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INSIDE

Getting the Drop on Drop Attacks

ABSTRACT & COMMENTARY

Synopsis: *A standardized work-up will reveal a cause for drop attacks in 90% of cases.*

Source: Parry SW, Kenny RA. *J Am Geriatr Soc*. 2005;53:74-78.

A DROP ATTACK IS A SUDDEN COLLAPSE WITHOUT LOSS OF CONsciousness. Elderly women seem to suffer more frequently than men. Parry and Kenny conducted a study of 93 consecutive patients presenting to the Royal Victoria Infirmary emergency department and its Falls and Syncope Service in Newcastle Upon Tyne, United Kingdom, with 3 or more unexplained attacks. Their goal was to ascribe diagnoses to these patients following a standardized assessment. The assessment included a detailed history and physical exam with attention paid to the neurologic, skeletal, cardiovascular systems. Testing included visual acuity, Mini-Mental State Exam (MMSE), gait, balance, electrocardiogram (ECG), carotid sinus massage (CSM), orthostatic blood pressure (BP), biochemical profile, and complete blood count. Gait was addressed by the Get Up and Go Test,[1] which requires patients to stand up from a chair, walk a short distance, turn around, return, and sit down again. Balance was measured by the one-legged stand test,[2] which requires patients to stand on one leg for 5 seconds. Should the initial work-up have proved unfruitful, a tilt table test with or without nitroglycerin provocation and 24-hour ambulatory ECG and BP monitoring were ordered. If the history or physical suggested another diagnosis, then echocardiogram, cervical spine x-rays, hip x-rays, brain imaging, electroencephalogram, electrophysiologic studies, or toxicology studies were ordered.

Since a drop attack is a symptom and not a diagnosis, it was important to have a strict definition of what constitutes a drop attack, to avoid including other conditions (for instance, a seizure). Parry and Kenny defined it as follows: ". . .a sudden fall event whereby the patient landed on the ground or another lower level, with no prodrome, no awareness of loss of consciousness, and no overt extraneous triggering event such as a slip or a trip." They also defined what constituted a diagnosis; once a risk factor was detected, there had to be an association of symptoms with a positive test or physical exam,

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or a 50% reduction in drop attacks after addressing the risk factor or disease.

Inclusion criterion was age 55 or older. Excluded were patients with syncope, myocardial infarction, stroke, infection, malignancy, electrolyte abnormality, gastrointestinal hemorrhage, fracture, head injury, or a MMSE score < 15. Because CSM was an important part of the work-up, patients with a relative contraindication to CSM (for instance, transient ischemic attack in the previous 3 months) were also excluded. The 93 patients were an average age of 77, 75% female, and 80% living independently in private homes and were followed for 18 months. On entry, these patients averaged 6 drop attacks.

A diagnosis was made in 84 patients (90%). Cardiovascular disorders accounted for the largest group of diagnoses (53%), followed by neurological disorders (29%), and gait and balance problems (17%). Carotid sinus hypersensitivity was diagnosed in 37 patients, vestibular disorders in 9, orthostatic hypertension in 5, visual impairment in 5, cerebrovascular disease in 5, vasovagal syncope in 3, sick sinus syndrome in 2, and congestive heart failure and atrial fibrillation in 1 a piece. Other disorders were diagnosed infrequently (1 or 2 occurrences each). Sixty-eight patients had only one diagnosis, 17 had two, and 3 had three. Polypharmacy was a contributing risk factor in 28%. History, physical exam, and initial testing made the diagnosis in most patients. Ambulatory BP and ECG monitoring helped very infrequently.

COMMENT BY ALLAN J. WILKE, MD

If you are thinking that drop attacks and their work-up look suspiciously like syncope and its work-up, welcome to the club! As an editorialist noted, "The distinctions between falls, dizziness, syncope, and cardiovascular disease have become increasingly blurred."[3] In 2001, *Internal Medicine Alert* reviewed[4] a study by Sarasin[5] that detailed a work-up of syncope that looks very similar to this one. Drop attacks seem to be syncope without the loss of consciousness, but Parry and Kenny hint at a subtler explanation. They point to several articles where elders who were undergoing CSM had unconsciousness and were amnesic for the loss of conciousness.

The patients in this study may not be similar to those in your practice. They were recruited from a falls and syncope clinic and had experienced multiple drop attacks before entering the study.

