elevations in blood pressure (SNRIs).[34] Only time and the evolution of the antidepressant market will determine the ultimate niche of vilazodone in clinical practice.

Vortioxetine (Brintellix™). Vortioxetine (Brintellix™) was approved by the FDA in 2013 for the treatment of major depression.[37] Vortioxetine is an SSRI-type antidepressant with various agonist and antagonist functions at several 5HT sub-receptor sites, including $5HT_1$, $5HT_3$, and $5HT_7$ (i.e., multiaction).[37] Being a new antidepressant, vortioxetine is not available in a generic formulation.

Vortioxetine contains 3 chemical rings that are separated from each other.[37] The drug is extensively metabolized through the P-450 isoenzyme system.[37] While the 2D6 pathway appears to be predominant, vortioxetine is also partially metabolized through the 3A4, 2C19, 2C9, 2A6, 2C8, and 2B6 isoenzymes.[37] The predominance of the 2D6 metabolic route indicates that vortioxetine is subject to various drug interactions as well as genetic polymorphism. With regard to coprescribed drugs, the list of potential interactions is broad.[38] With regard to genetic polymorphism, compared with extensive metabolizers, poor metabolizers demonstrate twice the serum levels of vortioxetine.[37] The half-life of vortioxetine is approximately 66 hours and the drug does not have any active metabolites.[37]

Vortioxetine is formulated in 5 mg, 10 mg, 15 mg, and 20 mg tablets.[37] The general starting dose is 10 mg per day, with gradual titration to 20 mg per day as tolerated. According to the prescribing information, the most common side effects of this antidepressant are nausea, constipation, and vomiting, each with an incidence of ≥ 5% and at least twice the rate of placebo.[37] Vortioxetine may also cause sexual dysfunction, which appears to be a dose-related risk,[37] but the prevalence remains unclear and likely is low. This SSRI hybrid appears to be relatively weight neutral and has no apparent effects on blood pressure.[37]

Like vilazodone, vortioxetine is likely to be a treatment option for patients who do not respond to or cannot tolerate SSRIs or SNRIs. As for niche possibilities, vortioxetine is relatively weight neutral, suggesting an indication for patients who are sensitive to weight gain with SSRIs/SNRIs. However, cost, the possible presence of sexual dysfunction, and the risk of drug interactions will likely be deterrents to widespread prescription. On an interesting side note, vortioxetine has demonstrated the ability to enhance memory functioning in animal studies.[39] In a study in humans, in comparison with placebo, the drug significantly improved cognitive functioning.[40] The full clinical relevance of this finding is yet to be determined.

Inflammation: A Possible Link between Some Physical Illnesses and Some Types of Depression

We will now examine research findings that provide an emerging perspective on the inter-relationship between some physical illnesses and some depressive illnesses. Without a doubt, mood disorders and medical diseases co-occur with some frequency.[41] In support of this impression, Benros and colleagues examined nearly 4 million Danish participants to determine relationships between the presence of either an autoimmune disease or an infectious disease, and the subsequent risk of a mood disorder in the aftermath of hospitalization.[41] In this sample, hospitalization for an autoimmune disease increased the risk of a subsequent mood disorder by 45% and hospitalization for an infectious disease increased the risk of a subsequent mood disorder by 62%.[41] The number of autoimmune and/or infectious diseases increased the risk of mood disorders in a dose-response fashion.

The suggestion of inter-relationships between some medical diseases and some types of depression is not novel. In 1988, Hart published a paper on the topic of sick behavior.[42] In this paper, he described illness behavior in animals and humans as ubiquitous, and characterized this behavior as "lethargic, depressed, anorexic…." Hart interpreted this behavior, which encompasses a number of depressive-like symptoms, as an adaptive and desirable effect of illness — a response that was critical to the survival of the animal.

