

For Best Results, Consider Migraine Complex

BY BRUCE K. DIXON

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SCOTTSDALE, ARIZ. — Acute migraine cannot be managed effectively without a therapeutic partnership between doctor and patient, and a full understanding of the disabling features of each patient's headache episodes, Dr. Lawrence C. Newman said.

"Most of us are focused on the head pain, but when you talk to patients, many

[of them] will say they are not disabled by the head pain as much as they are by some of the migraine-associated features such as nausea and vomiting. So by focusing on the head pain, you're not truly helping that individual," Dr. Newman said at a symposium sponsored by the American Headache Society.

It's important to consider the entire migraine complex, to treat pain and associated symptoms using the stratified care approach, and to specifically ask patients

about disability, said Dr. Newman, who is director of the Roosevelt Headache Institute in New York City.

"All too often we get a history that says the patient is getting, for example, two headaches a month and we leave it at that and give him medications to take on those 2 days acutely, but if you delve a bit more into that history, you'll see that one of those attacks is so severe that the patient isn't going to work regularly," he said.

Dr. Newman said his colleagues must

make sure they know what medications each patient has taken in the past, what the dosages were, what has or has not worked, and how frequently the attacks occur.

Once a correct migraine diagnosis is made, therapy can be undertaken based on the disability that the headaches generate, said Dr. Newman, who explained that stratified care based on disability has been shown to be superior to step care (JAMA 2000;284:2599-605).

"Using the MIDAS [Migraine Disability Assessment] Questionnaire, stratify the patient into a low-need group (MIDAS score 0-5), a moderate-need group (6-10), or a high-need group (11+)," he said. "Again, you have to specifically ask the patient about the disability caused by her headaches.

"For those [patients] with a low need, start with an NSAID or other nonspecific agent. If it doesn't work, then step up the care to a specific agent for migraine.

"But as the disability increases, you're more apt to target right away using a specific agent, whether it's a triptan or a dihydroergotamine or ergotamine tartrate, and in the upper stages you need to consider placing the patient on prophylactic therapy as well," Dr. Newman explained.

Unlike preventive medications, which are started at low doses, Dr. Newman explained that medications for acute migraine are useful when started at higher doses, and decreased if there is a tolerability issue. "The reason I say that is that all too often patients are put on a low dose, they come back saying it doesn't work, and they will not go back on what was potentially a useful medication."

Dr. Newman said in studies of acute migraine treatment, especially those involving triptans, patients on higher doses had better therapeutic responses than those on lower doses, but did not have more adverse events.

Nor should physicians worry about early use of short-term medications leading to overuse. "In fact, those patients who treat their attacks early are much more likely to take one tablet, or one injection, or one nasal spray, be done with their headache and not have to take more medication," he said.

To increase the effectiveness of treatment, medicate early and at the appropriate dose. "If necessary, increase the dose, or add adjuvants such as metoclopramide or an NSAID, which can increase the effectiveness of the acute medication," Dr. Newman said.

Similarly, if the first triptan doesn't work, don't hesitate to try a different drug in the same class. "The good news is that among patients who don't respond to a specific triptan, about half of them will respond to a different triptan," Dr. Newman said, adding that it's important to be aware of drug interactions and co-occurring conditions such as hypertension/hypotension, angina, ulcer disease, vertigo, asthma, and allergies.

Dr. Newman declared relationships with Allergan, Endo Pharmaceuticals, Pfizer Inc., Merck & Co., and Ortho-McNeil Inc., as a consultant and/or member of the advisory board or speakers' bureau. ■

Infrequent - cellulitis, dental caries, vaginitis, vaginal infection, cystitis, vaginal mycosis, eye infection, gastroenteritis, onychomycosis, vaginal candidiasis, otitis media, folliculitis, candidiasis, otitis externa, pyelonephritis, rash pustular; *Rare* - appendicitis, septic shock.

Injury, Poisoning, and Procedural Complications: Frequent - fall, skin laceration, contusion, fracture; *Infrequent* - blister, scratch, joint sprain, burn, muscle strain, periorbital haematoma, arthropod bite/sting, head injury, sunburn; *Rare* - joint dislocation, alcohol poisoning, road traffic accident, self mutilation, eye penetration, injury asphyxiation, poisoning, heat exhaustion, heat stroke.