Proceeding on a work-up of a patient with multiple drop attacks is more than reasonable. These patients are elderly females for the most part and prone to grievous injury from falls. What to do with the patient who presents with a first drop attack? At the very least, a detailed, directed history and physical and some testing (gait and balance testing, orthostatic BPs, CBC, and basic metabolic profile) are warranted with more extensive testing if the work-up suggests a diagnosis or the problem persists. ■

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Holidays, Birthdays and Postponement of Cancer Death

ABSTRACT & COMMENTARY

Synopsis: *Contradicting previous studies, no evidence was found in a large review of cancer patients that deaths were postponed relative to significant life events.*

Source: Young DC, et al. *JAMA*. 2004;292:3012-3016.

Death certificate data for the entire state of Ohio for the years 1989-2000 were reviewed to determine if a reduction of cancer deaths was seen in the week preceding Christmas, Thanksgiving or the individual's birthday. The deaths in the week before the event were compared to deaths in the week following. Nearly 310,000 cancer deaths were analyzed out of a total of some 1.3 million deaths.

No significant difference was found in the proportion of patients dying after the event compared to the week before, and no difference was found either when analyzed by sex, age less than or greater than 70 years, or race. Small differences were noted in actual increases of women dying before their birthdays and African Americans dying before, rather than after, Thanksgiving. There was no seasonal variation in cancer deaths.

COMMENT BY MARY ELINA FERRIS, MD

Widespread beliefs that death can be postponed by an individual's will to reach a significant event have recently been contradicted by large analyses such as this study for cancer deaths, and a 30-year literature review in the psychological literature.[1] However, smaller studies focusing on specific cultural holidays such as Chinese Harvest Moon[2] and the Sabbath (Saturday) for Jewish residents of Israel[3] have found a decrease in all-cause mortality before these events, although they have been criticized for small sample size.

Deaths from other causes, such as accidents and cardiovascular sudden death, have actually been shown to increase during the Christmas and New Year's period. Also supported is seasonal variation in deaths from all causes, particularly in the winter months when respiratory illness are thought to contribute to an increase in deaths.

While epidemiological analyses may miss individual cases with the ability to control the timing of death, and also cannot determine which life events are the most significant for each individual (eg, marriages, relative's events), this seems to be another case of *evidence-based medicine* refuting our long-held popular beliefs. While individuals can influence their deaths by their acceptance or refusal of nutrition and therapies, evidence does not support their ability to determine the exact date of death.

Young and associates suggest that physicians and the public have a cognitive bias to recall mainly those deaths that occur after an important event because they are so striking, and assign to them an exaggerated importance. While this may comfort our patients and their families facing imminent death, the evidence here suggests otherwise. ■

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Trichuris suis Therapy in Crohn's Disease

ABSTRACT & COMMENTARY

Synopsis: *Administration of sterile viable* Trichuris suis *eggs to patients with active Crohn's disease led to impressive clinical improvement.*

Source: Sommers RW, et al. *Gut*. 2005;54:87-90.

Crohn's disease is an often severely debilitating chronic illness that involves inflammation that can occur throughout the GI tract. It is now believed that this disorder results from inappropriate host immune responsiveness to normal gut flora. Helminths that infect the human intestine are known to reduce inflammation in several animal models of colitis, and they also demonstrably down-regulate host immune responses to unrelated antigens. In this study from Iowa, 29 patients with moderately active Crohn's disease on various forms of conventional stable therapy received 2,500 live Trichuris suis ova every 3 weeks for 24 weeks. Viable eggs were derived from T. suis-infected pathogen-free pigs. Eggs were subsequently cultured in vitro and rendered virus and bacteria free. Patients had a mean age of 34, were 45% male, and had Crohn's disease for a median of 3.9 years. Only 5/29 were not taking medication at baseline, and 10 of these had previously tried corticosteroids and immunosuppressive drugs. All patients were ill at enroll-

ment with a Crohn's Disease Activity Index (CDAI) of 296.7 ± 46.9 (moderate severity). No patients were lost to follow-up, and all were compliant. Twenty-two patients (75.9%) responded favorably by week 12 with a drop in CDAI of > 100 points. At week 24, 23 patients had responded (79.3%) and 21/29 were in remission. Results were not affected by age, sex, disease duration, smoking status (9/29 smoked), or disease location. There was a suggestion that patients receiving immunosuppression concurrently might have responded better (P = 0.017 for response at 24 weeks among this subgroup). Ileal resection may have lessened the likelihood of a favorable clinical response (P = 0.046). T. suis was very well tolerated. Sommers and colleagues strongly recommend that larger controlled trials should be undertaken.