Twenty years later, Dantzer described the phenomenon of "sickness behavior," a syndrome characterized by nausea, feeling feverish, loss of appetite, anhedonia, fatigue, fragmented sleep, mild cognitive difficulties, depression, and irritability.[43] Again, this description suggests overlap between medical and depressive symptoms. As for an explanation of these mutually shared symptoms, Dantzer attributed both sickness behavior and depressive symptoms in these cases to elevations of pro-inflammatory cytokines.[43]

In support of Dantzer's impression, Almond proffered that both stress and some forms of depression are associated with elevations of pro-inflammatory cytokines.[44] She stated that administering pro-inflammatory cytokines (e.g., interferon) to humans increases the risk of depression whereas administering anti-inflammatory cytokines improves mood in some cases and can be achieved with antidepressants as well as aspirin.[44]

How might pro-inflammatory cytokines relate to mutual symptoms

Table 2: Examples of Typical and Atypical Antipsychotics

Typical Antipsychotics	Atypical Antipsychotics
Chlorpromazine/Thorazine™	Aripiprazole/Abilify™
Fluphenazine/Prolixin™	Asenapine/Saphris™
Haloperidol/Haldol™	Clozapine/Clozaril™
Loxapine/Loxitane™	Iloperidone/Fanapt™
Mesoridazine/Serentil™	Lurasidone/Latuda™
Molindone/Moban™	Olanzapine/Zyprexa™
Perphenazine/Trilafon™	Paliperidone/Invega™
Thioridazine/Mellaril™	Quetiapine/Seroquel™
Thiothixene/Navane™	Risperidone/Risperdal™
Trifluoperazine/Stelazine™	Ziprasidone/Geodon™

in some forms of medical illness and depressive illness? Pro-inflammatory cytokines appear to have an overall detrimental effect on serotonin levels.[44] Pro-inflammatory cytokines degrade tryptophan, the precursor to serotonin, as well as re-channel tryptophan away from serotonin production. In addition, pro-inflammatory cytokines increase tryptophan uptake in the brain, shorting out serotonin production.[43] The summary effect seems to be an overall reduction in available serotonin, which according to longstanding monoamine theory, accounts for the evolution of depressive symptoms.

Importantly, elevations in pro-inflammatory cytokines are not always present in depressive illness and therefore, this pathway to depressive illness does not account for all types of depressive disorders. However, in the medical setting, these inter-relationships are potentially relevant due to the high rates of comorbid medical illness and depressive illness. In such cases, clinicians may in the future modify their approaches to the treatment of these disorders. Only further research will tease out the inter-relationships among various forms of medical illness and depressive illness.

Neurotoxicity With the Typical Antipsychotics?

Antipsychotics (e.g., chlorpromazine/Thorazine™) have been available in the U.S. market since the 1950s. Since that time, the development of these drugs has diverged into two broad categories — 1) the typical antipsychotics (older) and 2) the atypical antipsychotics (newer) (*see Table 2*). While all antipsychotics currently available in the United States block dopamine (D_2) receptors, the typical antipsychotics are non-selective or indiscriminant D_2 blockers whereas the atypical antipsychotics are selective or discriminating D_2 blockers. (On a side note, the atypical antipsychotics have additional influences that contribute to their antipsychotic efficacy, including serotonergic effects and in some cases rapidly reversible receptor-site binding.) Given their D_2 binding variances, the older typical antipsychotics block D_2 receptors in brain areas that may result in extrapyramidal side effects as well as prolactin elevation whereas the newer atypical antipsychotics selectively block dopamine receptors with minimal effects in these areas. In addition to their selectivity and reduced risk for extrapyramidal side effects and prolactin elevation, the atypical antipsychotics are also allegedly effective for the treatment of negative symptoms in schizophrenia (e.g., social withdrawal, low motivation) and can augment the effects of antidepressants in mood disorders (e.g., aripiprazole/Abilify™).

According to Nasrallah, accumulating data indicate that the atypical or newer antipsychotics may be more innocuous than the typical or older antipsychotics.[45] Specifically, Nasrallah cited 28 published articles in this area of research and summarized a number of possible neurotoxic features of typical antipsychotics on brain cells, including: 1) inhibition of cell growth, 2) impaired glutamate transport, 3) mitochondrial damage, 4) decreased cell viability, and 5) cell apoptosis and necrosis.[45] Nasrallah suggests that these neurotoxic effects may be particularly pronounced with haloperidol/Haldol™.[45] He also indicates that the atypical antipsychotics appear to be neuroprotective — i.e., that they promote neurogenesis and increase neurotrophic factors.[45]

While these findings are intriguing, the preceding data should be tempered by the following caveats: 1) some of these findings are from animal studies and their translation to humans is unclear; 2) some of the observed detrimental changes in neuronal tissue may, in part, be related to psychosis itself, and not antipsychotic exposure; 3) potential investigator biases may be affecting the interpretation of existing data; and 4) at this juncture, it is not patently clear that atypical antipsychotics are absolutely safer than typical antipsychotics. These issues will only be resolved through further examination of unfolding data over the next few years.

