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Atypical Antipsychotics from a Primary Care Perspective

Antipsychotics are an incredibly influential class of drugs in our society. They were the highest-grossing group of medications in 2009, with revenue reaching $14.6 billion.[1] Given their extensive use and expense, antipsychotics have given rise to several significant litigation streams. First, allegations of inappropriate off-label marketing prompted AstraZeneca to pay $520 million in fines for quetiapine, a $4.9 billion per year grossing atypical antipsychotic.[2] Pfizer and Bristol-Myers-Squibb have also paid large fines for allegations of inappropriate marketing of ziprasidone and aripiprazole. Eli Lilly paid more than $1 billion to settle claims from state Medicaid programs arising from the alleged adverse metabolic effects and off-label marketing of olanzapine.

Antipsychotic-related lawsuits highlight ethical dilemmas that arise when physicians try to determine appropriate use of these agents. Although still referred to by the term antipsychotics, the medications are more broadly called neuroleptics in deference to their multiple uses beyond primary psychosis. One could argue that the (mis)use of neuroleptics is largely determined by the primary care community, as they are the de facto providers of psychiatric services in many communities. A 2009 study reported up to 46% of patients present to general practitioners with psychological disorders.[3] The fact that primary care providers provide psychiatric care is not surprising given the sheer number of patients with diagnosable mental health conditions. In the United States, the National Institutes of Health estimated 57.7 million adults suffered from mental illness in 2009.[4] Given the variety of approved indications (schizophrenia, bipolar, depression, and autism), as well as the extensive off-label use (anxiety, insomnia, tics), many of these patients could have an atypical antipsychotic prescribed for reasons other than psychosis. In fact, one study concluded 66.5% of patients prescribed antipsychotics were given the medication for symptoms other than psychosis.[5]

Given the burden of mental illness and the extensive use of atypical antipsychotics in primary care, a review of some of the key factors about atypical antipsychotics from the perspective of a family physician is warranted. This article attempts to clarify the landscape of atypical antipsychotics by reviewing each approved drug for key points relating to its clinical use. Despite some key differences among the agents, they all have significant risk for adverse events such as extrapyramidal side effects (EPS) and metabolic complications. Therefore, specific recommendations regarding monitoring are provided. Additionally, special considerations are outlined for the primary care provider to balance in the risk/benefit equation when utilizing these medications across the life cycle. Finally, the safety of atypical antipsychotics as compared with other psychiatric medications in the setting of an overdose is discussed.

—The Editor

Introduction

In many ways the term "antipsychotic," which is commonly used in clinical settings, is an inappropriate label. This class of drugs is more appropriately

Executive Summary

- Atypical antipsychotics are actually neuroleptic agents with clinical uses beyond the treatment of psychosis.
- Their mechanisms of action involve the antagonism of dopamine Type 2 and serotonin Type 2 receptors.
- Adverse effects include extrapyramidal symptoms, neuroleptic malignant syndrome, elevated prolactin, weight gain, hyperglycemia, and metabolic syndrome.
- The FDA "black box" warning is related to increased mortality in elderly dementia patients, highlighting the benefit of shared decision-making, documentation of need and risk, and close monitoring for efficacy and adverse events.

referred to as "neuroleptics." The difference between these terms is mostly semantic, but using the antipsychotic label implies psychosis is the sole symptom that is treated. This fails to take into account the current uses of these drugs, which are much more diverse. As introduced above, neuroleptics are used for symptoms such as anxiety or insomnia, and as described later in this paper, are used in the treatment of behaviors associated with autism.

The antipsychotic medications are separated into typical (also referred to as first-generation or conventional) and atypical (or second-generation) groups. Clozapine is widely regarded as the first atypical antipsychotic. Currently, 8 newer atypical antipsychotics are available on the U.S. market. Atypical antipsychotics differ from typicals in that they are generally less likely to induce parkinsonian side effects and are also used to treat schizophrenics with negative symptoms or those who resist the more classic treatments. Due to a lower potential for neurological adverse events with the newer atypical antipsychotics and the variety of emerging indications for their use, these newer agents are prescribed much more frequently than their older counterparts.

Pharmacology

Similar to typical antipsychotics, atypical antipsychotics manage positive symptoms but generally have a more beneficial effect on negative symptoms than the older agents. Although originally thought to be solely due to their effects on dopamine transmission in the brain, their true mechanism of action involves the antagonism of dopamine Type 2 (D2) and serotonin Type 2 (5-HT2) receptors. The potential to be therapeutically effective and cause EPS depends on actions on both the D2 and 5-HT2 receptors.[6] Two key differences in D2 and 5-HT2 activity exist among the class. Aripiprazole is the only atypical antipsychotic medication that acts as a D2 and 5-HT2 receptor partial agonist. Quetiapine and clozapine rapidly disassociate from and have low binding affinity for the D2 receptor. This results in a lower incidence of EPS for both clozapine and quetiapine.

Almost all of the atypical antipsychotics affect multiple receptors in the brain. For example, the medications also have binding affinity for several additional serotonin, dopamine Type 1 (D1), glutamatergic, muscarinic, alpha-1 and alpha-2 adrenergic and histamine H1 receptors.[6] It is often the specific interaction on these other receptors that leads to the subtle differences in side effect profiles. Moreover, by broadening the focus to receptors other than dopamine, ongoing drug development has created new models of psychosis. This is important because despite the early focus on dopamine modifiers, medications that antagonize only the D1 receptor have not been shown to be clinically effective for psychosis.[7] Alpha-1 receptor antagonism can lead to orthostatic hypotension, and histamine H1 receptor antagonism can result in sedation and weight gain.[8] These medications are highly protein bound, metabolized by the liver, and have variable oral bioavailability.

Dosage and Indications

With the exception of clozapine, there is little evidence to support the superior efficacy of one atypical antipsychotic over another. Prescribers should familiarize themselves with the definitive National Institute of Mental Health (NIMH)-sponsored study in the area of prescribing atypical antipsychotics titled the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE).[9] This was a large, randomized trial comparing different antipsychotics for maintenance treatment of schizophrenia. Data from the initial phase of the CATIE trial showed patients were significantly less likely to discontinue treatment with olanzapine than perphenazine, quetiapine, risperidone, or ziprasidone.[10] However, other measures of efficacy and severity of side effects were comparable among all agents. Based on the CATIE trial, which demonstrated comparable efficacy among the atypical antipsychotics, it is reasonable to base treatment choice on individual patient response, side effect profile, and cost. The American Psychiatric Association (APA) guidelines for the treatment of schizophrenia recommend that selection of an antipsychotic medication should be guided by the patient's past response to treatment, the medication's side effect profile, and the presence of co-morbidities.[11] Tables 1 and 2 list FDA-approved indications and dosing information for the available atypical antipsychotic medications.