COMMENT BY MALCOLM ROBINSON MD, FACP, FACG

This trial was, of course, open label and of very limited size. Placebo response cannot be ruled out. Nevertheless, the reported clinical results are extremely impressive. As Sommers et al point out, Crohn's disease is known to involve hyper reactive Th1 immune pathways. It has been suggested that the Th2 immune effects of infestation with helminths like *T. suis* may directly antagonize the immune pathways responsible for Crohn's pathophysiology. In any case, various parasitic infections have been demonstrated to be capable of blocking experimental intestinal inflammation. It is certain that the administration of *T. suis* affects Crohn's disease by mechanisms quite dissimilar to any of our current conventional therapeutic modalities. Crohn's disease can be a terrible scourge, and we should be open-minded in our quest for safer and more efficacious therapy.

Community-Acquired Pneumonia: Outpatient Care or Hospitalization?

ABSTRACT & COMMENTARY

Synopsis: *In selected patients with community-acquired pneumonia, outpatient treatment with levofloxacin was as safe and effective as hospitalization.*

Source: Catarrala J, et al. *Ann Intern Med*. 2005;142: 165-172.

THIS STUDY WAS AIMED AT EVALUATING WHETHER outpatient care of pneumonia-severity-index (PSI) low-risk patients with community-acquired pneumonia (CAP) was as safe and effective as hospitalization. It was designed as an unblinded, randomized, controlled trial over a 2-year period of time at 2 tertiary care hospitals in Barcelona, Spain. Those immunocompetent patients who were at least 18 years of age and that received the diagnosis of CAP in the emergency department were eligible for inclusion. Patients with neutropenia, HIV infection, transplantation, splenectomy or those who were taking immunosuppressive drugs were excluded from the trial. CAP was defined as the presence of a new infiltrate on chest radiograph plus at least one of the following: fever (temperature ≥ 38.0°C) or hypothermia (temperature < 35.0°C), new cough with or without sputum production, pleuritic chest pain, dyspnea, or altered breath sounds on auscultation.

Patients with CAP were stratified into PSI risk classes. Those patients in risk classes I, IV, and V were excluded as well as those patients who were pregnant, those with allergy to fluorquinolones, concomitant comorbid conditions necessitating hospitalization for treatment, complicated pleural effusions, respiratory failure or severe social problems precluding adequate outpatient treatment. The primary end point of the trial was the percentage of patients with an overall successful outcome, defined as meeting all 7 predefined criteria: cure of pneumonia, absence of medical complications during treatment, no need for additional visits, no changes in the initial treatment, absence of subsequent hospital admission in the 30 days after randomization, and absence of death from any cause in the 30 days after randomization.

A total of 224 patients were randomly assigned and included in an intention-to-treat analysis for the primary end point. Of these, 110 received outpatient care and 114 were hospitalized. Outpatients were treated with oral levofloxacin for 10.19 ± 1.97 days. Inpatients received intravenous therapy with levofloxacin for 2.25 ± 0.94 days before switching to oral levofloxacin. Mean length of hospitalization was 5.1 ± 2.07 days and a total length of antibiotic therapy of 10.00 ± 2.56 days. Overall successful outcome was achieved in 83.6% of outpatients and 80.7% of hospitalized patients (absolute difference, 2.9 percentage points (95% CI, -7.1 to 12.9 percentage points). Subsequent hospital admissions and overall mortality were similar in the outpatient and hospitalization groups. In addition, in a follow up survey, more outpatients were more satisfied with their overall care than hospitalized patients.

COMMENT BY JOSEPH VARON, MD, FACP, FCCP, FCCM

CAP accounts for 10 million physician office visits each year in the United States. The estimated cost of an episode of CAP for hospitalized patients is $6,000 to $7,000 dollars as compared with less than $200 for outpatient treatment. Clinicians are often confronted with the decision as to whether or not to admit these patients to the hospital. Clinical prediction guidelines and severity scoring systems have been developed in an attempt to predict the outcome of patients with CAP.[1,2]

The study by Carratala and associates is important as it presents interesting and compelling data about the safety and efficacy favoring outpatient care for selected low-risk patients with CAP.[3] According to their results, patients in PSI risk classes II and III can be safely treated with levofloxacin as outpatients in the absence of respiratory failure, complicated pleural effusions or social problems compromising outpatient care.

