Antipsychotic Medications

An evidence-based review of the mechanisms of action, adverse effects, and contraindications of these commonly used drugs.

ABSTRACT: Antipsychotic medications are primarily used to manage various symptoms of psychosis. In recent years, more adults—and teenagers—are taking at least one type of psychotropic medication, the majority of which are prescribed by primary care and family physicians. Because nurses are now caring for people of varying ages, and with varying diagnoses, who are taking these types of medications, they need to develop a working knowledge of the agents available and know when it's appropriate to prescribe them for mental health disorders as well as for disorders unrelated to mental health. This article is the first in a series on commonly used psychotropic medications.

Keywords: antipsychotic medications, mental health, mental illness, psychosis, psychotropic medications, schizophrenia

Throughout history, people with mental illness have been subjected to public ridicule, warehoused, and worse. Theories about the causes of mental illness have included the belief that a person is possessed by spirits, demons, or the devil[1]; that she or he has a weakness of character[2]; or that the person had a "refrigerator" mother, someone whose coldness led to the child developing insanity.[3] Those with mental health issues were treated with a variety of therapies that are now considered to be questionable and inhumane: being chained and shackled in institutions for the insane and put into insulin-induced comas; having a lobotomy; being subjected to malarial therapy, exorcism, and prayer; being placed into ice water baths or put on near-starvation diets; having organs surgically removed that were believed to be the cause; being bled; and even being temporarily drowned.[4-6]

Over time, these therapies started to change. The 1950s saw the introduction of chlorpromazine, which belongs to a class of drugs now referred to as first-generation antipsychotics or typical, traditional, or conventional antipsychotics,[5,7,8] as well as the introduction of several antidepressants,[9] including monoamine oxidase inhibitors and tricyclic antidepressants.[10] Since those early days, more agents have been added to the list, including newer antidepressants—selective serotonin reuptake inhibitors—and second-generation antipsychotic medications, both of which are used to manage a wider range of symptoms than their earlier counterparts. Today's arsenal of tools for the treatment of mental illness also includes anxiolytics, which are used to manage anxiety disorders, and medications typically used to manage other health problems, such as anticonvulsants, which have been found to be beneficial in the management of several mental health disorders.

It's been estimated that approximately 20% of adults are taking at least one type of psychotropic medication, an increase of 22% from 2001 to 2010,

Diagnosed with acute schizophrenia as a young man, British painter Bryan Charnley began his final work, the *Self Portrait Series*, while experimenting with decreasing doses of his antipsychotic medications. At left is what he called a "conventional portrait"; at right is "an extremely complicated picture as I feel I am closing in on the essential image of my schizophrenia." The 17 self-portraits depict his mental state over the six months before his death by suicide in July 1991 (he was only 42). Images courtesy of the estate of Bryan Charnley.

according to a report from Medco Health Solutions.[11] Another study revealed that these adults are not alone—between 2005 and 2010, more than 6% of adolescents reported using psychotropic medications within the past month.[12] It is therefore not surprising that nurses are finding themselves caring for people of varying ages who have varying diagnoses and are taking at least one type of psychotropic medication. Wegmann, who is a pharmacist and social worker, points out that the majority of these medications are prescribed by primary care and family physicians, which means that patients are usually not under the care of a mental health provider, in a program of monitored drug use, or involved in psychotherapy.[8] For these reasons, it's important that all health care providers become familiar with psychotropic medications.

This article is the first in a series that will take a closer look at commonly used psychotropic medications. The goal is to help nurses understand how these drugs act, which disorders they are typically used to manage, and which adverse effects to be concerned about.

UNDERSTANDING MENTAL ILLNESS: SCHIZOPHRENIA

Although there are many forms of mental illness, perhaps the one that has concerned and frightened the public the most is schizophrenia, one of several types of mental illnesses classified as psychotic disorders. As such, it is characterized by any number of psychotic symptoms, including hallucinations, delusions, disorganized thinking, and bizarre speech, all of which result in the person's inability to connect with reality, which at times results in strange and frightening behavior. It is therefore not surprising that among the earliest medications brought to market were antipsychotics, which are primarily used to manage psychotic symptoms in people with schizophrenia.