Conclusion

The field of psychiatry continues to morph and evolve. As it does, these changes will impact primary

care clinicians. Recent changes in psychiatry include the introduction of the DSM-5 and its structural and diagnostic changes; the debut of several new antidepressants, specifically levomilnacipran, vilazodone, and vortioxetine; increasing awareness of the contributory role of pro-inflammatory cytokines in the generation of symptoms in some types of medical and depressive illnesses; and the emerging and indistinct data on the potential neurotoxicity of the older typical antipsychotics. These changes may all potentially involve a refinement in practice approach, both in psychiatry and in primary care. However, the degree to which these changes will impact clinical practice will only be born out with time. Perhaps the only reliable prediction is that there will be more changes to come.

References

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 5th Edition. Washington, DC: American Psychiatric Publishing, Inc.; 2013.
2. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision. Washington, DC: American Psychiatric Association; 2000.
3. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition. Washington, DC: American Psychiatric Association; 1994.
4. Linzer M, Spitzer R, Kroenke K, et al. Gender, quality of life, and mental disorders in primary care: Results from the PRIME-MD 1000 study. *Am J Med* 1996;101:526-533.
5. Ansseau M, Dierick M, Buntinkx F, et al. High prevalence of mental disorders in primary care. *J Affect Disord* 2004;78:49-55.
6. Roca M, Gili M, Garcia-Garcia M, et al. Prevalence and comorbidity of common mental disorders in primary care. *J Affect Disord* 2009;119:52-58.
7. Gold Standard, Inc. Venlafaxine. Clinical Pharmacology [database online]. Available at: http://www.clinicalpharmacology.com. Accessed Jan. 8, 2014.
8. Olver JS, Burrows GD, Norman TR. The treatment of depression with different formulations of venlafaxine: A comparative analysis. *Hum Psychopharmacol* 2004;19:9-16.
9. Montgomery SA. Tolerability of serotonin norepinephrine reuptake inhibitor antidepressants. *CNS Spectr* 2008;13:27-33.
10. Janicak PG, Davis JM, Preskorn SH, et al. *Principles and Practice of Psychopharmacotherapy*, 2nd ed. Baltimore: Lippincott, Williams & Wilkins; 1997.
11. Gold Standard, Inc. Duloxetine. Clinical Pharmacology [database online]. Available at: http://www.clinicalpharmacology.com. Accessed Jan. 8, 2014.
12. Kuo F, Gillespie TA, Kulanthaivel P, et al. Synthesis and biological activity of some known and putative duloxetine metabolites. *Bioorg Med Chem Lett* 2004;14:3481-3486.
13. Hunziker ME, Suehs BT, Bettinger TL, et al. Duloxetine hydrochloride: A new dual-acting medication for the treatment of major depressive disorder. *Clin Ther* 2005;27:1126-1143.
14. Stahl SM, Grady MM, Moret C, et al. SNRIs: Their pharmacology, clinical efficacy, and tolerability in comparison with other classes of antidepressants. *CNS Spectr* 2005;10:732-747.
15. Turcotte JE, Debonnel G, de Montigny C, et al. Assessment of the serotonin and norepinephrine reuptake blocking properties of duloxetine in healthy subjects. *Neuropsychopharmacol* 2001;24:511-521.
16. Gold Standard, Inc. Desvenlafaxine. Clinical Pharmacology [database online]. Available at: http://www.clinicalpharmacology.com. Accessed Jan. 8, 2014.
17. Desvenlafaxine Package Insert. Available at: http://labeling.pfizer.com/showlabeling.aspx?id=497. Accessed Jan. 9, 2014.
18. Perry R, Cassagnol M. Desvenlafaxine: A new serotonin-norepinephrine reuptake inhibitor for the treatment of adults with major depressive disorder. *Clin Ther* 2009;31:1374-1404.
19. Lourenco MT, Kennedy SH. Desvenlafaxine in the treatment of major depressive disorder. *Neuropsychiatr Dis Treat* 2009;5:127-136.
20. Seo HJ, Sohi MS, Patkar AA, et al. Desvenlafaxine succinate: A newer antidepressant for the treatment of depression and somatic symptoms. *Postgrad Med* 2010;122:125-138.
21. Cohen LJ. Desvenlafaxine: Frequently asked questions. *Prim Psychiatry* 2009;16:1-8.
22. Deecher DC, Beyer CE, Johnston G, et al. Desvenlafaxine succinate: A new serotonin and norepinephrine reuptake inhibitor. *J Pharmacol Exp Ther* 2006;318:657-665.
23. Kasper S, Pail G. Milnacipran: A unique antidepressant? *Neuropsychiatr Dis Treat* 2010;6:S23-31.
24. Gold Standard, Inc. Milnacipran. Clinical Pharmacology [database online]. Available at: http://www.clinicalpharmacology.com. Accessed on July 9, 2013.
25. Delini-Stula A. Milnacipran: An antidepressant with dual selectivity of action on noradrenaline and serotonin reuptake. *Hum Psychopharmacol* 2000;15:255-260.
26. National Center for Biotechnology Information. Milnacipran compound summary. Located at: http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=65833. Accessed Jan. 9, 2014.
27. Gold Standard, Inc. Levomilnacipran. Clinical Pharmacology [database online]. Available at: http://www.clinicalpharmacology.com. Accessed Jan. 14, 2014.
28. Auclair AL, Martel JC, Assie MB, et al. Levomilnacipran (F2695), a norepinephrine-preferring SNRI: Profile in vitro and in models of depression and anxiety. *Neuropharmacology* 2013;70:338-347.
29. Clinical Trials.Gov. Safety and efficacy of levomilnacipran SR in major depressive disorder. Located at: http://clinicaltrials.gov/ct2/show/NCT01377194. Accessed on July 17, 2013.
30. Forest Pharmaceuticals, Inc. Fetzima. Highlights of prescribing information. Located at: https://