In an era of cost-containment and resource constrains, adequate resource allocation is of extreme importance. Therefore, the findings by Carratala et al have significant economic implications. Clinicians caring for patients with low risk CAP must individually consider each patient and based on the results of this study, consider outpatient therapy in selected patients as long as close follow up is available. ■

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Pharmacology Update

Solifenacin Succinate (VESicare)

By William T. Elliott, MD, FACP and James Chan, PharmD, PhD

SOLIFENACIN SUCCINATE HAS BEEN APPROVED FOR THE treatment of overactive bladder, the third new agent to be approved for this indication in the last 7 months. Solifenacin may be the most bladder specific muscarinic receptor antagonist currently available. The drug is manufactured by Yamanouchi Pharma Technologies Inc in Norman Oklahoma and will be marketed by Yamanouchi Pharma America and GlaxoSmithKline as VESicare™.

Indications

Solifenacin is indicated for the treatment of overactive bladder with symptoms of urge incontinence, urgency, and urinary frequency.[1]

Dosage

The recommended starting dose is 5 mg once daily. The dose may be increased to 10 mg once daily if tolerated. For patients with moderate hepatic impairment or severe renal impairment, or in patients with receiving concomitant administration of a potent CYP3A4 inhibitor, the dose should not exceed 5 mg once daily. Solifenacin is not recommended for patients with severe hepatic impairment.[1] In contrast, drugs that are CYP3A4 inducers may reduce the effect of solifenacin.

Potential Advantages

Solifenacin appears to be more M3 receptor subtype selective for bladder smooth muscle than salivary gland compared to oxybutynin, tolterodine, or darifenacin.[2]

Potential Disadvantages

Most common side effects are dry mouth (10.9%-27.6% vs 4.2 % for placebo) and constipation (5.4%-13.4% vs 2.9%).[1]

Comments

Solifenacin was evaluated in 4 12-week, double-blind, randomized, placebo-controlled trials.[1,3] The drug showed a reduction in number of micturitions/24 hours, reduction in number of urge incontinence episodes/24 hours, and an increase in void volume per micturition. Solifenacin 5 mg and 10 mg showed statistically significant placebo subtracted difference in the reduction in number of micturitions/24 hours of 0.7 to 1.5, reduction in the number of incontinence episodes/24 hours of 0.3 to 0.9, and increase in volume per micturition of 25.5 mL to 44.5 mL. Solifenacin 10 mg daily showed a statistically significant decrease in nocturia by 0.73 compared to 0.52 for placebo. The 5-mg dose did not reach statistical significance.[3] In a dose-finding, active-controlled study, tolterodine (2 mg twice daily) showed a smaller increase in volume voided and a smaller decrease in the frequency of daily voids, but an insignificant difference in the number of incontinent episodes.[4] However the number of subjects randomized to each arm was relatively small (35-41). Solifenacin has an extremely long half-life (45-68 hours). The wholesale cost of solifenacin is $2.80 per day for both strengths.

Clinical Implications

Solifenacin is the newest antimuscarinic agent

approved. While in vitro data suggest that it may be the most bladder specific M3 receptor antagonist clear clinical advantage has not been demonstrated. As with other drug of the class the effects are modest with a large placebo response.[5,6] ■

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CME Questions

9. Consumption of 2500 viable ova of *Trichuris suis* every 3 weeks for 24 weeks had which of the following effects on patients with active Crohn's disease?

a. 50% of patient had severe disease exacerbations.
b. 10% of patients couldn't tolerate worm therapy
c. Over 70% of patients achieved complete remission at 24 weeks.
d. Patients with ileal resections had better results than those with intestinal continuity.
e. Concurrent immunosuppressive therapy improved disease response/remission rates.

10. Which of the following holidays have been shown to affect cancer mortality?

a. Christmas
b. Thanksgiving
c. Birthdays
d. Variable results depending on gender
e. None of the above

11. Initial work-up of drop attacks should include all of the following, *except*:

a. complete blood count.
b. orthostatic blood pressures.
c. visual acuity.
d. gait and balance testing.
e. tilt table testing.