Four of the eight oral atypical antipsychotics have FDA-approved indications for use in pediatric patients. Approved indications include schizophrenia, bipolar disorder, and irritability associated with autism. For patients between the ages of 13 and 17, quetiapine, risperidone, and

olanzapine are approved for acute schizophrenia. Aripiprazole, quetiapine, and risperidone are also indicated for maintenance therapy for schizophrenia in the same age range. Aripiprazole, quetiapine, and risperidone are indicated for acute bipolar disorder in patients between the ages of 10 and 17. Olanzapine is also indicated for this purpose in patients between the ages of 13 and 17. For maintenance therapy of bipolar disorder, olanzapine and quetiapine are indicated for patients aged 13-17 years and 10-17 years, respectively. The most recent indication for the treatment of irritability associated with autism has been approved for aripiprazole and risperidone for patients as young as 6 and 5 years of age, respectively.

Individual Highlights

Aripiprazole. Aripiprazole is approved for the treatment of schizophrenia in adults and adolescents, acute bipolar and maintenance of bipolar disorder, and acute agitation associated with schizophrenia or bipolar disorder. (*See Tables 1 and 2.*) In 2007, it was the first atypical to be FDA approved for the adjunctive treatment of major depressive disorder in adult patients who do not respond to antidepressants alone. Generally, at least two trials of antidepressant monotherapy should be initiated at therapeutic doses for sufficient duration before considering augmentation with an atypical antipsychotic. Most recently, it was approved for treatment of irritability associated with autism in adolescents and children 6-17 years old. As mentioned previously, this particular drug is unique among the class for its mixed antagonist/agonist profile, which is thought to contribute to some side effect mitigation. Another less common feature is the existence of an injectable form for episodes of acute agitation. Finally, prescribers need to be aware of the longer half-life associated with this particular medication, implying a longer time to steady state concentrations but also some protection against short-term fluctuations secondary to missed doses. It is thought to represent one of the more metabolically neutral antipsychotics based on data collected to date and thus may be considered when treating a patient with glucose, lipid, or weight abnormalities.[12]

Asenapine. Asenapine is the newest atypical antipsychotic agent, and it is approved for the acute treatment of both schizophrenia and bipolar disorder in adults. (*See Table 1.*) The efficacy of asenapine beyond the acute treatment period (3-6 weeks) has not been studied. It is unique for its sublingual form, which may be useful in for patients with paranoia who tend to "cheek" medications. However, several other atypical agents have oral rapidly dissolving forms that also can be used for this purpose.

Iloperidone. Similarly to asenapine, the safety and efficacy of iloperidone beyond acute treatment (6 weeks) has not yet been assessed in controlled trials. Iloperidone requires very slow dose titration (beginning at 1 mg twice daily) to reduce the risk of orthostatic hypotension. Thus, control of symptoms may be delayed during the first 1-2 weeks of treatment compared to some other antipsychotic drugs that do not require a similar titration.

Olanzapine. The immediate-release injection is used for the treatment of acute agitation, while the sustained-release injection is used for the maintenance treatment of schizophrenia when tolerability to the oral dosage form has already been established. Extended-release olanzapine for intramuscular injection must be administered at a registered health care facility with access to emergency response services.[13] In addition, patients must be observed for at least 3 hours following administration. These precautions are due to the risk of post-injection delirium/sedation syndrome, which is unique to this particular agent's injectible dosage form. Symptoms of post-injection delirium/sedation syndrome include confusion, agitation, anxiety, sedation, coma, and/or delirium. During initial drug trials, this syndrome occurred in less than 0.1% of injections and in about 2% of patients who received the injection for up to 46 months.[6] The risk of post-injection delirium/sedation syndrome increases as the patient receives more injections. Due to the significant risks associated with its use, sustained-release olanzapine for intramuscular injection is available only through a restricted distribution program that requires registration of the prescriber, patient, health care facility, and pharmacy.

Paliperidone. Risperidone is metabolized to an active agent called paliperidone. Liver metabolism can be bypassed by directly administering the active metabolite. This may be a key factor in patients with significant hepatic impairment. Phase III studies to assess the efficacy and safety of paliperidone in the acute treatment of bipolar disorder were recently completed. Only high doses of paliperidone (12 mg/day) showed a statistically significant improvement in symptom severity compared to placebo.[14] Studies of the use of paliperidone for obsessive compulsive disorder (OCD) and post-traumatic stress disorder (PTSD) are currently in the recruiting phase.

Paliperidone is currently available as an extended-release tablet and as an extended-release suspension designed for once monthly intramuscular injection. Both the initial and usual maintenance doses of oral paliperidone are 6 mg once daily. (*See Table 2.*) The dose may be titrated up by 3 mg/day every 5 days up to a maximum dose of 12 mg/day.[15]

Quetiapine. The manufacturer sought FDA approval for quetiapine as monotherapy for major depressive disorder and as a treatment for generalized anxiety disorder. However, an FDA advisory panel voted in April 2009 that safety had not been adequately established for these indications. In May 2007, an extended-release version of quetiapine was released and has additional FDA approval for the maintenance treatment of schizophrenia and as an adjunct to antidepressant therapy for the treatment of major depressive disorder (MDD).

The off-label use of quetiapine

Table 1: FDA Approved Indications in Adults for Select Atypical Antipsychotics

Drug and dosage form	Schizophrenia (acute)	Schizophrenia (maintenance)	Bipolar disorder (acute)	Bipolar disorder (maintenance)	Bipolar depression	Acute agitation	Adjunctive treatment of MDD	Schizoaffective disorder	Treatment of irritability associated with autism
Aripiprazole (Abilify)									
Oral	X	X	X*	X			X		X
IM injection						X			
Asenapine (Saphris)									
Oral	X		X						
Iloperidone (Fanapt)									
Oral	X								
Olanzapine (Zyprexa)									
Oral	X		X*	X*			X (in combination with fluoxetine)		
IR injection						X			
ER injection		X							
Paliperidone (Invega)									
Oral		X						X**	
Quetiapine (Seroquel)									
Oral (IR)	X		X*	X¶	X				
Oral (XR)	X	X		X¶	X		X		
Risperidone (Risperdal)									
Oral	X	X	X*						X
IM injection	X§	X		X*					
Ziprasidone (Geodon)									
Oral	X	X	X	X¶					
IM injection						X			

* As monotherapy or in combination with lithium or valproate

** As monotherapy or as an adjunct to mood stabilizers and/or antidepressants

¶ As an adjunct to lithium or divalproex

§ Oral risperidone should be started or continued for 3 weeks after the first depot injection, then discontinued.

Data from medication package inserts.

is extensive. A retrospective study of quetiapine use conducted in a psychiatric hospital found that only 28.5% of patients had one of the diagnoses for which the drug is approved, and the majority of patients were receiving as-needed quetiapine for agitation, anxiety, or insomnia.[16] Off-label use of quetiapine for the treatment of insomnia in patients with and without comorbid psychiatric conditions is common. Some practitioners believe that using low-dose quetiapine will retain the sedating properties of the drug while minimizing the risk for negative metabolic effects associated with therapeutic dosages. An open-label pilot study on the use of quetiapine for primary insomnia showed low-dose quetiapine (mean dose 37.5 mg/day) for 6 weeks improved total sleep time (TST), sleep efficiency, and subjective sleep.[17] The average TST was 358 minutes at baseline, 406.3 minutes at 2 weeks, and 395.6 minutes at 6 weeks. Even though the difference in TST at baseline and after 6 weeks of quetiapine use was considered statistically significant (p=0.03), one could argue the clinical significance of increasing TST by 38 minutes with quetiapine use.