Although these patients were historically shunned and feared by the public, we now know that the neurotransmitter dopamine, among others, plays a role in this disorder, and that there are four pathways in the brain through which dopamine travels: the mesolimbic, mesocortical, nigrostriatal, and tuberoinfundibular.[13] The more dopamine in the mesolimbic pathway, either because of medication or disease, the more "positive symptoms"—such as hallucinations, delusions, difficulty understanding, disorganized thinking, and poor concentration[13,14]—the patient will exhibit. These are referred to as positive symptoms because they do not occur in an otherwise mentally healthy person.[15] Negative symptoms, which indicate that someone is not acting or behaving as she or he usually would, are believed to be caused by a decreased dopamine level in the mesocortical pathway, whether due to medications or disease.

These symptoms include anhedonia, alogia, avolition, apathy, and flat affect.[13, 14, 16]

If dopamine receptors in the nigrostriatal pathway, which is involved in posture and muscle movement, are blocked, patients can experience symptoms similar to those seen in people who have Parkinson's disease. When the tuberoinfundibular pathway is affected by anything that prevents dopamine from inhibiting prolactin's release by the pituitary gland, female patients may experience galactorrhea, amenorrhea, and sexual dysfunction.[13, 14, 16, 17]

First-Generation, Typical Antipsychotic Medications and Their Adverse Effects[8, 20-24]

Medications

- chlorpromazine (Thorazine)[a]
- haloperidol (Haldol, Haldol Decanoate[b])
- fluphenazine (Prolixin,[a] Prolixin Decanoate[a, b])
- thioridazine (Mellaril)[a]
- thiothixene (Navane)[a]
- trifluoperazine (Stelazine)[a]

Adverse Effects

- Dry mouth
- Blurred vision
- Sedation
- Orthostatic hypotension
- Weight gain
- Photosensitivity
- Seizures
- Constipation
- Hyperprolactinemia
- Sexual dysfunction
- Cardiac arrhythmias
- Dermatologic rash
- Neuroleptic malignant syndrome, which results from medications that block dopamine receptors. It's characterized by a fever of 103° or higher, blood pressure lability, tachycardia and tachypnea, agitation, and diaphoresis. This is a medical emergency, and the drug should be immediately stopped.
- Tardive dyskinesia, which is characterized by involuntary facial movements involving the mouth, tongue, and lips. This neurologic syndrome, which can be permanent, can be managed with various medications, including diphenhydramine (Benadryl), trihexyphenidyl (Artane),[a] benztropine (Cogentin), lorazepam (Ativan), or propranolol (Inderal and others).
- Extrapyramidal symptoms, which are caused by a blockade of dopamine receptors, include dystonia (involuntary, purposeless muscle contractions), akathisia (restlessness), and pseudoparkinsonism (tremors, shuffling gait, cog-wheel rigidity, and mask-like facial expression).

[a] While this drug is still available as a generic formulation, the branded product has been discontinued by the manufacturer.
[b] This is a long-acting injectable formulation.

ANTIPSYCHOTIC MEDICATIONS

Beginning in the mid-20th century, several medications became available for the treatment of mental illness.

First-generation, typical antipsychotic medications were discovered in France. Several researchers were involved in the development and promotion of chlorpromazine. Chief among them was Henri Laborit, a French army surgeon, who used it as a preanesthetic to help prevent shock in patients prior to surgery. Because it lowered their blood pressure too much, it was deemed unacceptable for that purpose, but Laborit noticed that the medication had a calming effect, something he believed would be useful for psychiatric patients, especially those who had schizophrenia.[13, 18] His efforts were met with skepticism; however, he continued advocating among his peers and other medical professionals, and chlorpromazine eventually was accepted for use in Europe.

The medication made its way to North America via Canada, arriving in the United States in 1954. It was first approved for use only as an antiemetic.[18] Interestingly, part of the initial reluctance to using it as a psychiatric medication in the United States was attributed to the then strongly held belief among practitioners that the psychoanalytic approach was the best way to treat patients with mental illness.[18] Eventually, through concerted efforts by the pharmaceutical company Smith, Kline and French, the medication became accepted as a valid form of treatment for several conditions.[18] Although not a cure for schizophrenia, it was noted that the drug did improve several symptoms and provided some measure of relief for patients. This observation opened the door to the realization that people with mental illness could be helped by taking medication and thus began the era of the biological approach to managing mental illness.[13, 19]

Although chlorpromazine was the first antipsychotic medication, others soon followed (see *First-Generation, Typical Antipsychotic Medications and Their Adverse Effects*[8, 20-24]). These medications were primarily used for the treatment of schizophrenia.