Answers: 9 (c); 10 (e); 11 (e)

Readers are Invited

Readers are invited to submit questions or comments on material seen in or relevant to *Internal Medicine Alert*. Send your questions to: Rob Kimball—Reader Questions, *Internal Medicine Alert*, c/o American Health Consultants, P.O. Box 740059, Atlanta, GA 30374. ■

By Louis Kuritzky, MD

Air Contrast Barium Enema, CT Colonography, and Colonoscopy

CLINICIANS SHARE A COMMON GOAL in respect to early diagnosis and treatment of colon cancer, yet the optimum pathway with which to reach this goal is controversial. Colonoscopy (COL), air contrast barium enema (ACBE), and computed tomographic colonography (CTC, also known as virtual colonoscopy) all have their advocates, but no comparative trial of these methods in the same population has been yet carried out.

Rockey and colleagues recruited a group of patients who were acknowledged to be at high risk for colon cancer: subjects with positive FOBT, a recent history of rectal bleeding, iron deficiency anemia, or a strong family history for colon cancer. This selected population (n = 614) underwent *all three investigations*, accomplished within 14 days of whenever ACBE was performed.

As you may have suspected intuitively, colonoscopy won out on all accounts. For colonic lesions greater than 10 mm, there was no statistically significant difference between ACBE and CTC (sensitivities 48% and 59%, respectively), but COL had a sensitivity of 98%. A similar picture emerged for smaller lesions (6-9 mm). CTC did offer the diagnostic advantage that additional extracolonic abnormalities were discovered in literally over 50% of persons, although most of these abnormalities ultimately were not considered clinically important. On the other hand, 16 highly significant findings were uncovered on CTC: 12 abdominal aortic aneurysms and 4 malignant masses. The results of this trial would encourage colonoscopy being the preferred investigation method, though future evolution in CTC may ultimately challenge this conclusion. ■

Rockey DC, et al. Lancet. 2005;365: 305-311.

Risk Stratification for In-Hospital Mortality in Acutely Decompensated Heart Failure

HEART FAILURE (CHF) REMAINS THE most common diagnosis resulting in hospital admission in the United States. Because the risk for mortality amongst CHF patients at the time of acute decompensation is not insubstantial, it would be valuable to be able to discern which individuals with acutely decompensated CHF are at greatest risk, and provide correspondingly enhanced intensive management strategies to their care (eg, intensive care unit monitoring, rather than telemetry). Risk factors for increased mortality in the setting of chronic heart failure are fairly well defined, and include such parameters as age, ejection fraction, and BNP levels.

The ADHERE population (Acute Decompensated Heart Failure National Registry) has captured data from hospitalized patients at 263 sites in the United States. Using data provided from 33,046 hospitalizations, a mortality risk factor profile was developed. Subsequently, a similar population (n = 33,229) was used to validate the risk stratification system derived retrospectively from the first population.

The single best predictor for mortality was an elevated BUN (> 43 mg/dL). The next best predictors were low SBP (< 115 mm Hg) and elevated creatinine (> 2.75 mg/dL). CHF patient populations stratified using these 3 readily measured items demonstrated a marked 12.9 increased in mortality odds ratio, compared to those with lowest risk as assessed by the same markers. Identifying acutely decompensated CHF patients with unfavorable BUN, SBP, and Creatinine at admission may provide a useful tool for risk stratification and resource allocation. ■

Fonarow GC, et al. JAMA. 2005;293:572-580.

Obesity, Weight Gain, and the Risk of Kidney Stones

THE LIFETIME PREVALENCE OF KIDNEY stones in American men and women (10% and 5%, respectively) merits attention from the clinical community to help identify modifiable risk factors. It has been suggested that insulin resistance, a consistent concomitant of obesity, favors formation of calcium stones and alters metabolism of ammonium, which can unfavorably impact urine pH. Overweight adults excrete more uric acid, which also may favor formation of urate stones.

In an effort to identify relationships between weight, weight gain, BMI, and waist circumference with subsequent kidney stone formation, Taylor and colleagues performed a prospective study that included more than 245,000 individuals, comprised of cohorts from the Health Professionals Follow-up Study, and the Nurses Health Study.

Over a total of 46 years of follow-up, clear patterns of increased risk for stone formation emerged: men or women who weighed more than 220 pounds, men or women who gained more than 35 pounds after young adulthood (age 21 for men, 18 for women) regardless of actual weight attained, and those with BMI over 30 all had increased relative risk of experiencing a kidney stone.

Excessive weight gain and obesity are associated with an augmented risk for kidney stones, and provide another reason to intervene in patients who have weight management issues. ■

Taylor EN, et al. JAMA. 2005;293: 455-462.