Despite the low doses typically used for insomnia, metabolic effects can still occur. A retrospective chart

Table 2: Dosing of Select Atypical Antipsychotics

Drug	Dosage Forms	Daily Dosage*	Comments
Aripiprazole (Abilify)	Oral tablet Oral disintegrating tablet Oral solution Solution for IM injection	Initial dose: 2-15 mg/day Usual dose: 5-15 mg/day Maximum dose: 15-30 mg/day	Initial doses for adjunctive treatment of MDD are 2-5 mg/day; separate injections by at least 2 hours
Asenapine (Saphris)	Sublingual tablet	Initial, usual, and maximum dose: 10 mg/day (schizophrenia, acute) 20 mg/day (bipolar disorder, acute)	Do not eat or drink within 10 minutes of dose; ineffective if tablet is swallowed whole
Iloperidone (Fanapt)	Oral tablet Titration pack	Initial dose: 2 mg/day Usual and maximum dose: 24 mg/day	Requires slow dose titration to minimize orthostatic hypotension
Olanzapine (Zyprexa)	Oral tablet Oral disintigrating tablet Immediate release IM injection Extended release IM injection	Initial dose: 2.5-10 mg/day Usual dose: 10 mg/day Maximum dose: 20 mg/day (PO); 30 mg/day (immediate release IM); 300 mg q 2 weeks or 405 mg q 4 weeks (extended release IM)	Use lower doses for children, the elderly, and patients at increased risk of hypotension; extended release injection available through restricted access program
Paliperidone (Invega)	ER oral tablet Extended release IM injection	Initial dose: 6 mg/day Usual dose: 3-12 mg/day Maximum dose: 12 mg/day (PO) or 234 mg/mo (IM)	
Quetiapine (Seroquel)	IR oral tablet XR oral tablet	Initial dose: 50 mg/day Usual dose: 300 mg/day Maximum dose: 800 mg/day; 600 mg/day for ≥ 10 y.o. (IR)	
Risperidone (Risperdal)	Oral tablet Oral disintigrating tablet Oral solution Long-acting IM injection	Initial dose: 0.25-3 mg/day Usual dose: 0.5-6 mg/day Maximum dose: 8 mg/day (PO) or 50 mg q 2 weeks (IM); 6 mg/day (PO 10-12 y.o.); 1-3 mg/day (PO 5-9 y.o., depending on weight)	Use lower doses for children and the elderly (0.5-2 mg/day); do not use IM unless patient has been received PO risperidone titration
Ziprasidone (Geodon)	Oral capsule IM injection	Initial dose: 20-40 mg BID (PO) or 10-20 mg (IM) Usual dose: 40-80 mg BID Maximum dose: 80 mg BID (PO) or 40 mg/day (IM)	IM injections should be used for no longer than 3 consecutive days; injections should be separated by 2 hours (for 10-mg dose) and 4 hours (for 20-mg dose)

IM = intramuscular; MDD = major depressive disorder; IM = immediate release; ER = extended release
* Dose depends on age, route of administration, indication, and presence/absence of drug interactions.
Data from medication package inserts.

review conducted at a community mental health center assessed the metabolic consequences of using low-dose quetiapine for insomnia in psychiatric outpatients.[18] Patients who received quetiapine (mean dose 120.3 mg/day) for the explicit indication of insomnia for an average of 11 months experienced statistically significant increases in weight and BMI. The patients in this study gained an average of 4.9 pounds, with 25% of patients gaining more than 20 pounds.

Risperidone. Risperidone is the only generically available atypical antipsychotic. In 2006, it was also the first atypical antipsychotic to be

approved for the treatment of irritability in patients with autism. For patients who are acutely agitated, both the liquid and oral dissolving forms can be used; however, they are actually absorbed in the stomach, not the mucosal layer, so serum peak concentration remains the same. [19] One unique use of the oral disintegrating tablets is for the patient who is only minimally cooperative due to the ability of the tablets to dissolve rapidly in only a minimal amount of saliva. This delivery system ensures the medication given in a directly observed therapy setting is actually taken by the patient by preventing the patient from storing the medication between the cheek and gums or under the tongue.

The usual dosage range for oral risperidone is 2-8 mg/day for adults with psychosis and bipolar disorder. (*See Table 2.*) However, the target dosage range for the best efficacy and tolerability in many adults with psychosis or bipolar disorder is 2-6 mg/day (average 4.5 mg/day).[20] The usual dosage range of oral risperidone for children and the elderly is lower, at 0.5-2 mg/day. The long-acting depot formulation is designed to be administered intramuscularly every 2 weeks for patients who have already demonstrated tolerability to oral risperidone. Oral risperidone should be given with the first injection and continued for 3 weeks, then discontinued. One of the primary reasons to proceed with long acting depot antipsychotics, such as risperidone or olanzapine, is to avoid the decompensation associated with medication nonadherence. Studies are also underway or completed suggesting that patients treated with longer-acting depot type medications may have an overall better prognosis even after controlling for adherence related issues.[21]

Ziprasidone. Available dosage forms include oral capsules and a solution for intramuscular injection. (*See Table 1.*) The usual dosage range for oral ziprasidone is 40-200 mg/day or 80-160 mg/day for the treatment of schizophrenia or bipolar disorder, respectively. Doses higher than 120 mg/day have been shown to be the most efficacious.[22] Ziprasidone has limited bioavailability of approximately 60% and therefore should be administered with food to increase its absorption. This may pose a significant obstacle in the chronic mentally ill individual who is at times homeless and thus without reliable sources of food to aid medication absorption.

Ziprasidone has been linked to QT interval prolongation. In one study, the mean QTc change from baseline was 20.3 msec for ziprasidone, 14.5 msec for quetiapine, and 9.1 msec for risperidone.[23] Ziprasidone is contraindicated in patients with congenital long QT syndrome, a history of QT interval prolongation, uncompensated heart failure, or recent acute myocardial infarction. It should not be used in patients taking other medications that are known to prolong the QT interval. These include Class Ia and III anti-arrhythmics, tacrolimus, mefloquine and moxifloxacin. It should also be used with caution in patients taking medications that can lower potassium or magnesium levels. Checking a pre-treatment serum potassium or magnesium level is advisable. A routine ECG prior to ziprasidone treatment is not recommended for all patients at this time.

