

Handling Difficult Encounters

Chapter FastFACTS

- 1. A patient's fear, anxiety, or illness could trigger a difficult encounter.**
- 2. Collaborating with the patient instead of withdrawing can help defuse conflict.**
- 3. Active listening and staying calm are among effective ways to cope with an angry patient.**
- 4. While there are some exceptions, it's usually best to deliver bad news in person.**
- 5. End-of-life discussions should take place with little fanfare and routinely with all patients.**

When George Blackall, PsyD, MBA, worked at a chronic pain clinic, one patient called daily, demanding and aggressive because he was still in pain and angry that they hadn't been able to help relieve it. The staff became angry and frustrated by his calls because they felt powerless to influence any change in his behavior. "Instead of calling the patient and yelling at him for calling the clinic six times that week, I sat down with him and said, 'I wonder if you're feeling very alone with your pain,' and 'I wonder if you're scared by your pain,'" says Dr. Blackall, now professor of pediatrics and humanities at Penn State Hershey Medical Children's Hospital, Hershey, Pa. The patient's answers helped him and his staff better understand this patient's struggles and led to a more collaborative relationship.

Difficult patient situations can cause more than just a bad day; they can affect how you feel about medicine overall, according

7 out of 10 patients
with untreated hypertension present with an
overactive RAAS^{1,2}

IN HYPERTENSION

VALTURNA offers both superior BP efficacy and more comprehensive RAAS inhibition than valsartan*

A SMART VALTURNATIVE



Indication

VALTURNA is indicated for the treatment of hypertension in adults.

VALTURNA may be substituted for the titrated components. VALTURNA may be used in patients whose blood pressure is not adequately controlled on aliskiren or any ARB monotherapy and as initial therapy in patients who are likely to need multiple medications to achieve their blood pressure goals.

The choice of VALTURNA as initial therapy should be based on an assessment of potential benefits and risks. The decision to use a combination as initial therapy should be individualized and should be shaped by considerations such as baseline blood pressure, target goal, and the incremental likelihood of achieving goal with a combination product compared to monotherapy.

Important Safety Information

WARNING: AVOID USE IN PREGNANCY: When pregnancy is detected, discontinue VALTURNA as soon as possible. When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin-aldosterone system (RAAS) can cause injury and even death to the developing fetus. [See *Warnings and Precautions* (5.1)]

Angioedema: Angioedema of the face, extremities, lips, tongue, glottis, and/or larynx has been reported in patients treated with aliskiren and has necessitated hospitalization and intubation. This may occur at any time during treatment and has occurred in patients with and without a history of angioedema with ACE inhibitors (ACEIs) or angiotensin receptor antagonists. Discontinue aliskiren immediately in patients who develop angioedema, and provide appropriate therapy and monitoring until signs and symptoms resolve. Aliskiren should not be readministered.

Hypotension: In clinical trials, an excessive fall in blood pressure (hypotension) was seen rarely (<0.5%) in patients with uncomplicated hypertension treated with VALTURNA. Initiate therapy cautiously in patients with heart failure or recent myocardial infarction (MI) and in patients undergoing surgery or dialysis.

Volume- and/or Salt-depletion: Volume- and/or salt-depletion should be corrected in patients prior to administering VALTURNA or symptomatic hypotension may occur. Patients taking VALTURNA should be observed for clinical signs of fluid or electrolyte imbalance.

Renal Considerations: Care should be used when dosing VALTURNA in patients with severe renal impairment. As a consequence of inhibiting the RAAS, changes in renal function may be observed in susceptible individuals (eg, patients with renal artery stenosis or severe heart failure). Patients with severe renal impairment were excluded from clinical trials with VALTURNA in hypertension.

In studies of ACEIs in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen have been reported. There has been no long-term use of valsartan in patients with unilateral or bilateral renal artery stenosis, but an effect similar to that seen with ACEIs should be anticipated.

In patients with severe heart failure whose renal function may depend on the activity of the RAAS, treatment with ACEIs and angiotensin receptor antagonists has been associated with oliguria or progressive azotemia and (rarely) with acute renal failure or death. Similar outcomes have been reported with valsartan.

- Greater SBP reductions vs valsartan
- More comprehensive RAAS inhibition than an ARB
- Established safety and tolerability
- Single-tablet dosing
- \$15 co-pay available for most patients*

The clinical implications of differences in effect on RAAS components are not known.