www.fetzima.com/?guid=google577. Accessed on July 31, 2013.

31. Mago R, Forero G, Greenberg WM, et al. Safety and tolerability of levomilnacipran ER in major depressive disorder: Results from an open-label, 48-week extension study. *Clin Drug Investig* 2013;33:761-771.
32. Gold Standard, Inc. Vilazodone. Clinical Pharmacology [database online]. Available at: http://www.clinicalpharmacology.com. Accessed on Jan. 9, 2014.
33. National Center for Biotechnology Information. Vilazodone HCl (Viibryd). Located at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3278186/. Accessed Jan. 9, 2014.
34. Schwartz TL, Siddiqui UA, Stahl SM. Vilazodone: A brief pharmacological and clinical review of the novel serotonin partial agonist and reuptake inhibitor. *Ther Adv Psychopharmacol* 2011;1:81-87.
35. Cruz MP. Vilazodone HCl (Viibryd): a serotonin partial agonist and reuptake inhibitor for the treatment of major depressive disorder. *PT* 2012;37:28-31.
36. Forest Pharmaceuticals, Inc. Viibryd prescribing information. Located at: http://www.viibrydhcp.com/. Accessed Jan. 9, 2014.
37. Takeda Pharmaceutical USA, Inc. Brintellix prescribing information. Located at: https://www.brintellixhcp.com/. Accessed Jan. 10, 2014.
38. Medscape. Vortioxetine. Interactions. Located at: http://reference.medscape.com/drug/brintellix-vortioxetine-999882#3. Accessed Jan. 10, 2014.
39. Mork A, Montezinho LP, Miller S, et al. Vortioxetine (Lu AA21004), a novel multimodal antidepressant, enhances memory in rats. *Pharmacol Biochem Behav* 2013;105:41-50.
40. Editors, Hospital Pharmacy Europe. Brintellix improvement in adult patients with major depression. Located at: http://www.hospitalpharmacyeurope.com/editors-pick/brintellix%C2%AE-improvement-adult-patients-major-depression. Accessed Jan. 10, 2014.
41. Benros ME, Waltoft BL, Nordentoft M, et al. Autoimmune diseases and severe infections as risk factors for mood disorders: a nationwide study. *JAMA Psychiatry* 2013. DOI: 10.1001/jamapsychiatry.2013.1111.
42. Hart BL. Biological basis of the behavior of sick animals. *Neurosci Biobehav Rev* 1988;12:123-137.
43. Dantzer R, O'Connor JC, Freund GG, et al. From inflammation to sickness and depression: When the immune system subjugates the brain. *Nat Rev Neurosci* 2008;9:46-56.
44. Almond M. Depression and inflammation: Examining the link. *Curr Psychiatry* 2013;12:25-32.
45. Nasrallah HA. Haloperidol clearly is neurotoxic. Should it be banned? *Curr Psychiatry* 2013;12:7-8.