The Atypical Atypical: Clozapine. Clozapine was the first atypical antipsychotic to be introduced in 1989. Like the agents above, it is atypical in that it carries less risk of extrapyramidal side effects and tardive dyskinesia. It also has a more pronounced effect on positive symptoms than most of the traditional neuroleptics, which makes it useful for the treatment of refractory psychosis. However, despite these positive findings, a severe adverse event, agranulocytosis, was discovered in about 1% of patients shortly after its widespread release into the market.[24] Unfortunately, this was fatal in some patient cases and resulted in the drug being pulled from the market. Clozapine was eventually made available again following the creation of a company-sponsored registry and strict monitoring guidelines.

Clozapine still plays a role in psychopharmacy, particularly in treatment-resistant schizophrenia. Reports vary, but about 20-50% of treatment-resistant disease responds to clozapine.[25,26] Weekly white blood cell counts are required for at least the first 6 months of therapy for patients taking clozapine. This can eventually decrease in frequency to every 3 or 4 weeks after a full year of normal white blood cell and absolute neutrophil counts. Patients with treatment-resistant schizophrenia or those on clozapine therapy are best cared for in specialty psychiatry clinics devoted to this population.

Adverse Events

Extrapyramidal Symptoms. The adverse effects of extrapyramidal symptoms (EPS) associated with atypical antipsychotic use have been well characterized and generally include dystonias, parkinsonism, akathisia, and tardive dyskinesia.[27-30] The symptoms are thought to be due to the medication's dopamine receptor blockade and can be categorized by acuity as well as clinical presentation.[31-34] Although exceptions exist, most symptoms are generally mild and capable of being treated with anticholinergic medications or reducing the dose of antipsychotic medication. Acute dystonic reactions involving the airway can be fatal and represent an airway emergency. When patients on chronic medications progress to tardive dyskinesia, this condition often is irreversible and can cause significant distress for the patient.

Although the risk of EPS is significantly decreased with atypical antipsychotics,[35] the incidence may be greater than originally thought.[36] A comparison of different drugs within the atypical antipsychotic class shows variable incidence rates of EPS, ranging from least risk or incidence with clozapine and quetiapine to most risk with risperidone at high doses.[37,38]

It is important to watch for the clinical manifestations of EPS because it is one of the primary reasons for medication discontinuation by the patient.[39] Treatment options include

stopping or reducing the dose of the offending medication, switching to an atypical antipsychotic with lower risk of EPS, or adding a new medication specifically targeting the EPS symptom. Anticholinergic drugs, such as benztropine 1-3 mg per day in divided doses or trihexyphenidyl 2-5 mg BID, are the most common treatments for dystonic reactions. Parkinsonism treatments would include the above, as well as amantadine 100 mg BID to QID, dopamine agonists, or L-dopa replacement. Akathisia treatment options include beta-blockers, anti-muscarinic agents, amantadine, clonidine, and others. Many of the above can be used to try to mitigate tardive dyskinesias.

Since schizophrenia is a chronic lifelong illness, patients often are exposed to antipsychotic medications for decades. This exposure typically means about 5% of patients will develop TD per year of treatment with typical antipsychotics, whereas switching to atypical drugs drops the rate to less than 2% annually.[40] As stated above, TD is often irreversible and there is a long history of litigation related to the development of TD in psychiatric patients. More recently, TD has been documented in patients receiving chronic administration of the gastrointestinal agent metoclopramide, which is also a dopamine antagonist.[41] Because of these concerns, clinicians need to carefully document the development and progression of any movement disorders in patients who are administered chronic neuroleptic medications. The most widely used monitoring instrument is the Abnormal Involuntary Movement Scale (AIMS). It should be performed at the time of medication initiation and then every 6 to 12 months for most adult patients. Since the elderly are at increased risk of developing TD, frequent monitoring is especially important for providers encountering geriatric patients on antipsychotics. The AIMS form is widely available on the Internet and should be placed in the patient's chart regardless of whether the primary care provider is the one actually prescribing the antipsychotic. The Hillside Akathisia Scale (HAS) instrument exists for monitoring akathisia and comparing quantifiable results across time.

Neuroleptic Malignant Syndrome (NMS). Neuroleptic malignant syndrome is a rare but potentially fatal adverse effect that can occur following any antipsychotic medication usage.[42] NMS represents a tetrad of symptoms developing over 1-3 days while on a neuroleptic medication comprising initial mental status changes, followed usually by muscular rigidity, then hyperthermia >38°C, and finally autonomic dysregulation consisting of tachycardia, tachypnea, hypertension, and diaphoresis.[43] Without a specific lab test or diagnostic study that is pathognomonic for NMS, the diagnosis is a clinical one. Usually symptoms occur within two weeks of initiation of drug therapy, but timing can be widely variable and may occur after several years. The following are thought to be risk factors for the development of NMS: psychomotor agitation, confusion, disorganization, higher neuroleptic doses, neuroleptic dose increase in last 5 days, and extrapyramidal signs.[44] The most worrisome complications include rhabdomyolysis with resulting acute renal failure, liver failure, cardiac arrhythmias or arrest, respiratory failure, DVTs, DIC, seizures, sepsis, and electrolyte abnormalities. Treatment is primarily supportive but should include stopping neuroleptic agents, ICU transfer for hyperthermia or autonomic dysregulation symptoms, and treatment of associated complications. There is limited support in the literature for the use of medications specifically treating NMS. However, dantrolene, bromocriptine, and amantadine often are used.[45] In cases of treatment-resistant disease past one week or residual catatonia, ECT can be considered.[46] Mortality after developing NMS is 10-20%. This results from systemic complications and autonomic dysregulation. Continued early detection and increased suspicion for the diagnosis have improved mortality rates, which were estimated at greater than 75% just 50 years ago.

Elevated Prolactin. Elevated prolactin levels are a risk when taking atypical antipsychotics. Dopamine is a tonic inhibitor of prolactin release, therefore relieving this inhibition through the administration of dopamine-blocking antipsychotic agents elevates prolactin levels. A study of risperidone found 40% of female subjects and 15% of male subjects had an elevated prolactin level.[47] Presenting symptoms in women are mainly amenorrhea, galactorrhea, cessation of normal cyclic ovarian function, and loss of libido.[48] In men, presenting symptoms include impotence, loss of libido, and hypospermatogenesis. Currently, there is no generally agreed-upon recommendation for monitoring prolactin levels with antipsychotic therapy.

Metabolic Complications. Atypical antipsychotics have been established to cause weight gain, dyslipidemias, and glucose irregularities.[49] As evidence continued to mount regarding the metabolic effects associated with the atypical antipsychotics, the FDA issued a warning on a class effect basis. Weight gain among patients with schizophrenia treated with atypical antipsychotics can be quite significant. Defects in glucose regulation actually represent a spectrum of disorders. The initial defect may be isolated hyperglycemia, which if left unchecked over time may progress to impaired glucose tolerance and diabetes. Although multiple factors influence the development and progression of metabolic syndrome, certain antipsychotics pose more metabolic risk than others. Clozapine and olanzapine are the most disruptive in the regulation of weight, glucose, and lipid levels.[50]

Having firmly established the scope of the issue, the APA and ADA issued their consensus paper discussing metabolic monitoring recommendations (see article in this reference for table of specific monitoring parameters and frequency) for patients treated with atypical antipsychotics.[12] A year after the APA/ADA consensus in 2004,

the CATIE study comparing the efficacy of the atypicals was published and subsequent data analysis from this study has specifically focused on the metabolic impact of antipsychotics.[51] Although studies reveal individual clinician knowledge about the potential metabolic consequences of prescribing atypical antipsychotics and the associated criteria for metabolic syndrome is present, it does not appear to have translated into increased frequency of monitoring.[52] Good patient care involves metabolic monitoring and defensive medicine suggests careful documentation of an individual clinician's monitoring system.