Unusual Atrial Flutter?

By Ken Grauer, MD

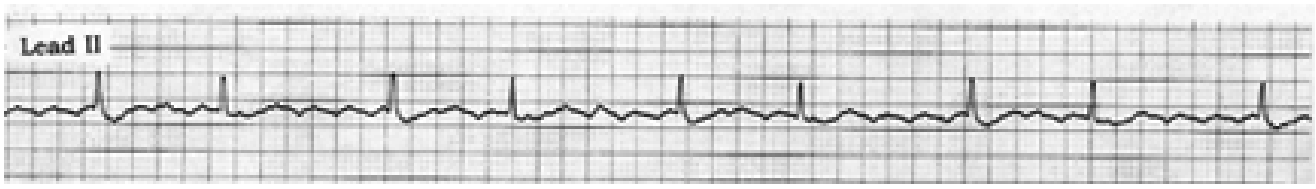

Figure. Rhythm strip obtained from a patient in atrial flutter. What is unusual about this example of atrial flutter?

Clinical Scenario: The lead II rhythm strip shown in the Figure was taken from a patient in atrial flutter. Although difficult to see due to artifact in the baseline, an underlying sawtooth pattern is nevertheless present. In addition, there is something distinctly unusual about this example of atrial flutter. What is it? What clinical diagnosis is suggested as a possible cause of this ECG finding?

Interpretation/Answer: As noted above, despite the presence of significant baseline artifact, there is still suggestion of the underlying sawtooth pattern of atrial flutter. The unusual aspect of this example of atrial flutter is patterned beating of ventricular response, which regularly occurs with alternating short-long cycles. This presence of grouped beating suggests Wenckebach conduction, which is a highly characteristic finding of digitalis toxicity. Since the underlying rhythm is atrial flutter, the only place that Wenckebach conduction can be occurring in this supraventricular (narrow QRS complex) rhythm is at the lower level of the AV node. A distinct pattern of group beating in a patient with either atrial fibrillation or atrial flutter is therefore indicative of Wenckebach conduction *out of* the AV node, and should strongly suggest digitalis toxicity if the patient is taking this medication. ■

In Future Issues:

Sugar is Sweet but Snoring is Boring

PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.*

The Risk of Aspirin Withdrawal in ACS Patients

Stopping aspirin may be hazardous to your health, according to recent research. Patients with heart disease who developed acute coronary syndrome (ACS) were questioned to determine whether their aspirin therapy had recently been interrupted. Thirteen percent of patients with recurrent ACS had stopped aspirin within the previous month. The incidence of ST-segment elevation ACS was higher in those who stopped aspirin, compared to those who did not stop aspirin (39% vs 18%; *P*=0.001). The risk of stopping aspirin was particularly high for patients who had uncoated stents. The mean delay between aspirin withdrawal and acute coronary event was 10 days. Patients withdrew from aspirin for a number of reasons including minor surgery, endoscopy, dental treatment, bleeding, and noncompliance. The authors conclude that aspirin withdrawal in patients with coronary disease represents a risk for the occurrence of a new coronary event (*J Am Coll Cardiol.* 2005;45:456-459). The risk of ischemic stroke may be as much as 3 times higher with interruption of aspirin therapy, according to presentation at the International Stroke Conference. Researchers from Switzerland noted that the odds ratio for stroke or TIAs associated with aspirin discontinuation was 3.25 (95% CI). Seventy-seven percent of ischemic strokes related to aspirin discontinuation occurred in the first 8 days after aspirin was stopped, with remaining strokes occurring from day 9 to day 30. The reasons cited for discontinuing aspirin were primarily minor bleeding and minor surgical procedures—many of which can safely be performed (many dental procedures, cataract surgery among others) while patients are taking aspirin (strokeconference.americanheart.org /portal /strokeconference/sc/02.02.05c).