Earn AOA Credits Now!

Primary Care Reports now offers American Osteopathic Association CME credits. You can earn up to 30 AOA Category 2-B credits.

The American Osteopathic Association has approved this continuing education activity for up to 30 AOA Category 2-B credits. To earn credit for this activity, please follow the CME instructions above.

AMERICAN OSTEOPATHIC ASSOCIATION

Primary Care Reports CME Objectives

Upon completion of this activity, participants should be able to:

1. Summarize recent, significant studies related to the practice of primary care medicine;
2. Evaluate the credibility of published data and recommendations related to primary care medicine;
3. Discuss the advantages and disadvantages of new diagnostic and therapeutic procedures in the primary care setting.

CME Instructions

To earn credit for this activity, please follow these instructions.

1. Read and study the activity, using the provided references for further research.
2. Scan the QR code to the right, or log on to www.cmecity.com to take a post-test; tests can be taken after each issue or collectively at the end of the semester. First-time users will have to register on the site using the 8-digit subscriber number printed on their mailing label, invoice or renewal notice.
3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
4. After successfully completing the last test of the semester, your browser will be automatically directed to the activity evaluation form, which you will submit online.
5. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly.

Physician CME Questions

1. With regard to the new DSM-5, which of the following statements is false?
   a. DSM-5 debuted in 2013.
   b. DSM-5 retained the multi-axial system for psychiatric diagnosis.
   c. DSM-5 eliminated the bereavement exclusion for major depression.
   d. DSM-5 separated panic disorder and agoraphobia into two separate disorders.
   e. DSM-5 morphed somatization disorder into a broader new category entitled, "somatic symptom disorder."
2. Regarding the SNRIs, which of the following is false?
   a. All current SNRIs have a relatively simple pharmacology compared to most other antidepressants
   b. Of the SNRIs, duloxetine has the most FDA indications
   c. All SNRIs demonstrate equal effects with regard to serotonin and norepinephrine reuptake inhibition
   d. Venlafaxine has both an immediate-release and extended-release formulation
   e. Levomilnacipran is the more active racemer of milnacipran
3. Which of the following is true?
   a. Both venlafaxine and duloxetine demonstrate sequential inhibition effects
   b. Both milnacipran and levomilnacipran demonstrate sequential inhibition effects
   c. Desvenlafaxine demonstrates sequential inhibition effects
   d. All SNRIs demonstrate sequential inhibition effects
   e. No SNRI demonstrates sequential inhibition effects
4. Vilazodone is characterized by all of the following *except*:
   a. A 5-ring chemical structure
   b. Low rates of sexual dysfunction
   c. Minimal effects on blood pressure
   d. Potential drug interactions, primarily through the 3A4 isoenzyme
   e. Weight gain
5. Vortioxetine is characterized by all of the following *except*:
   a. Probable low rates of sexual dysfunction
   b. Cognitive impairment
   c. Potential drug interactions through the 2D6 isoenzyme
   d. Weight neutrality
   e. Gastrointestinal side effects
6. All of the following are true for pro-inflammatory cytokines *except*:
   a. Pro-inflammatory cytokines are elevated in a number of medical diseases
   b. Pro-inflammatory cytokines are elevated in some types of depression
   c. Pro-inflammatory cytokines increase serotonin levels in the brain
   d. Pro-inflammatory cytokines decrease serotonin levels in the brain
   e. Pro-inflammatory cytokines decrease tryptophan levels in the brain
7. Regarding antipsychotics, which of the following is false?
   a. In contrast to the atypical antipsychotics, the typical antipsychotics are the older antipsychotics
   b. Atypical antipsychotics may increase neurogenesis and neurotrophic factors
   c. The proposed role of typical antipsychotics in neurotoxicity is clearly evident
   d. Antipsychotics were initially developed in the 1950s
   e. All antipsychotics block D_2 receptors

In Future Issues: Hyperlipidemia Management

Primary Care Reports™ (ISSN 1040-2497) is published monthly by AHC Media LLC, One Atlanta Plaza, 950 East Paces Ferry Road NE, Suite 2850, Atlanta, GA 30326. Telephone: (800) 688-2421 or (404) 262-7436.

Executive Editor: Leslie Coplin
Managing Editor: Neill Kimball
Editorial Director: Lee Landenberger

GST Registration No.: R128870672

Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

POSTMASTER: Send address changes to Primary Care Reports, P.O. Box 550669, Atlanta, GA 30355.