*Valid for those patients with private insurance only.

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Patient is responsible for reporting receipt of program rewards to any private insurer that pays for or reimburses any part of the prescriptions filled with this program.

This offer will expire on 12/31/2010.

To learn more about Valturna, talk to your Novartis sales representative.

Important Safety Information (cont'd)

Hepatic Considerations: As a majority of valsartan is eliminated in the bile, valsartan should be used with care in patients with mild-to-moderate hepatic impairment, including patients with biliary obstructive disorders, because of lower valsartan clearance.

Patients With CHF and Post-MI: Include assessment of renal function when evaluating patients with heart failure or post-MI. Dosage reduction and/or discontinuation of a diuretic and/or valsartan may be required.

Hyperkalemia: In short-term controlled trials of VALTURNA, the incidence of hyperkalemia ($K^+ > 5.5$ mEq/L) was about 1%-2% higher than with corresponding monotherapies or placebo.

Electrolyte Imbalance: Periodic determinations of serum electrolytes to detect possible electrolyte imbalances is advised, particularly in patients at risk for hyperkalemia such as those with renal impairment.

Cyclosporine: It is not recommended to prescribe VALTURNA for patients who also take cyclosporine.

Furosemide: When aliskiren was coadministered with furosemide, the AUC and C_{max} of furosemide were reduced by about 30% and 50%, respectively. Patients receiving furosemide could find its effect diminished after starting aliskiren.

Common AEs: The most common adverse events (AEs) that occurred more frequently with VALTURNA than placebo were fatigue (2.6% vs 1.4%), nasopharyngitis (2.6% vs 2.2%), diarrhea (1.4% vs 0.9%), upper respiratory tract infection (1.4% vs 1.1%), urinary tract infection (1.4% vs 0.6%), influenza (1.1% vs 0.2%), and vertigo (1.1% vs 0.3%).

Please see Brief Summary of Prescribing Information, including Boxed WARNING, on following pages.

References: 1. Blumenfeld JD, Laragh JH. Renin system analysis: a rational method for the diagnosis and treatment of the individual patient with hypertension. *Am J Hypertens.* 1998;11(7): 894-896. 2. Alderman MH, Cohen HW, Sealey JE, Laragh JH. Plasma renin activity levels in hypertensive persons: their wide range and lack of suppression in diabetic and in most elderly patients. *Am J Hypertens.* 2004;17(1):1-7. 3. Valturna [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2010.

 **Valturna**[®]
(aliskiren and valsartan, USP) tablets

150/160 • 300/320 mg

A smart option in BP lowering

 **NOVARTIS**

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C-VAT-100016

Valturna *(aliskiren and valsartan, USP)* Tablets

Initial U.S. Approval: 2009

BRIEF SUMMARY: Please see package insert for full prescribing information.

WARNING: AVOID USE IN PREGNANCY

When pregnancy is detected, discontinue Valturna as soon as possible. When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin-aldosterone system can cause injury and death to the developing fetus. [See *Warnings and Precautions (5.1)*].

1 INDICATIONS AND USAGE

Valturna is indicated for the treatment of hypertension.

Add-on Therapy

A patient whose blood pressure is not adequately controlled with aliskiren alone or valsartan (or another angiotensin receptor blocker) alone may be switched to combination therapy with Valturna.

Replacement Therapy

Valturna may be substituted for the titrated components.

Initial Therapy

Valturna may be used as initial therapy in patients who are likely to need multiple drugs to achieve their blood pressure goals.

The choice of Valturna as initial therapy should be based on an assessment of potential benefits and risks.

Patients with Stage 2 hypertension are at a relatively high risk for cardiovascular events (such as strokes, heart attacks, and heart failure), kidney failure, and vision problems, so prompt treatment is clinically relevant. The decision to use a combination as initial therapy should be individualized and should be shaped by considerations such as baseline blood pressure, the target goal, and the incremental likelihood of achieving goal with a combination compared to monotherapy. Individual blood pressure goals may vary based upon the patient's risk.