Investigations: Frequent - weight decreased, blood creatine phosphokinase increased; *Infrequent* - blood glucose increased, heart rate increased, body temperature increased, alanine aminotransferase increased, blood cholesterol increased, white blood cell count increased, haemoglobin decreased, aspartate aminotransferase increased, blood urea increased, electrocardiogram ST segment abnormal (including depression, elevation), haematocrit decreased, hepatic enzyme increased, blood bilirubin increased, blood glucose decreased, blood creatinine increased, blood alkaline phosphatase increased, blood pressure decreased, blood potassium decreased, blood urine present, electrocardiogram QT corrected interval prolonged; *Rare* - transaminases increased, blood triglycerides increased, blood uric acid increased, cardiac murmur, eosinophil count increased, neutrophil count increased, platelet count increased, red blood cell count decreased, white blood cell count decreased, white blood cells urine positive, bacteria urine identified, blood lactate dehydrogenase increased, blood potassium increased, neutrophil count decreased, urine output decreased, blood creatine phosphokinase MB increased, ECG signs of myocardial ischemia, electrocardiogram T-wave inversion, heart rate decreased, tuberculin test positive, glucose urine present, glycosylated haemoglobin increased, glucose tolerance decreased, glycosylated haemoglobin decreased, muscle enzyme increased.

Metabolism and Nutrition Disorders: Frequent - decreased appetite (including diet refusal, markedly reduced dietary intake), dehydration; *Infrequent* - anorexia, increased appetite, hypercholesterolaemia, hypokalaemia, hyperglycaemia, diabetes mellitus, hypoglycaemia, hyponatraemia, diabetes mellitus non-insulin-dependent, hyperlipidaemia, obesity (including overweight), polydipsia; *Rare* - hypertriglyceridaemia, gout, hypernatraemia, weight fluctuation, diabetes mellitus inadequate control.

Musculoskeletal and Connective Tissue Disorders: Frequent - musculoskeletal pain (including neck, jaw, chest wall, bone, buttock, groin, flank, musculoskeletal chest, pubic, and sacral), muscle rigidity, muscle cramp; *Infrequent* - muscle twitching, joint swelling, muscle spasms, muscle tightness, arthritis, osteoarthritis, muscular weakness, joint range of motion decreased, sensation of heaviness; *Rare* - tendonitis, osteoporosis, trismus, arthropathy, bursitis, osteostosis, night cramps, coccydynia, joint contracture, localised osteoarthritis, osteopenia, rhabdomyolysis, costochondritis, rheumatoid arthritis, torticollis.

Nervous System Disorders: Frequent - lethargy, dyskinesia; *Infrequent* - disturbance in attention, parkinsonism, dystonia, drooling, cogwheel rigidity, dysarthria, paraesthesia, hypoaesthesia, loss of consciousness (including depressed level of consciousness), hypersomnia, psychomotor hyperactivity, balance disorder, cerebrovascular accident, hypokinesia, tardive dyskinesia, memory impairment, amnesia, ataxia, dementia, hypotonia, burning sensation, dysgeusia, restless leg syndrome, hypertension, Parkinson's disease, akinesia, dysphasia, transient ischaemic attack, facial palsy, hemiparesis, myoclonus, scintillating scintillations, bradykinesia, coordination abnormal, cognitive disorder, syncope vasovagal, carpal tunnel syndrome, hyporeflexia, intention tremor, muscle contractions involuntary, sleep apnea syndrome, dementia Alzheimer's type, epilepsy, hyperreflexia, mastication disorder, mental impairment, nerve compression, parkinsonian gait, tongue paralysis, aphasia, choreoathetosis, formication, masked facies, neuralgia, paresthesia oral, parkinsonian rest tremor, cerebral haemorrhage, dizziness exertional, hyperaesthesia, haemorrhage intracranial, ischaemic stroke, judgment impaired, subarachnoid haemorrhage.