It's now suspected that several neurotransmitters are likely a factor in schizophrenia, including serotonin and glutamate, but early on, schizophrenia was believed to be caused by an excess of the neurotransmitter dopamine in the cortical areas of the brain.[8, 13-17] The effectiveness and therapeutic value of the first-generation, typical antipsychotic class of medications was therefore attributed to its ability to decrease the excess dopamine by its blockade of D_2 receptors.[17] However, while they decrease the excessive levels of dopamine in one part of the brain—thus lessening the impact of the positive symptoms of schizophrenia—these medications do not help to improve all symptoms of the disorder. They tend to exacerbate negative symptoms by blocking dopamine in the mesocortical

pathway, thus further decreasing what is already a low supply there.

Adverse effects. As is the case with any class of medications, first-generation antipsychotics have several adverse effects. Aside from their impact on dopamine levels in the mesolimbic and mesocortical pathways, these medications cause problems in the two other pathways. By blocking dopamine receptors in the nigrostriatal pathway, they cause extrapyramidal symptoms, including tardive dyskinesia, as well as muscle and movement problems such as akinesia, akathisia, pseudoparkinsonism, and dystonia.[21, 22] Tardive dyskinesia, which can be permanent and requires the use of medications to manage, involves dysfunction of the voluntary muscles of the mouth, tongue, and lips and can result in tongue protrusion, lip smacking, and bizarre mouth movements.[21] For women, as noted above, a disruption in dopamine balance in the tuberoinfundibular pathway can lead to galactorrhea, amenorrhea, and sexual dysfunction.[13, 14, 16, 17]

Second-generation, atypical antipsychotics. In the 1990s, another class of antipsychotic medications, referred to as atypical, or second-generation, antipsychotics, became available.[8, 25] Unlike their predecessors, which do not selectively target different dopamine tracts, these medications are more selective in their targets; in addition, they are used to manage both the positive and negative symptoms of schizophrenia, thereby providing broader and more comprehensive relief to patients.[13, 14, 25, 26] One of the hallmarks of schizophrenia is its negative impact on a person's cognitive abilities: the ability to think, understand, and perceive the world around her or him. Executive functioning, such as being able to reason, plan, and problem solve, can also be diminished by the disorder. Second-generation antipsychotics, unlike first-generation antipsychotics, can be used to address the cognitive symptoms of schizophrenia and improve associated executive function difficulties.[22] They are also less likely to cause extrapyramidal symptoms and tardive dyskinesia.[14]

Like its predecessor, this class of drugs blocks dopamine in the mesolimbic pathway and thereby reduces positive symptoms. Because these medications function as serotonin–dopamine antagonists that have the ability to block serotonin, which inhibits dopamine, they allow for a dopamine increase in the mesocortical pathway, thus causing a decrease in negative symptoms as well.[16, 17, 25, 26]

Adverse effects. The first medication of this generation, clozapine was introduced in the United States in 1990 and was widely hailed as a great treatment success compared with its predecessors.[8, 27] However, this medication has a serious adverse effect: agranulocytosis. For this reason, and although clozapine can be effective in managing schizophrenia, it is now used as a last resort and under strict guidelines, including frequent laboratory testing mandated by the U.S. Food and Drug Administration (FDA) and monitoring by the provider and patient for any signs and symptoms—such as sore throat, chills, sudden fever, and mouth ulcers—that could indicate the beginning of agranulocytosis.[7, 8, 13]

Several other second-generation antipsychotics were subsequently developed (see *Second-Generation, Atypical Antipsychotic Medications and Their Adverse Effects*[8, 20-24]). Because they are known to have fewer adverse effects than first-generation antipsychotics and can manage both the positive and negative symptoms of schizophrenia, these medications are used as first-line treatment in people who experience psychosis.[7, 13, 25, 26] Yet, first-generation antipsychotics—including haloperidol, which is indicated for and

Second-Generation, Atypical Antipsychotic Medications and Their Adverse Effects[8, 20-24]

Medications

- clozapine (Clozaril and others)
- aripiprazole (Abilify, Abilify Maintena[a])
- ziprasidone (Geodon)
- olanzapine (Zyprexa, Zyprexa Relprevv[a])
- quetiapine (Seroquel)
- risperidone (Risperdal, Risperdal Consta[a])
- lurasidone (Latuda)
- paliperidone (Invega, Invega Sustenna,[a] Invega Trinza[a])
- asenapine (Saphris)
- iloperidone (Fanapt)