Data from the high-dose multifactorial study [see *Clinical Studies (14)* in the full prescribing information] provide estimates of the probability of reaching a target blood pressure with Valturna compared to aliskiren or valsartan monotherapy. The figures below provide estimates of the likelihood of achieving systolic or diastolic blood pressure control with Valturna 300/320 mg, based upon baseline systolic or diastolic blood pressure. The curve of each treatment group was estimated by logistic regression modeling. The estimated likelihood at the right tail of each curve is less reliable because of a small number of subjects with high baseline blood pressures.

Figure 1: Probability of Achieving Systolic Blood Pressure (SBP) <140 mmHg in Patients at Endpoint

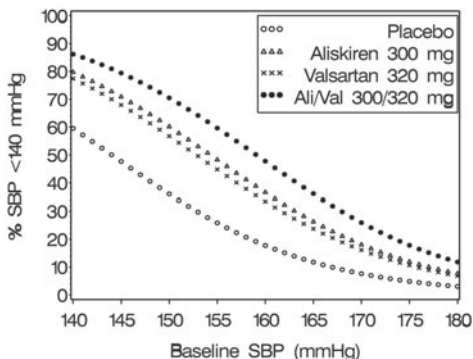


Figure 2: Probability of Achieving Diastolic Blood Pressure (DBP) <90 mmHg in Patients at Endpoint

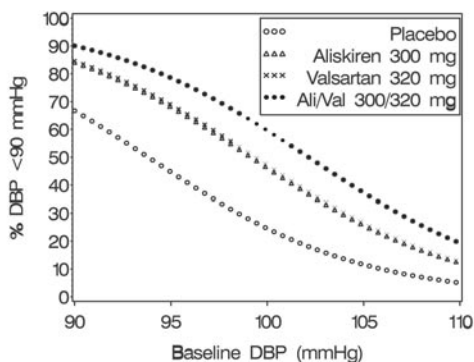


Figure 3: Probability of Achieving Systolic Blood Pressure (SBP) <130 mmHg in Patients at Endpoint

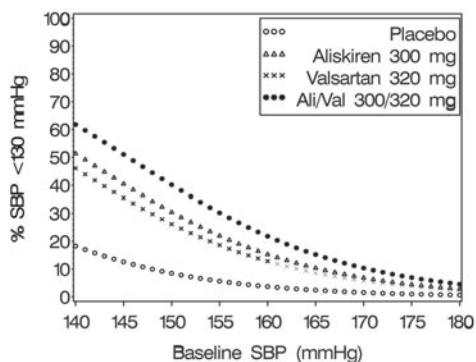
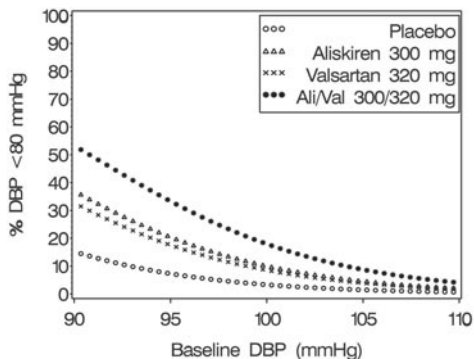


Figure 4: Probability of Achieving Diastolic Blood Pressure (DBP) <80 mmHg in Patients at Endpoint



At all levels of baseline blood pressure, the probability of achieving any given diastolic or systolic goal is greater with the combination than for either monotherapy. For example, the mean baseline SBP/DBP for patients participating in this multifactorial study was 154/100 mmHg. A patient with a baseline blood pressure of 154/100 mmHg has about a 51% likelihood of achieving a goal of <140 mmHg (systolic) and 46% likelihood of achieving <90 mmHg (diastolic) on aliskiren alone, and the likelihood of achieving these goals on valsartan alone is about 47% (systolic) and 47% (diastolic). The likelihood of achieving these goals on Valtorna rises to about 62% (systolic) and 60% (diastolic). The likelihood of achieving these goals on placebo is about 28% (systolic) and 25% (diastolic) [see *Dosage and Administration (2) and Clinical Studies (14) in the full prescribing information*].

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Fetal/Neonatal Morbidity and Mortality

Valtorna can cause fetal harm when administered to a pregnant woman. If this drug is used during pregnancy, or if a patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus.