Psychiatric Disorders: Frequent - schizophrenia (including schizoaffective disorder), depression (including depressive symptom), hallucination (including auditory, visual, tactile, mixed, olfactory, and somatic), mood altered (including depressed, euphoric, elevated, and mood swings), paranoia, irritability, suicidal ideation, confusional state, aggression, mania, delusion (including persecutory, perception, somatic, and grandeur); *Infrequent* - tension, nervousness, nightmare, excitability, panic attack (including panic disorder, panic disorder with agoraphobia, and panic reaction), abnormal dreams, apathy, libido decreased, hostility, suicide attempt, bipolar disorder (including bipolar I), libido increased, anger, delirium, acute psychosis, disorientation, bruxism, hypomania, obsessive-compulsive disorder (including obsessive thoughts), mental status changes, crying, dysphoria, completed suicide, flat affect, impulsive behaviour; *Rare* - blunted affect, cognitive deterioration, logorrhea, psychomotor agitation, social avoidant behaviour, psychomotor retardation, suspiciousness, affect lability, anorgasmia, fear, homicidal ideation, tic, premature ejaculation, dysphemia, bradyphrenia, derealisation, depersonalisation.

Renal and Urinary Disorders: Infrequent - pollakiuria, dysuria, haematuria, urinary retention, renal failure (including acute and chronic), urinary hesitation, enuresis, nephrolithiasis, micturition urgency, polyuria; *Rare* - nocturia, proteinuria, glycosuria, calculus urinary, azotaemia.

Reproductive System and Breast Disorders: Infrequent - erectile dysfunction, vaginal discharge, amenorrhoea, vaginal haemorrhage, menstruation irregular, menorrhagia, premenstrual syndrome, testicular pain, genital pruritus female, ovarian cyst, benign prostatic hyperplasia, prostatitis; *Rare* - gynaecomastia, priapism (including spontaneous penile erection), breast pain, pelvic pain, epididymitis, galactorrhoea, uterine haemorrhage.

Respiratory, Thoracic, and Mediastinal Disorders: Frequent - dyspnoea (including exertional); *Infrequent* - sinus congestion, rhinorrhoea, wheezing, epistaxis, asthma, hiccups, productive cough, chronic obstructive airways disease (including exacerbated), rhinitis allergic, pneumonia aspiration, pulmonary congestion, sinus pain, respiratory distress, dry throat, hoarseness; *Rare* - bronchopneumopathy, haemoptysis, respiratory arrest, sneezing, hypoxia, pulmonary embolism, pulmonary oedema (including acute), respiratory failure, bronchospasm, nasal dryness, paranasal sinus hypersecretion, pharyngeal erythema, rhonchi, tonsillar hypertrophy, asphyxia, Mendelson's syndrome.

Skin and Subcutaneous Tissue Disorders: Infrequent - hyperhidrosis, erythema, pruritis (including generalised), dry skin, decubitus ulcer, dermatitis (including allergic, seborrhoeic, acneiform, exfoliative, bullous, neurodermatitis), ecchymosis, skin ulcer, acne, eczema, hyperkeratosis, swelling face, skin discoloration, photosensitivity reaction, skin irritation, alopecia, rash maculopapular, cold sweat, scab, face oedema, dermal cyst, psoriasis, night sweats, rash erythematous; *Rare* - rash scaly, urticaria, rash maculopapular, rosacea, seborrhoea, periorbital oedema, rash vesicular.

Vascular Disorders: Frequent - hypotension; *Infrequent* - hot flush (including flushing), haematoma, deep vein thrombosis, phlebitis; *Rare* - pallor, petechiae, varicose vein, circulatory collapse, haemorrhage, thrombophlebitis, shock.

Other Adverse Events Observed During the Premarketing Evaluation of Aripiprazole Injection

Following is a list of MedDRA terms that reflect treatment-emergent adverse events as defined in the introduction to the ADVERSE REACTIONS section reported by patients treated with aripiprazole injection at

doses ≥ 1 mg/day during any phase of a trial within the database of 749 patients. All reported events are included except those already listed in Table 2 or 3, or other parts of the ADVERSE REACTIONS section, those considered in the WARNINGS or PRECAUTIONS, those event terms which were so general as to be uninformative, events reported with an incidence of $\leq 0.05\%$ and which did not have a substantial probability of being acutely life-threatening, events that are otherwise common as background events, and events considered unlikely to be drug related. It is important to emphasize that, although the events reported occurred during treatment with aripiprazole injection, they were not necessarily caused by it.