Adverse Effects

- Compared with first-generation antipsychotics, the second-generation agents have many of the same adverse effects, albeit to varying degrees. These include sedation, postural hypotension, weight gain, and QT-interval prolongation. There are, however, fewer adverse effects related to neuroleptic malignant syndrome, extrapyramidal symptoms, or tardive dyskinesia, and prolactin levels tend to rise less.
- Using these medications in older patients with dementia-related psychosis or who have behavioral problems increases the risk of death.
- Agranulocytosis is a serious, possibly life-threatening adverse effect of clozapine.
- People taking second-generation antipsychotics are at increased risk for developing type 2 diabetes and metabolic syndrome, which is characterized by obesity, hypertension, dyslipidemia, and hyperglycemia.

Recommendations

- Patients taking these medications should have their glucose, lipid, and cholesterol levels monitored.
- Smoking can increase the need for higher doses.

[a] This is a long-acting injectable formulation.

often used to manage psychiatric emergencies[22]—are still prescribed for some patients.

It's important to keep in mind that patients can have serious adverse reactions to any medication. Even if the second-generation medications generally have fewer adverse effects than their predecessors, some atypical medications can still pose serious health risks. Health care providers must not only be aware of the adverse profiles of each generation of antipsychotics, but also be familiar with the adverse effects and contraindications of each medication.[20]

OTHER INDICATIONS

Although not necessarily first-line treatment for conditions other than psychotic disorders, antipsychotic medications may be used to help manage several other mental health conditions. These include delirium, depression, the manic phase of bipolar disorder, eating disorders, attention deficit–hyperactivity disorder, posttraumatic stress disorder, generalized anxiety disorder, obsessive–compulsive disorder, oppositional defiant disorder, and conduct disorder. They may also be used in psychiatric emergencies to help contain a patient who is out of control.

The second-generation antipsychotic quetiapine, for example, is also FDA approved for the treatment of bipolar disorder depressive and manic episodes as well as for maintenance. Aripiprazole is approved for use in bipolar maintenance and acute mania; it's also used as an adjunct medication in managing depression. Antipsychotics can also be used for the treatment of early-stage Huntington's disease, impulse control disorders, nausea, pruritus, intractable vomiting, hiccups, vertigo, and irritability in autism.[7, 28-30]

NURSING IMPLICATIONS

Although antipsychotic medications can effectively control symptoms, they can also have sedative effects.[31] Patients have explained to me that this can leave them feeling "zombie-like." They've said they feel like their senses are dulled and that they have slowed down. They complain of losing their "essence" and "spirit" while taking antipsychotics. As one patient told me: "I feel like I'm living my life underwater."

Medications cannot be used to manage patients' feelings of isolation and alienation,[8] and this is an important issue for nurses to address. Many people with mental illness have emotional and spiritual needs that are unmet. Although medication can be used to alleviate and control symptoms, psychotherapy is often recommended as a way of addressing these other needs.

A major drawback of antipsychotic medications is that they need to be taken daily and for long periods of time. This can be challenging for people experiencing psychosis or schizophrenia, who often lose track of their medication schedule. Both first- and second-generation antipsychotics offer long-acting injectable, or depot, versions that are especially useful for patients who have difficulty adhering to a daily dose regimen or have a poor adherence history.[15, 32] Typically, these are given every two to four weeks, depending on the medication. The first-generation antipsychotics haloperidol and fluphenazine have long-acting injectable formulations, as do the second-generation antipsychotics paliperidone, risperidone, olanzapine, and aripiprazole.[15, 22] It is important to first assess the patient's response to the medication with a trial of a short-acting form before offering a long-acting injectable.

Nurses need to be aware of the potential for some antipsychotic medications, especially the second-generation antipsychotics, to be abused, both on the street and by those seeking to self-medicate.