Drugs that act directly on the renin-angiotensin-aldosterone system can cause fetal and neonatal morbidity and death when administered to pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus [see *Use in Specific Populations (8.1)*]. In several dozen published cases, use of ACE inhibitors during the second and third trimesters of pregnancy was associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. In addition, first trimester use of ACE inhibitors has been associated with birth defects in retrospective data.

5.2 Head and Neck Angioedema

Aliskiren

Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with aliskiren and has necessitated hospitalization and intubation. This may occur at any time during treatment and has occurred in patients with and without a history of angioedema with ACE inhibitors or angiotensin receptor antagonists. If angioedema involves the throat, tongue, glottis or larynx, or if the patient has a history of upper respiratory surgery, airway obstruction may occur and be fatal. Patients who experience these effects, even without respiratory distress, require prolonged observation since treatment with antihistamines and corticosteroids may not be sufficient to prevent respiratory involvement. Prompt administration of subcutaneous epinephrine solution 1:1000 (0.3 to 0.5 mL) and measures to ensure a patent airway may be necessary.

Discontinue aliskiren immediately in patients who develop angioedema and do not readminister.

5.3 Hypotension

An excessive fall in blood pressure (hypotension) was rarely seen (<0.5%) in patients with uncomplicated hypertension treated with Valtorna in controlled trials.

In patients with an activated renin-angiotensin-aldosterone system, such as volume- or salt-depleted patients receiving high doses of diuretics, symptomatic hypotension may occur in patients receiving renin-angiotensin-aldosterone system (RAAS) blockers. Correct these conditions prior to the administration of Valtorna, or start the treatment under close medical supervision.

Initiate therapy cautiously in patients with heart failure or recent myocardial infarction and in patients undergoing surgery or dialysis. Patients with heart failure or post-myocardial infarction patients given valsartan commonly have some reduction in blood pressure, but discontinuation of therapy because of continuing symptomatic hypotension usually is not necessary when dosing instructions are followed. In controlled trials in heart failure patients, the incidence of hypotension in valsartan-treated patients was 5.5% compared to 1.8% in placebo-treated patients. In the Valsartan in Acute Myocardial Infarction Trial (VALIANT), hypotension in post-myocardial infarction patients led to permanent discontinuation of therapy in 1.4% of valsartan-treated patients and 0.8% of captopril-treated patients.

If an excessive fall in blood pressure occurs with Valturna, place the patient in the supine position and, if necessary, give an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

5.4 Patients with Severe Renal Impairment

Valturna

Patients with severe renal impairment were excluded from clinical trials with Valturna in hypertension.

Aliskiren

Patients with severe renal dysfunction (creatinine 1.7 mg/dL for women and 2.0 mg/dL for men and/or estimated GFR <30 mL/min), a history of dialysis, nephrotic syndrome, or renovascular hypertension were excluded from clinical trials of aliskiren in hypertension. Safety information with aliskiren and the potential for other drugs acting on the renin-angiotensin-aldosterone system to increase serum creatinine and blood urea nitrogen are not available.

Valsartan

In studies of ACE inhibitors in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen have been reported. In a 4-day trial of valsartan in 12 hypertensive patients with unilateral renal artery stenosis, no significant increases in serum creatinine or blood urea nitrogen were observed. There has been no long-term use of valsartan in patients with unilateral or bilateral renal artery stenosis, but an effect similar to that seen with ACE inhibitors should be anticipated.

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may occur particularly in volume depleted patients. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists has been associated with oliguria or progressive azotemia and (rarely) with acute renal failure or death. Similar outcomes have been reported with valsartan.

5.5 Patients with Hepatic Impairment

Valsartan

As the majority of valsartan is eliminated in the bile, patients with mild-to-moderate hepatic impairment, including patients with biliary obstructive disorders, showed lower valsartan clearance (higher AUCs).

5.6 Patients with Congestive Heart Failure and Post-Myocardial Infarction

Valsartan

Some patients with heart failure have developed increases in blood urea nitrogen, serum creatinine, and potassium on valsartan. These effects are usually minor and transient, and they are more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or valsartan may be required. In the Valsartan Heart Failure Trial, in which 93% of patients were on concomitant ACE inhibitors, treatment was discontinued for elevations in creatinine or potassium (total of 1.0% on valsartan vs. 0.2% on placebo). In the Valsartan in Acute Myocardial Infarction Trial (VALIANT), discontinuation due to various types of renal dysfunction occurred in 1.1% of valsartan-treated patients and 0.8% of captopril-treated patients. Include assessment of renal function when evaluating patients with heart failure or post-myocardial infarction.