Events are further categorized by MedDRA system organ class and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Ear and Labyrinth Disorders: Infrequent - hyperacusis.

General Disorders and Administration Site Conditions: Infrequent - injection site stinging, abnormal feeling, injection site pruritus, injection site swelling, venipuncture site bruise.

Infections and Infestations: Infrequent - bacteruria, urinary tract infection, urosepsis.

Investigations: Infrequent - blood pressure abnormal, heart rate irregular, electrocardiogram T-wave abnormal.

Psychiatric Disorders: Infrequent - intentional self-injury.

Respiratory, Thoracic, and Mediastinal Disorders: Infrequent - pharyngolaryngeal pain, nasal congestion.

Vascular Disorders: Infrequent - blood pressure fluctuation.

Other Events Observed During the Postmarketing Evaluation of Aripiprazole

Voluntary reports of adverse events in patients taking aripiprazole that have been received since market introduction and not listed above that may have no causal relationship with the drug include rare occurrences of allergic reaction (eg, anaphylactic reaction, angioedema, laryngospasm, oropharyngeal spasm, pruritis, or urticaria), grand mal seizure, and jaundice.

DRUG ABUSE AND DEPENDENCE

Controlled Substance

ABILIFY (aripiprazole) is not a controlled substance.

Abuse and Dependence

Aripiprazole has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. In physical dependence studies in monkeys, withdrawal symptoms were observed upon abrupt cessation of dosing. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of ABILIFY misuse or abuse (eg, development of tolerance, increases in dose, drug-seeking behavior).

OVERDOSAGE

MedDRA terminology has been used to classify the adverse events.

Human Experience

A total of 76 cases of deliberate or accidental overdose with oral aripiprazole have been reported worldwide. These include overdoses with oral aripiprazole alone and in combination with other substances. No fatality was reported from these cases. Of the 44 cases with known outcome, 33 recovered without sequelae and one recovered with sequelae (mydriasis and feeling abnormal). The largest known acute ingestion with a known outcome involved 1080 mg of oral aripiprazole (36 times the maximum recommended daily dose) in a patient who fully recovered. Included in the 76 cases are 10 cases of deliberate or accidental overdose in children (age 12 and younger) involving oral aripiprazole ingestions up to 195 mg with no fatalities.

Common adverse events (reported in at least 5% of all overdose cases) reported with oral aripiprazole overdose (alone or in combination with other substances) include vomiting, somnolence, and tremor. Other clinically important signs and symptoms observed in one or more patients with aripiprazole overdoses (alone or with other substances) include acidosis, aggression, aspartate aminotransferase increased, atrial fibrillation, bradycardia, coma, confusional state, convulsion, blood creatine phosphokinase increased, depressed level of consciousness, hypertension, hypokalaemia, hypotension, lethargy, loss of consciousness, QRS complex prolonged, QT prolonged, pneumonia aspiration, respiratory arrest, status epilepticus, and tachycardia.

Management of Overdosage

No specific information is available on the treatment of overdose with aripiprazole. An electrocardiogram should be obtained in case of overdose and, if QTc interval prolongation is present, cardiac monitoring should be instituted. Otherwise, management of overdose should concentrate on supportive therapy, maintaining an adequate airway, oxygenation and ventilation, and management of symptoms. Close medical supervision and monitoring should continue until the patient recovers.

Charcoal: In the event of an overdose of ABILIFY, an early charcoal administration may be useful in partially preventing the absorption of aripiprazole. Administration of 50 g of activated charcoal, one hour after a single 15-mg oral dose of aripiprazole, decreased the mean AUC and C_{max} of aripiprazole by 50%.

Hemodialysis: Although there is no information on the effect of hemodialysis in treating an overdose with aripiprazole, hemodialysis is unlikely to be useful in overdose management since aripiprazole is highly bound to plasma proteins.

Tablets manufactured by Otsuka Pharmaceutical Co., Ltd., Tokyo, 101-8535 Japan or


Bristol-Myers Squibb Company, Princeton, NJ 08543 USA

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