Across the Life Spectrum

The Pregnant or Breast-feeding Patient. Treating mental illness in pregnancy is a challenge. Clinical decision-making involves a risk-benefit analysis of taking the psychotropic medication versus not treating the disease during pregnancy — both carry risks for the mother and fetus.[53] Schizophrenia itself has been shown to increase the risk of negative outcomes such as low birth weight and small for gestational age pregnancies.[54] While the risks of untreated schizophrenia are clear, the data are divided as to the actual risks of atypical antipsychotic use to mother and fetus, so caution should be used.[54-57] These medications have been found to cross into fetal circulation to varying degrees.[58] At a minimum, the known common side effects of atypical antipsychotics, weight gain, hyperglycemia, sedation, and hypertension are all particularly problematic during pregnancy. In general, pregnant patients with schizophrenia should be considered high risk.[59] The family physician may consider using a typical antipsychotic due to relatively greater exposure data available due to length of use as compared to the newer atypical agents. These patients may be best cared for in a high-risk obstetrics practice or in concert with a psychiatric provider.

Atypical antipsychotics are lipophilic and therefore are likely passed to breast milk. Data on actual passage are sparse. The data are also unclear as to the safety of using these medications for the breast-feeding infant. The authors of one study stated that although no general conclusions could be drawn on the safety of using these medications while breast-feeding, olanzapine and clozapine should be avoided until more evidence is available due to what appear to be more significant risks.[60] Despite the general recommendation to breast-feed, pregnant patients with a significant mental health history may be advised to bottle-feed, thereby avoiding unnecessary risk to the infant as well as the risk of nontreatment of the mother.

The Pediatric Patient. While children experience their share of psychotic behavior, several of the atypical antipsychotics don't have any FDA indications for use in children. There is a growing body of research on the use of atypical antipsychotics in children; however, relatively few studies are randomized controlled trials and most only look at short-term outcomes.[61] Aripiprazole, olanzapine, risperidone, and quetiapine now have various pediatric indications for schizophrenia and bipolar disorder. More recently, aripiprazole and risperidone were approved to treat irritability associated with autism.

Since much of this drug class is not approved for use in children, most prescribing to children is done off-label and includes indications such as schizophrenia, bipolar, and autism. These drugs may also be useful in treating Tourette's disorder, mental retardation, conduct disorder, and severe ADHD.[62]

Side effects in children are similar to those in adults. The most common side effects for most of the atypical antipsychotics are sedation and fatigue (20-54% combined), although classic antipsychotic symptoms such as EPS and galactorrhea secondary to prolactin elevation also occur.[61] Olanzapine was associated with a higher percentage (22%) of increased appetite and weight gain, and clozapine resulted in more cardiovascular side effects of tachycardia (28%) and orthostatic hypotension (12%). Children may be at increased risk of drug overdose with the atypical antipsychotics, in part because children generally metabolize these drugs more quickly into their active metabolites and typically have less fat tissue than adults, therefore resulting in a smaller volume of distribution.[63] For primary care physicians, it is probably best to stick with drugs with FDA-approved indications in children and, of course, monitor closely for adverse reactions.

Medically Ill Adult Patient. Antipsychotic medications are often given in the hospital setting to patients who are not using these medications at home. Delirium is a common reason for initiating treatment, and atypical antipsychotics are often chosen and used off-label for this purpose. Other uses in the hospital setting include prevention of post-operative delirium, treatment of steroid-induced psychosis, and management of acute agitation.

Delirium is a common problem in acutely ill hospitalized patients and is associated with increased mortality, especially if left untreated. Historically, haloperidol was the most commonly used antipsychotic for delirium. Now attention is being paid to using atypical antipsychotics in place of haloperidol due to their more favorable side-effect profile. A meta-analysis comparing several atypical drugs to haloperidol revealed equal efficacy and fewer EPS side effects with the atypical drugs.[64] The authors noted that the dosages used for delirium often were lower than those used to treat schizophrenia. Since delirium usually resolves in 7-10 days following resolution of the medical illness, atypical antipsychotics shouldn't be used for this purpose for more than 2 weeks. A tool such as the Delirium Rating Scale (DRS) should be used often to monitor for resolution or the need to titrate the dose of the medication.

Post-operative delirium is also a common problem in hospitalized patients. Potential risk factors include pain, stress on the body, immobility, sleep problems, and sedative medications. Recently, fentanyl exposure and

longer duration of pre-operative fasting have been associated with greater risk of postoperative delirium.[65] Haloperidol prophylaxis has been studied for the prevention of postoperative delirium with mixed results. More recently, atypical antipsychotics have been studied. One trial showed that a single dose of risperidone, once consciousness was regained, reduced the incidence of delirium compared to placebo.[66] Obviously further studies are needed before making any general statements about the utility of atypical antipsychotics for prevention of postoperative delirium.

A final inpatient issue to discuss is steroid-induced psychosis and mania. High-dose corticosteroids are used frequently in hospitals for myriad reasons. Side effects include weight gain, osteoporosis, and blood sugar elevation as well as a variety of psychiatric side effects.[67] Many times, reducing the steroid dose, or even discontinuing it, can alleviate these symptoms. However, sometimes additional pharmacologic treatment is necessary.[68] Atypical antipsychotics have been used with success in case reports including olanzapine in adults[69,70] and risperidone in children.[71]

Patients of Advanced Age. Antipsychotics are used for different reasons in the elderly than in younger patients. While schizophrenia and bipolar disorder account for 70% of prescribed atypical in patients younger than 65 years old, these account for only 38% of use in patients 65 years and older.[72] This is mostly attributed to 28% being used for agitation associated with cognitive impairment in the older group. Some reviews of evidence show an improvement in symptoms,[73] while others conclude that atypical drugs are largely ineffective and any benefit is outweighed by side effects.[74,75]

A serious issue with prescribing in this population involves the concern in recent years because of an FDA "black box" warning placed on atypical antipsychotics based on evidence of increased mortality in elderly dementia patients as well as new information about increased stroke risk. In 2005, in response to reports of increased stroke risk in elderly dementia patients taking atypical antipsychotics, the FDA commissioned a study in this patient population. This meta-analysis involving 17 trials and more than 5000 patients found a 1.6- to 1.7-fold increase in mortality in elderly patients being treated with atypical antipsychotics.[76] Most deaths were due to cardiac or infectious causes. Based on these data, the FDA began requiring a label on all atypical antipsychotics about the increased mortality risk in patients with dementia.