5.7 Serum Electrolyte Abnormalities

Valturna

In the short-term controlled trials of various doses of Valturna, the incidence of hyperkalemia (serum potassium >5.5 mEq/L) was about 1%-2% higher in the combination treatment group compared with the monotherapies aliskiren and valsartan, or with placebo.

In a long-term, uncontrolled study with median treatment duration of about one year, about 4% of the patients had at least one serum potassium >5.5 mEq/L at some time during the study; about 0.8% of patients discontinued study treatment and had a high serum potassium at some point during the study. Patients with hyperkalemia were older (median age 65 vs. 55) with slightly lower mean baseline estimated creatinine clearance compared to patients without

hyperkalemia. While about 25% of the hyperkalemic episodes occurred in the first two months, other initial episodes were reported throughout the study.

Periodic determinations of serum electrolytes to detect possible electrolyte imbalances is advised, particularly in patients at risk for hyperkalemia such as those with renal impairment.

Caution is advised with concomitant use of Valtorna with potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, or other drugs that increase potassium levels may lead to increases in serum potassium.

5.8 Renal Artery Stenosis

Aliskiren

No data are available on the use of aliskiren in patients with unilateral or bilateral renal artery stenosis or stenosis of the artery to a solitary kidney.

Valsartan

In studies of ACE inhibitors in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen have been reported. In a 4-day trial of valsartan in 12 hypertensive patients with unilateral renal artery stenosis, no significant increases in serum creatinine or blood urea nitrogen were observed. There has been no long-term use of valsartan in patients with unilateral or bilateral renal artery stenosis, but an effect similar to that seen with ACE inhibitors should be anticipated.

5.9 Cyclosporine

Aliskiren

When aliskiren was given with cyclosporine, the blood concentrations of aliskiren were significantly increased. Concomitant use of aliskiren with cyclosporine is not recommended [see *Drug Interactions (7)*].

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

The following serious adverse reactions are discussed in greater detail in other sections of the label:

- Risk of fetal/neonatal morbidity and mortality [see *Warnings and Precautions (5.1)*]
- Head and neck angioedema [see *Warnings and Precautions (5.2)*]
- Hypotension [see *Warnings and Precautions (5.3)*]

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in clinical trials of another drug and may not reflect the rates observed in practice.

Valtorna

Valtorna has been evaluated for safety in more than 1,225 patients, including over 316 patients for over 1 year. In placebo-controlled clinical trials, discontinuation of therapy because of a clinical adverse event (including uncontrolled hypertension) occurred in 1.4% of patients treated with Valtorna versus 2.7% of patients given placebo.

Adverse events in placebo-controlled trials that occurred in at least 1% of patients treated with Valtorna and at a higher incidence than placebo included fatigue (2.6% vs. 1.4%), nasopharyngitis (2.6% vs. 2.2%), diarrhea (1.4% vs. 0.9%), upper respiratory tract infection (1.4% vs. 1.1%), urinary tract infection (1.4% vs. 0.6%), influenza (1.1% vs. 0.2%), and vertigo (1.1% vs. 0.3%).

Hyperkalemia has been observed as a serum electrolyte abnormality in Valtorna clinical trials [see *Warnings and Precautions (5.7)*].

Aliskiren

Aliskiren has been evaluated for safety in 6,460 patients, including 1,740 treated for longer than 6 months, and 1,250 for longer than 1 year. In placebo-controlled clinical trials, discontinuation of therapy because of a clinical adverse event, including uncontrolled hypertension occurred in 2.2% of patients treated with aliskiren, versus 3.5% of patients given placebo.

Two cases of angioedema with respiratory symptoms were reported with aliskiren use in the clinical studies. Two other cases of periorbital edema without respiratory symptoms were reported as possible angioedema and resulted in discontinuation. The rate of these angioedema cases in the completed studies was 0.06%.

In addition, 26 other cases of edema involving the face, hands, or whole body were reported with aliskiren use, including 4 leading to discontinuation.