Precautions and contraindications. Both generations of antipsychotic medications are not to be used or taken lightly. In fact, some argue that all psychotropic medications, including antipsychotics, are overprescribed.[6, 8] An antipsychotic medication is not a magic bullet and should not be seen as a cure. Rather, it is more realistic to expect symptom relief and an improved quality of life.[30] Contraindications of both generations of antipsychotics include having a known sensitivity or allergy to these medications, Parkinson's disease, central nervous system depression, confusion, and liver or blood disease or blood dyscrasias; in addition, these medications are not recommended for use in children or adolescents, the elderly (there are black box warnings about the increased risk of death with their use in elderly patients who have dementia), and pregnant or nursing women.[8, 21-23, 29, 33, 34] Caution needs to be taken when patients have preexisting medical issues, such as glaucoma, severe liver or

cardiac disease, a history of drug or alcohol abuse, diabetes, and renal impairment.[23, 29]

When treating patients who take other medications, nurses need to be aware of potential drug–drug interactions. Possible life-threatening reactions include neuroleptic malignant syndrome, which can include a fever of 103° or greater; tachycardia; tachypnea; agitation; diaphoresis; and changes in blood pressure. For patients experiencing any signs or symptoms of neuroleptic malignant syndrome, extrapyramidal symptoms, or tardive dyskinesia, or for those having any untoward effects, nurses should consult with the patient's health care provider and, in some cases, withhold the medication and seek emergency care. The Abnormal Involuntary Movement Scale (AIMS) should be used to assess for tardive dyskinesia.[35] Because these medications increase the risk of diabetes and metabolic syndrome, nurses should routinely monitor the patient's blood pressure, lipid, and glucose levels; weight and waist circumference; body mass index; and glycated hemoglobin level.[21]

Off-label prescribing. All medications can be used as FDA guidelines indicate, but there is also the practice of prescribing drugs off label—for the treatment of diseases or disorders for which clinicians and practitioners believe there is good cause to do so. Manufacturers, however, are not allowed to advocate for the medication's off-label use.[28]

Antipsychotics are no exception to off-label practices, although at times they can be prescribed unnecessarily.[28] Despite a lack of research assessing the safety and efficacy of using antipsychotic medications to treat people with anxiety disorders, for instance, Comer and colleagues found that the percentage of psychiatrist office visits that led to the off-label prescribing of antipsychotics for people with anxiety doubled during a 12-year period—from 10.6% between 1996 and 1999 to 21.3% between 2004 and 2007.[36]

Of particular concern, and especially important for nurses who work with children to be aware of, is the use of these medications to chemically restrain children who have behavioral issues or are in foster care.[37-39] In my home state of Pennsylvania, a report examining the use of antipsychotic medications among children receiving Medicaid revealed the following[38]:

> For youth ages 6-18 years old in 2012, . . . the use of psychotropic medications was nearly three times higher among youth in foster care than youth in Medicaid overall (43% versus 16%). The use of antipsychotics, a class of psychotropic medications, was four times higher among youth in foster care (22%) than youth in Medicaid overall (5%). More than half of youth antipsychotic users in Medicaid had a diagnosis of attention deficit hyperactivity disorder (ADHD). This is concerning, as the majority of these youth did not have another diagnosis that clinically indicated the use of antipsychotics. . . . Polypharmacy . . . occurred at a rate four times higher for youth in foster care than all youth in Medicaid (12% versus 3%). While 90% of youth prescribed multiple psychotropic medications had at least one visit with a health or behavioral health provider for their behavioral health concerns within the year the medication was prescribed, notably, one in ten youth did not. Youth in foster care were more likely to have not received any visits with a provider for their behavioral health concerns within the year they were using psychotropic medications.

Resources on Psychotropic Medications

Web Sites

NAMI: National Alliance on Mental Illness
Mental Health Medications
www.nami.org/Learn-More/Treatment/Mental-Health-Medications

National Institute of Mental Health
Mental Health Medications
www.nimh.nih.gov/health/topics/mental-health-medications/index.shtml

Publications

Lichtblau L. *Psychopharmacology demystified.* Clifton Park, NY: Delmar Cengage Learning; 2011.

Muench J, Hamer AM. Adverse effects of antipsychotic medications. *Am Fam Physician* 2010;81(5):617-22.

Natal SM, et al. Psychotic disorders. In Leahy LG, Kohler CG, editors. *Manual of clinical psychopharmacology for nurses.* Washington, DC: American Psychiatric Publishing; 2013. p. 129-54.

Rappa L, Viola J. *Condensed psychopharmacology 2013: a pocket reference for psychiatry and psychotropic medications.* Fort Lauderdale, FL: RXPSYCH, LLC; 2012.