As expected, the FDA advisory resulted in a trend of decreasing atypical antipsychotic use in this population, but it also resulted in a "spill-over" decrease in use for younger patients and approved indications.[77] Also, 9% of prescriptions to elderly dementia patients are still for atypical antipsychotics. There was concern that the advisory could shift prescribing to typical neuroleptics, which carry their own risk, and in 2008 the FDA extended the warning to typical antipsychotics. At least one study did not find an increased use of typical antipsychotics.[77] The FDA advisory appears to have had its intended effect but also may have resulted in less prescribing in other patients for approved indications.

The obvious problem is what to prescribe for these patients when there is no effective alternative to antipsychotics. The alternatives typically include no treatment, other psychotropic medications, or behavioral restraints.[78] No drug is specifically indicated for the treatment of psychosis or agitation in dementia, and there is even less evidence supporting the benefits of medications outside the realm of antipsychotics. Some drugs that have been studied and demonstrated modest promise include cholinesterase inhibitors,[79] memantine,[80] and donepezil.[81]

In general, elderly patients are more likely to have multiple comorbidities and polypharmacy; caution should be used when adding any medication, particularly centrally-acting agents such as antipsychotics. Specifically, the primary care physician should perform a detailed exam to confirm that the psychotic symptoms are not a result of a superimposed delirium secondary to an underlying medical illness that could be reversible with conventional treatment thereby alleviating the need for antipsychotic treatment. Current recommendations focus on shared decision-making with patients and families, documentation, treatment with antipsychotics only for severe and persistent or recurrent symptoms that have failed non-pharmacotherapy approaches, and close monitoring for efficacy and adverse events.[78,82]

Atypical antipsychotic medications have also found an off-label use for psychosis associated with Parkinson's disease, where typical antipsychotics are relatively contraindicated. Atypical antipsychotics, on the other hand, act at different cellular receptors and should have less of an effect on parkinsonian motor symptoms, although only clozapine[83] and quetiapine[84] seem to have little negative effect on motor symptoms.[85] Therefore, these two agents may be good initial choices by the family physician if treatment in patients with Parkinson's disease is indicated.

Toxicology in Overdose

Mental illness places a patient at increased risk for suicide. Ingesting one's medications is a common way to attempt suicide for these patients secondary to the ready access to pill bottles as well as the stigma the need for such medications represents to some patients. Primary care providers providing urgent care services or working in emergency rooms will undoubtedly come in contact with patients who have overdosed on their atypical antipsychotic medicine. In 2004, there were 38,315 atypical antipsychotic agent exposures reported to U.S. poison centers.[86] Of these exposures, major toxicity and death occurred in 5.5% and 0.2% of reported cases, respectively.[86] In the majority of patients, an overdose of atypical antipsychotics presents with symptoms arising from the individual agent's pharmacologic receptor profile, but generally causes only mild

to moderate toxicity. The specific doses associated with atypical antipsychotic toxicity are highly variable and dependent on the agent used, as well as patient-specific factors such as age, comorbid conditions, concomitant medication use, and previous drug exposure. Children, the elderly, and adults who have not been previously exposed to the medication are at greatest risk for atypical antipsychotic toxicity.[87] Symptoms usually present within 1-2 hours and peak 4-6 hours following ingestion. Resolution of symptoms usually occurs within 12-48 hours of ingestion but can take much longer in some situations.[88]

Owing to their complex pharmacologic profiles, the presentations of patients who have overdosed on atypical antipsychotics vary widely. The management and treatment of an acute atypical antipsychotic overdose is generally supportive.

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Physician CME Questions

8. Which of the following is correct regarding atypical antipsychotics?
   A. Ziprasidone is contraindicated in patients with uncompensated heart failure.
   B. Oral risperidone should be overlapped with IM risperidone for 3 months.
   C. Low-dose paliperidone maintains sedative activity while minimizing metabolic adverse events.
   D. Quetiapine is associated with post-injection delirium.

9. Clozapine is known for which dangerous adverse effect?
   A. aplastic anemia
   B. rhabdomyolysis
   C. agranulocytosis
   D. anaphylaxis

10. Which of the following statements about atypical antipsychotics in the elderly is *false*?
   A. This drug class is more often used for agitation and related complaints than in younger patients.
   B. This drug class is subject to an FDA "black box" warning due to increased mortality in elderly dementia patients.
   C. Elderly patients should be treated only for severe symptoms and after shared decision making with patients and/or families.
   D. Typical antipsychotics are more effective for Parkinson's-related psychosis than are atypical antipsychotics.

11. Which of the following groups of symptoms most closely describes a presentation of NMS?
   A. high fever, nuchal rigidity, increased CSF WBC only
   B. high fever, tachycardia, no history of neuroleptic use
   C. high fever, rigidity, tachycardia
   D. elevated CPK, afebrile, in restraints

12. Which of the following atypical antipsychotic medications has essentially no risk of dose-related EPS?
   A. olanzapine
   B. quetiapine
   C. risperidone
   D. a and b only

CME Answer Key

8. A; 9. C; 10. D; 11. C; 12. B

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Dietary added sugar and lipids

Source: Welsh JA, et al. *JAMA* 2010;303:1490-1497.

Processed foods often contain added sucrose or high-fructose corn syrup to enhance palatability. Such added sugars (aSUG) may comprise as much as 16% of Americans' caloric intake. The Institute of Medicine suggests a 25% maximum of daily calories from aSUG and the American Heart Association suggests a 5% maximum. The incidence of obesity, diabetes, and dental caries is associated with increased aSUG, but the relationship between aSUG and lipids is less well-defined.

Welsh et al studied the relationship between aSUG and lipids in NHANES participants (n = 6113). Overall, approximately 16% of calories daily were supplied by aSUG in this population of adults. Excluded from analysis were persons with dietary reports that appeared unreliable (e.g., < 600 calories/d), marked triglyceride elevation, BMI > 65 kg/m^2, and those taking cholesterol-lowering medications.

There was a statistically significant association between progressively higher levels of aSUG and lower HDL. Similarly, LDL and triglyceride levels were linearly related to aSUG, although the LDL results were not statistically significant in men.

The mechanism(s) by which aSUG consumption is related to lipid levels is incompletely understood, although it is recognized that fructose may stimulate hepatic lipid production and reduce peripheral lipid clearance. Although not demonstrated in a clinical trial, conceptually, reductions in aSUG on a population-wide basis could have important public health benefits. ■

Underrecognition of adverse effects

Source: Zimmerman M, et al. *J Clin Psychiatry* 2010;71:484-490.

The design of clinical trials sometimes allows for failed detection of adverse effects related to medication. Perhaps the most widely recognized disconnect is in relation to ACE inhibitors: Prescribing information suggests a very low incidence of cough (typically < 10%), yet clinical experience suggests twice that frequency. The primary reason for this incongruence is that most side effects are passively reported; for a variety of reasons, patients may fail to spontaneously report adversities that could be related to medication.