In the placebo-controlled studies, however, the incidence of edema involving the face, hands, or whole body was 0.4% with aliskiren compared with 0.5% with placebo. In a long-term active-controlled study with aliskiren and HCTZ arms, the incidence of edema involving the face, hands, or whole body was 0.4% in both treatment arms.

Aliskiren produces dose-related gastrointestinal (GI) adverse reactions. Diarrhea was reported by 2.3% of patients at 300 mg, compared to 1.2% in placebo patients. In women and the elderly (age ≥ 65) increases in diarrhea rates were evident starting at a dose of 150 mg daily, with rates for these subgroups at 150 mg similar to those seen at 300 mg for men or younger patients (all rates about 2%). Other GI symptoms included abdominal pain, dyspepsia, and gastro-esophageal reflux, although increased rates for abdominal pain and dyspepsia were distinguished from placebo only at 600 mg daily. Diarrhea and other GI symptoms were typically mild and rarely led to discontinuation.

Aliskiren was associated with a slight increase in cough in the placebo-controlled studies (1.1% for any aliskiren use vs. 0.6% for placebo). In active-controlled trials with ACE inhibitor (ramipril, lisinopril) arms, the rates of cough for the aliskiren arms were about one-third to one-half the rates in the ACE inhibitor arms.

Other adverse reactions with increased rates for aliskiren compared to placebo included rash (1% vs. 0.3%), elevated uric acid (0.4% vs. 0.1%), gout (0.2% vs. 0.1%), and renal stones (0.2% vs. 0%).

Single episodes of tonic-clonic seizures with loss of consciousness were reported in two patients treated with aliskiren in the clinical trials. One patient had predisposing causes for seizures and had a negative electroencephalogram (EEG) and cerebral imaging following the seizures; for the other patient, EEG and imaging results were not reported. Aliskiren was discontinued and there was no rechallenge in either case.

The following adverse events occurred in placebo-controlled clinical trials at an incidence of more than 1% of patients treated with aliskiren, but also occurred at about the same or greater incidence in patients receiving placebo: headache, nasopharyngitis, dizziness, fatigue, upper respiratory tract infection, back pain and cough.

No clinically meaningful changes in vital signs or in ECG (including QTc interval) were observed in patients treated with aliskiren.

Valsartan

Valsartan has been evaluated for safety in more than 4,000 hypertensive patients in clinical trials, including over 400 treated for over 6 months, and more than 160 for over 1 year.

In trials in which valsartan was compared to an ACE inhibitor with or without placebo, the incidence of dry cough was significantly greater in the ACE inhibitor group (7.9%) than in the groups who received valsartan (2.6%) or placebo (1.5%). In a 129 patient trial limited to patients who had had dry cough when they had previously received ACE inhibitors, the incidences of cough in patients who received valsartan, HCTZ, or lisinopril were 20%, 19%, and 69% respectively ($p < 0.001$).

Other adverse reactions, not listed above, occurring in $>0.2\%$ of patients in controlled clinical trials with valsartan are:

Body as a Whole: allergic reaction, asthenia

Musculoskeletal: muscle cramps

Neurologic and Psychiatric: paresthesia

Respiratory: sinusitis, pharyngitis

Urogenital: impotence

Other reported events seen less frequently in clinical trials were: angioedema.

Adverse reactions reported for valsartan for indications other than hypertension may be found in the prescribing information for Diovan.

6.2 Clinical Laboratory Test Abnormalities

RBC count, hemoglobin and hematocrit:

Small mean decreases from baseline were seen in RBC count, hemoglobin and hematocrit in both monotherapies and combination therapy. These changes were small, but changes in hemoglobin were slightly more pronounced with the combination therapy (-0.26 g/dL) than with monotherapy regimens (-0.04 g/dL in aliskiren or -0.13 g/dL in valsartan) or placebo (+0.07 g/dL).

Blood Urea Nitrogen (BUN)/Creatinine:

Elevations in BUN (>40 mg/dL) and creatinine (>2.0 mg/dL) in any treatment group were less than 1.0%. For creatinine, 0.5% (3/599) of patients on combination treatment had a creatinine level >1.5 mg/dL at the end of the study and a 30% increase from baseline compared to none in either monotherapy or placebo.