Back issues: $26. Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

Multiple copy prices: One to nine additional copies, $314 each; 10 or more additional copies, $279 each.

Subscriber Information

Customer Service: 1-800-688-2421

Customer Service E-Mail:
customerservice@ahcmedia.com

Editorial E-Mail:
leslie.coplin@ahcmedia.com

Online:
http://www.ahcmedia.com

Subscription Prices

1 year *with* free AMA Category 1/Prescribed credits: $379

Add $19.99 for shipping & handling

Online-only, single user price: $329

Discounts are available for group subscriptions, multiple copies, site-licenses or electronic distribution. For pricing information, call Tria Kreutzer at 404-262-5482.

All prices U.S. only.
U.S. possessions and Canada, add $30
plus applicable GST. Other international orders, add $30.

Accreditation

AHC Media is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

AHC Media designates this educational activity for a maximum of 36 *AMA PRA Category 1 Credits™*. Each issue has been designated for a maximum of 2.50 *AMA PRA Category 1 Credits™*. Physicians should claim only credit commensurate with the extent of their participation in the activity.

This enduring material activity, *Primary Care Reports,* has been reviewed and is acceptable for up to 27 Prescribed credit(s) by the American Academy of Family Physicians. AAFP accreditation begins January 1, 2014. Term of approval is for one year from this date with the option of yearly renewal. Each issue is approved for 2.25 Prescribed credits. Credit may be claimed for one year from the date of each issue. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

The American Osteopathic Association has approved this continuing education activity for up to 30 AOA Category 2-B credits.

This is an educational publication designed to present scientific information and opinion to health professionals, to stimulate thought, and further investigation. It does not provide advice regarding medical diagnosis or treatment for any individual case. It is not intended for use by the layman. Opinions expressed are not necessarily those of this publication. Mention of products or services does not constitute endorsement. Clinical, legal, tax, and other comments are offered for general guidance only; professional counsel should be sought for specific situations.

This CME activity is intended for primary care and family practice physicians. It is in effect for 24 months from the date of the publication.

Primary Care Reports

Reader Survey 2014

In an effort to ensure *Primary Care Reports* is addressing the issues most important to you, we ask that you take a few minutes to complete and return this survey.
Instructions: Mark your answers by filling in the appropriate bubbles. Please write in your answers to the open-ended questions in the space provided. Either fax the completed questionnaire to 404-492-5933, or return it in the enclosed postage-paid envelope. The deadline is **July 15, 2014.**

In future issues of *Primary Care Reports*, would you like to see more or less coverage of the following topics?

	A. more coverage	B. less coverage	C. about the same amount
1. Cardiology	○ A	○ B	○ C
2. Infectious disease	○ A	○ B	○ C
3. Neurology	○ A	○ B	○ C
4. Endocrinology	○ A	○ B	○ C
5. Psychiatry	○ A	○ B	○ C
6. Gastroenterology	○ A	○ B	○ C
7. Rheumatology	○ A	○ B	○ C
8. Allergy and immunology	○ A	○ B	○ C
9. Oncology	○ A	○ B	○ C
10. Pulmonology	○ A	○ B	○ C

11. What other topics would you like to see discussed in *PCR*?

_____

_____

12. What type of information not currently provided in *Primary Care Reports* would you like to see added?

_____

_____

18. Are the articles in *PCR* written about issues of importance and concern to you?

A. always ○
B. most of the time ○
C. some of the time ○
D. rarely ○
E. never ○

19. Please describe your work place.

A. private practice ○
B. hospital ○
C. government institution ○
D. research ○
E. other_____

Please rate your level of satisfaction with the items listed.

	A. excellent	B. good	C. fair	D. poor
13. quality	○ A	○ B	○ C	○ D
14. article selections	○ A	○ B	○ C	○ D
15. timeliness	○ A	○ B	○ C	○ D
16. quality of commentary	○ A	○ B	○ C	○ D
17. overall value	○ A	○ B	○ C	○ D

20. To what other publications or information sources about primary care do you subscribe?

21. Including *PCR,* which publication or information source do you find most useful, and why?

22. List the top three challenges you face in your job today?

23. What do you like most about *Primary Care Reports*?

24. What do you like least about *Primary Care Reports*?

25. What are the top three things you would add to *PCR* to make it more valuable for your money?

Contact information