Rhoads J, Murphy PJM. *Nurses' clinical consult to psychopharmacology*. New York, NY: Springer Publishing Company; 2012.

Sobel SV. *Successful psychopharmacology: evidence-based treatment solutions for achieving remission.* New York, NY: W.W. Norton and Company; 2012.

Stahl SM. *Stahl's essential psychopharmacology: prescriber's guide.* 5th ed. Cambridge, UK: Cambridge University Press; 2014.

Wegmann J. *Psychopharmacology: straight talk on mental health medications.* 3rd ed. Eau Claire, WI: PESI Publishing and Media; 2015.

Another concern is the abuse of some antipsychotics, especially quetiapine, which is sought for its sedating and anxiolytic effects.[40] This medication has been inappropriately prescribed as a sleeping aid in correctional settings,[41] where sleep medications are typically not given.[40-44] In fact, quetiapine is one of the most abused psychotropic medications in the correctional setting, such that it has been removed from the formulary of jails and prisons in several states, including in New Jersey,[41] as well as in the correctional facility in which I worked in Chester County, Pennsylvania.

Nurses need to be aware of the potential for some antipsychotic medications, especially the second-generation antipsychotics, to be abused, both on the street and by those seeking to self-medicate. For example, aside from overuse by prescribers in the correctional setting, quetiapine is frequently abused by those who have no diagnosable mental health issue. All nurses, but especially NPs who prescribe, should closely screen patients who may misrepresent their symptoms to obtain this medication.

NURSING ASSESSMENT

Polypharmacy is not unusual in the treatment of mental health patients, and nurses need to be careful about mixing medications that are linked to significant drug interactions and can be toxic. It is not considered good practice to prescribe several antipsychotics to a patient without being able to justify the reason for doing so. Although there are benefits to polypharmacy in psychiatry, this practice is complicated and requires knowledge of potential adverse effects and drug–drug interactions.[45]

These medications are not cure-alls and, as noted above, can be abused. They need to be taken regularly, but are not to be given as needed and should be stopped when they are clearly not helping the patient or when the adverse effects become intolerable. Generally, it's best to start low and go slow, giving the body and mind time to adjust to the medication. The exception to this rule is when antipsychotics are used to quickly manage violent or out-of-control behavior, which often requires a higher-than-usual dose.

What nurses should do when caring for a person taking antipsychotics is what we do for those taking any class of medications: assess the patient's response and look for adverse reactions. With antipsychotics, it's especially important to monitor for neuroleptic malignant syndrome, extrapyramidal symptoms, and tardive dyskinesia, and to realize that the seizure threshold is lowered in people taking these medications. For patients experiencing extrapyramidal symptoms, several medications, including anticholinergics, are available to help manage them. Glucose levels, lipid levels, and body weight should also be monitored in people taking antipsychotics, especially in those taking second-generation medications. For those who experience some common or mild adverse effects, such as dry mouth, constipation, or sensitivity to the sun, helpful suggestions include chewing sugarless gum, using stool softeners, and using sunscreen and sunglasses when outside.[32]

CONCLUSION

There is controversy about the use and benefits of psychotropic medications—whether they cause more harm than good, are overprescribed, or are prescribed for the wrong reasons.[4,6,46] Yet, when prescribed safely and responsibly, these medications can bring needed relief. For this reason, all nurses should develop a working knowledge of the medications available to help patients who have mental illness, and should know when it's appropriate for these medications to be prescribed for disorders unrelated to mental health.

Nurses should also be mindful that medications are not the only tool we have. Working with a therapist or receiving support from a peer mentor or support group can help patients experience symptom relief and improve their sense of well-being. Information about organizations such as the National Alliance on Mental Illness and local mental health agencies should be provided to patients and their families. Nurses can also benefit from the information these resources provide and from the additional information a variety of publications offer (see *Resources on Psychotropic Medications*). ▼

For 18 additional continuing nursing education activities on medication topics, go to www.nursingcenter.com/ce.

Donna Sabella is a psychiatric mental health NP and the Seedworks Endowed Associate Professor for Nursing and Social Justice, College of Nursing, University of Massachusetts Amherst. She also coordinates Mental Health Matters*: dsabella@umass.edu.* *The author and planners have disclosed no potential conflicts of interest, financial or otherwise.*

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