Zimmerman et al addressed this issue among depressed outpatients treated with a variety of antidepressants and anxiolytics. Subjects were seen by board-certified psychiatrists, and after their office visits, filled out questionnaires addressing adverse effects possibly related to medication.

Over a 6-week interval, more than 25% of the 2233 reported side effects occurred at least daily, but fortunately, the majority were rated low on the severity scale. Only about 20% of individuals rated adverse effects as 4-5 on a 5-point scale.

Overall, 20 times more adverse effects were identified by questionnaire than in psychiatrists' records. Comparison limited to either highly frequent or bothersome adverse effects still found that questionnaires identified 2-3 times as many adversities as clinicians had recorded.

A number of explanations can clarify some of this discrepancy: Psychiatrists may not record all adverse effects they see, patients may not report all issues that bother them (or minimize the bother), and some adverse effects may be so anticipated that their presence does not merit specific notice. In any case, it appears that patients shoulder a much higher level of adverse effect burden when treated for depression than would be readily apparent from review of their clinical records. ■

Female sexual dysfunction in diabetes

Source: Esposito K, et al. *Int J Impot Research* 2010;22:179-184.

Male sexual dysfunction is well recognized as a consequence of diabetes. Currently, there are no approved medications for treatment of female sexual dysfunction (FSD), though epidemiologic surveys suggest that the population prevalence of FSD rivals that of male sexual dysfunction. FSD is typically categorized as either disorders of desire, arousal, orgasm, or pain. Of course, FSD subcategories are commonly comorbid.

This study recruited adult type 2 diabetic women (mean age, 58 years) attending a clinic in Italy for routine care of diabetes to complete the Female Sexual Function Index, a validated instrument for assessing FSD.

Overall, the prevalence of FSD in the entire population was 53%. This is similar to, but even greater than, the prevalence reported in two large population surveys (both with broader age range, and not limited to diabetics), which indicated an FSD

prevalence of 43%. FSD was 30% more frequent in postmenopausal women than premenopausal women and was associated with depression. The only recognized protective factor was physical activity.

The etiology of FSD in diabetes is unclear, and may include vascular, neurologic, and endocrinologic factors. The high prevalence of FSD in diabetic women should motivate clinicians to be more proactive in its identification. ■

Vitamin D from the sun or supplements?

Source: Terushkin V, et al. *J Am Acad Dermatol* 2010;62:929.e1-9.

While I cannot speak for you, my recent experience is that under every rock I overturn is a vitamin D-deficient patient. At least that's what checking 25-OH vitamin D levels (the currently recommended test for vitamin D status) suggests. Should we recommend sun exposure, supplements, or both to address hypovitaminosis D?

Terushkin et al compared the amount of sun exposure necessary to provide the same plasma vitamin D levels as a 400 IU/d vitamin D supplement. They chose to study individuals in Miami, FL, and Boston, MA. Of course, sun exposure varies depending upon geography and season, as well as skin type. In July, the amount of sun time to provide as much systemic vitamin D as 400 IU orally was the same in both cities (3 min at 12 noon). A darker-skinned individual would require 5 min.

During winter months, there were marked differences in required exposure time. In Miami, 6 min of sun vs 23 min of sun in Boston would be required. Since most individuals do not expose 25% of the body surface (the face is only 3.5%) to sun during the winter in cities like Boston, a correspondingly greater time exposure would be required … an unlikely scenario.

Because of the concern about sun exposure and its relationship to photoaging and skin cancer, as well as the neglect of optimum sunscreen utilization, the authors of this article favor vitamin D supplementation over sun exposure as the safest way to maintain vitamin D adequacy. ■

Exenatide + rosiglitazone added to metformin

Source: DeFronzo RA, et al. *Diabetes Care* 2010;33:951-957.

It is widely recognized that approximately half of beta-cell function (BCF) has been lost by the time type 2 diabetes (DM2) is diagnosed. Additionally, it appears that despite vigorous treatment, loss of BCF continues inexorably.

The most recently published treatment algorithm for DM2 management by the ADA suggests that initial therapy should be lifestyle with metformin, unless a specific contraindication to metformin exists. Over time, however, most patients will require augmentation of treatment.

Exenatide (EXE) and rosiglitazone (ROS) are effective therapies for glucose control and work by complementary mechanisms of action. Additionally, sometimes thiazolidinedione therapy is compromised by weight gain, but since exenatide consistently provides weight loss, their combination is clinically sensible.

DM2 subjects already on treatment with lifestyle plus metformin (n = 101) were randomly assigned to add-on therapy with EXE alone, ROS alone, or EXE + ROS, and followed for 20 weeks. BCF was measured by the glucose disposition index.

In addition to the anticipated reduction in A1c by polypharmacy, EXE + ROS provided significant improvements in insulin secretion and overall BCF. Long-term studies are necessary to discern whether these favorable effects can be sustained and translated into risk reduction for macro- and/or microvascular outcomes. ■

Intensive BP control in diabetes

Source: Accord Study Group. *N Engl J Med* 2010;362:1575-1585.

Because it is recognized that type 2 diabetics (DM2) incur greater risk of CV outcomes than the general population, consensus groups have advocated BP < 130/80 mmHg as a preferred goal, in contrast to 140/90 mmHg for the general hypertensive population. Despite enthusiasm for this posture, and essentially global advocacy for the concept that lower is better in diabetes, no prospective, randomized trial has been done that confirms such benefits. The ACCORD trial was designed to compare CV outcomes achieved with tight BP control (SBP < 120 mmHg) vs standard therapy (SBP < 140 mmHg). The ACCORD trial had several limbs, including a glucose control and a lipid control arm, which were not addressed in this publication.

Almost 5000 diabetics were randomly assigned to intensive BP vs standard BP treatment and followed for the primary endpoint of (composite) nonfatal MI and stroke, or CV death over a mean 4.7-year follow-up.

The tight control arm managed to achieve an SBP of 119.3 mmHg, compared to the standard treatment group SBP of 133.5 mmHg; of course, the number of medications required to attain control was substantially greater in the tight control group (3.4 drugs vs 2.3 drugs). Intensive BP lowering did not reduce the primary endpoint. Intensive BP control was associated with more adverse events.

No hypertension guidelines have been issued since the publication and promulgation of the ACCORD BP trial. Expert opinions vary in interpretation of this outcome. I have suggested that, in the absence of proven benefit by greater BP lowering, achievement of < 140/90 mmHg now represents a reasonable goal until further literature suggests otherwise. ■

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Aggressive Modification of Cardiovascular Risk Factors

In this issue: Aggressive approach to CVD reduces MI, folic acid and vitamin B12 for CAD, corticosteroids for acute exacerbations of COPD, prescription drug abuse among young adults, and ARBs and cancer risk.