Neuropsychiatric Symptoms of Dementia

Treatment of neuropsychiatric symptoms in patients with dementia represents one of the biggest challenges in primary care. Dementia is diagnosed by the loss of cognitive function, but other symptoms are often more prominent including agitation, aggression, delusions, hallucinations, repetitive vocalizations, and wandering, among others. Many classes of psychiatric medications are used to treat neuropsychiatric symptoms in dementia including antidepressants, anxiolytics, anticonvulsants, cholinesterase inhibitors, typical antipsychotics, and atypical antipsychotics. Often these drugs are used in combination, and the cocktail can get confusing and even dangerous for patients and caregivers alike. A new review of the topic in the "Clinician's Corner" section of the February 2nd *Journal of the American Medical Association* helps clarify treatment options. The authors reviewed 29 articles that met their inclusion criteria. Among typical antipsychotics, which

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include haloperidol, thiothixene, chlorpromazine, trifluoperazine, and acetophenazine, there was no difference in the efficacy among these drugs in treating neuropsychiatric symptoms. Haloperidol may be somewhat more effective for treating aggression but not agitation. Side effects including extrapyramidal symptoms and somnolence are common with these agents. Antidepressants, including the SSRIs, were also relatively ineffective, except for treatment of depression associated with dementia. The best evidence for efficacy was found in the atypical antipsychotic group, especially risperidone (Risperdal) and olanzapine (Zyprexa). These drugs were found to have a modest effect on agitation/aggression, hallucinations, and delusions. A higher risk of stroke was found in the most recent trial (prompting a "Dear Doctor" letter from Janssen in April 2003). The cholinesterase inhibitors group including galantamine (Reminyl), donepezil (Aricept), and rivastigmine (Exelon) were somewhat disappointing with regard to neuropsychiatric symptoms, with minimal improvement of questionable clinical benefit. Memantine, the relatively new N-methly-D-asparte antagonist was seen to improve cognitive and functional parameters, but also did not improve neuropsychiatric symptoms. The authors stress that the management of neuropsychiatric symptoms in dementia "should always begin with an assessment of the medical (eg, pain and delirium) and environmental causes of the behavior." They also recommend starting with a cholinesterase inhibitor if the patient is not already receiving one, because they are relatively well tolerated and may benefit cognition and function (*JAMA.* 2005;293:596-608).

FDA Actions

Pfizer has received FDA approval to market pregabalin (Lyrica) for the treatment of painful diabetic neuropathy and post-herpetic neuralgia, the 2 most common types of neuropathic pain. Pregabalin was shown to be effective in a company-sponsored study of 338 patients with a 1-5 year history of painful, diabetic, peripheral neuropathy who were randomized to receive the drug at 1 of 3 doses or placebo for 5 weeks. Patients in the 300 and 600 mg/day doses showed improvements in mean pain score vs placebo ($P = 0.0001$), but no improvement was seen at the 75 mg/day dose. The higher doses also resulted in improvements in weekly pain score, sleep interferes score, patient global impression of change, clinical global impression of change, and lifestyle surveys. The most common side effects were dizziness and somnolence (*Neurology.* 2004;63:2104-2110). Pregabalin is a 3-substituted analogue of gamma-amino butyric acid (GABA), and is closely related to Pfizer's gabapentin (Neurontin), which recently lost its patent and is now available as a generic. Pregabalin is currently under review by the FDA for the treatment of partial seizures.

The FDA has also approved palifermin (Kepivance-Amgen) to decrease the incidence and duration of severe oral mucositis in patients with hematologic malignancies undergoing chemotherapy, with or without radiation, in preparation for bone marrow transplantation. The drug, which is the first agent to be approved for this indication, stimulates epithelial cell growth in mucous membranes. It is given prior to fractionated total body irradiation and high dose chemotherapy, and repeated after bone marrow transplantation. The drug's efficacy in non-hematologic malignancies has not been shown.

Citalopram (Celexa) is now available in generic tablets and liquid. The liquid formulation recently joined the tablet formulation for the popular SSRI antidepressant.

Extended release buproprion (Wellbutrin SR) is now available as a generic in the 200 mg strength.

Fosinopril/HCTZ (Monopril) has also joined the generic ranks in 10/12.5 mg and 20/12.5 mg strengths.

The FDA has also approved a generic fentanyl transdermal system (Duragesic) for the treatment of severe chronic pain. The new generic, which is produced by Mylan technologies, provides a constant dose of the drug for 72 hours.

Canada has suspended marketing of Adderall and Adderall XR because of reports of sudden unexplained death (SUD) in children taking the drugs. SUD has been associated with amphetamine abuse and has been reported in children with heart disease taking prescribed doses of amphetamines, including Adderall and Adderall XR. These latest reports of SUD have been in children without structural heart disease who were taking the drugs as prescribed. The FDA is looking at these reports, but “does not feel that any immediate changes are warranted in the FDA labeling or approved use of this drug.” More information is available on the FDA web site at FDA.gov.