CVD decreases with aggressive treatment

Aggressive modification of cardiovascular risk factors seems to be paying dividends, at least for a large population of insured patients in Northern California. In an analysis of nearly 18.7 million patient-years between 1999 and 2008, the rate of myocardial infarction (MI) increased in 1999 and 2000 and then decreased significantly every year thereafter (287 cases/100,000 person-years in 2000, decreasing to 208 cases/100,000 person-years in 2008; 24% relative decrease over the study period). The rate of ST-segment elevation MI decreased over the study period (133 cases/100,000 person-years in 1999 to 50 cases/100,000 person-years in 2008; $P < 0.001$) and the 30-day mortality rate decreased from 1999 to 2008 as well (adjusted odds ratio, 0.76; 95% confidence interval, 0.65-0.89). This occurred despite more aggressive diagnosis of MI.

The authors conclude, "The lower incidence of myocardial infarction — particularly ST-segment elevation myocardial infarction — is probably explained, at least in part, by substantial improvements in primary-prevention efforts, …" including statins and aggressive blood pressure reduction, as well as use of cardioprotective medications such as aspirin (*N Engl J Med* 2010;362:2155-2165).

An accompanying editorial points out that while these trends are generally the case in the United States, there are significant geographic differences. "The risk among residents of Oklahoma, the lower Mississippi corridor, and Appalachia, for example, is double that among other Americans, … " suggesting socioeconomic factors play a role. Hypertension and diabetes rates have increased slightly over the last decade, while smoking rates have decreased. Perhaps even more importantly, statin use has increased significantly (among those between age 45 and 64 years, statin use in men increased from 2.5% to 16.8% and from 1.9% to 13.5% in women; among those 65 years of age or older, statin use increased from 1.9% to 38.9% in men and from 3.5% to 32.8% in women). Aspirin, beta-blockers, and ACEIs/ARBs have also contributed to the decline in cardiovascular mortality in the United States (*N Engl J Med* 2010;362:2150-2153). ■

Folic acid and vitamin B12 for CAD

Unfortunately, lowering homocysteine with folic acid and vitamin B12 does not seem to be a benefit to patients with coronary artery disease. In a study from the United Kingdom, more than 12,000 survivors of myocardial infarction were randomized to 2 mg folic acid plus 1 mg vitamin B12 daily vs matching placebo, with the main outcomes being first major vascular event such as coronary event, stroke, or noncoronary revascularization. Folate and vitamin B12 were effective at reducing homocysteine levels by 28%; however, there was no difference in the rate of major vascular events over the 6.7 years of follow-up (25.5% active treatment vs 24.8% placebo; $P = 0.28$). Individually, there was no effect on major coronary events, stroke, or noncoronary

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revascularizations, nor was there a survival benefit from active treatment. Interestingly, the authors also looked at incidence of cancer and found no difference in that outcome either. The authors conclude that long-term reductions in blood homocysteine levels with folic acid and vitamin B12 do not have a beneficial effect on vascular or cancer outcomes (*JAMA* 2010;303:2486-2494). ■

Corticosteroids for exacerbations of COPD

Giving corticosteroids orally in lower doses is as effective as giving the drugs intravenously at higher doses for the treatment of acute exacerbation of COPD (ae-COPD), according to a recent study in the *Journal of the American Medical Association*. The records of nearly 80,000 patients in more than 400 hospital admissions for ae-COPD who received steroids were reviewed. The primary outcomes were treatment failure, defined as the initiation of mechanical ventilation, inpatient mortality, or readmission within 30 days. The vast majority of patients (92%) received IV steroids. After multivariate adjustment, the death rate was similar in the two groups (1.4% IV therapy vs 1.0% oral) and the composite outcome was also similar (10.9% IV vs 10.3% oral). In a propensity-matched analysis, the risk of treatment failure was actually significantly lower among orally treated patients (odds ratio, 0.84; 95% confidence interval, 0.74-0.95), as was the length of stay and cost. Of the orally treated patients, 22% were switched to IV therapy later in the hospitalization.

The authors conclude that for patients admitted for ae-COPD, low-dose steroids administered orally are as effective, and may be safer, than higher-dose IV steroids (*JAMA* 2010;303:2359-2367). An accompanying editorial suggests that rather than doing large non-inferiority studies to confirm these findings, sufficient evidence exists to change practice now with continued comparative effectiveness research via linked registries (*JAMA* 2010;303:2409-2410). ■

Prescription drug abuse in young adults

Prescription drugs are the new drugs of abuse among young adults. While drug use in general seems to be dropping in high schools, prescription drug abuse is skyrocketing. The recently published National Youth Risk Behavior Survey from the Centers for Disease Control and Prevention (CDC) showed that 1 of 5 high school students in the United States reported abusing a prescription drug at some time in their lives. The most commonly mentioned drugs were OxyContin®, Percocet®, Vicodin®, Adderall®, Ritalin®, and Xanax®. Prescription drug abuse was most common among white students (23%), followed by Hispanic students (17%), and then black students (12%). Not surprisingly, high school students were most likely to abuse drugs in their senior year (*MMWR* 2010;59:1-142). While many teens get their prescription drugs from medicine cabinets of family and friends, others order them online, and recently many drug dealers have begun specializing in prescription drugs.

Many young adults, however, seek opioids and benzodiazepines from physicians, especially in emergency departments (ED). A new report from *MMWR* reports that ED visits for nonmedical use of opioid analgesics increased 111% from 2004 to 2008 and increased 29% from 2007 to 2008 alone. The highest number of ED visits was recorded for oxycodone, hydrocodone, and methadone. ED visits for benzodiazepines also increased 89% over the same period. In 2008, the rates of visits for both opioids and benzodiazepines increased sharply after age 17 and peaked in the 21-24 year age group. During the 2004-2008 study period, the largest increase in ED visits to obtain drugs occurred among persons age 21-29 years. Findings were from the CDC and the Substance Abuse and Mental Health Services Administration, reviewing data from the Drug Abuse Warning Network (*MMWR* 2010;59:705-709). ■

ARBs and cancer risk

Do angiotensin receptor blockers (ARBs) increase the risk of cancer? In a widely reported study, researchers from Case Western Reserve performed a meta-analysis of 5 trials for which cancer data were available from more than 61,000 patients. Telmisartan was the ARB used in nearly 86% of the studies. Patients randomly assigned to receive ARBs had a rate of new cancer occurrence of 7.2% vs 6.0% for placebo (relative risk [RR], 1.08; 95% confidence interval [CI], 1.01-1.15; $P = 0.016$). The risk ratio was higher when the analysis was limited to trials where cancer was the prespecified endpoint (RR, 1.11; 95% CI, 1.04-1.18; $P = 0.001$). There was no difference in the rate of cancer deaths between the two groups. The authors conclude that this trial suggests that ARBs are associated with a modestly increased risk of new cancer diagnosis, but it is not possible to draw conclusions about the exact risk of cancer associated with each particular drug and further research is warranted (*Lancet Oncology* 14 June 2010; early online publication). ARBs are involved in the regulation of cell proliferation, angiogenesis, and tumor progression, which are possible mechanisms for these findings. ■