Serum Electrolytes: See Warnings and Precautions (5.7)

6.3 Post-Marketing Experience

The following adverse reactions have been reported in aliskiren post-marketing experience. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hypersensitivity: angioedema requiring airway management and hospitalization

Peripheral edema

7 DRUG INTERACTIONS

No drug interaction studies have been conducted with Valtorna and other drugs, although studies with the individual aliskiren and valsartan components are described below.

Aliskiren

Effects of Other Drugs on Aliskiren

Based on *in vitro* studies, aliskiren is metabolized by CYP 3A4.

Irbesartan: Coadministration of irbesartan reduced aliskiren C_{max} up to 50% after multiple dosing.

P-glycoprotein Effects: Pgp (MDR1/Mdr1a/1b) was found to be the major efflux system involved in absorption and disposition of aliskiren in preclinical studies. The potential for drug interactions at the Pgp site will likely depend on the degree of inhibition of this transporter. Coadministration of aliskiren with Pgp substrates or weak to moderate inhibitors such as atenolol, digoxin, and amlodipine did not result in clinically relevant interactions.

Atorvastatin: Coadministration of atorvastatin, a weak Pgp inhibitor, resulted in about a 50% increase in aliskiren C_{max} and AUC after multiple dosing.

Ketoconazole: Coadministration of 200 mg twice-daily ketoconazole, a moderate Pgp inhibitor, with aliskiren resulted in approximate 80% increase in plasma levels of aliskiren. A 400-mg once-daily dose was not studied but would be expected to increase aliskiren blood levels further.

Cyclosporine: Coadministration of 200 mg and 600 mg cyclosporine, a potent Pgp inhibitor, with 75 mg aliskiren resulted in an approximately 2.5-fold increase in C_{max} and 5-fold increase in AUC of aliskiren. Concomitant use of aliskiren with cyclosporine is not recommended.

Verapamil: Coadministration of 240 mg of verapamil, a moderate Pgp inhibitor, with 300 mg aliskiren resulted in an approximately 2-fold increase in C_{max} and AUC of aliskiren. However, no dosage adjustment is necessary.

Drugs with no clinically significant effects: Coadministration of lovastatin, atenolol, warfarin, furosemide, digoxin, celecoxib, hydrochlorothiazide, ramipril, valsartan, metformin and amlodipine did not result in clinically significant increases in aliskiren exposure.

Effects of Aliskiren on Other Drugs

Aliskiren does not inhibit the CYP450 isoenzymes (CYP1A2, 2C8, 2C9, 2C19, 2D6, 2E1, and CYP 3A) or induce CYP 3A4.

Furosemide: When aliskiren was coadministered with furosemide, the AUC and C_{max} of furosemide were reduced by about 30% and 50%, respectively. Patients receiving furosemide could find its effect diminished after starting aliskiren.

Drugs with no clinically significant effects: Coadministration of aliskiren did not significantly affect the pharmacokinetics of lovastatin, digoxin, valsartan, amlodipine, metformin, celecoxib, atenolol, atorvastatin, ramipril or hydrochlorothiazide.

Warfarin: The effects of aliskiren on warfarin pharmacokinetics have not been evaluated.

Valsartan

No clinically significant pharmacokinetic interactions were observed when valsartan was coadministered with aliskiren, amlodipine, atenolol, cimetidine, digoxin, furosemide, glyburide, hydrochlorothiazide, or indomethacin. The valsartan-atenolol combination was more antihypertensive than either component, but it did not lower the heart rate more than atenolol alone.

Warfarin: Coadministration of valsartan and warfarin did not change the pharmacokinetics of valsartan or the time-course of the anticoagulant properties of warfarin.

CYP 450 Interactions: *In vitro* metabolism studies have indicated that CYP450 mediated drug interactions between valsartan and coadministered drugs are unlikely because of low extent of metabolism [see *Pharmacokinetics – Valsartan (12.3) in the full prescribing information*].

Transporters: The results from an *in vitro* study with human liver tissue indicate that valsartan is a substrate of the hepatic uptake transporter OATP1B1 and the hepatic efflux transporter MRP2. Coadministration of inhibitors of the uptake transporter (rifampin, cyclosporine) or efflux transporter (ritonavir) may increase the systemic exposure to valsartan.

As with other drugs that block angiotensin II or its effects, concomitant use of potassium sparing diuretics (e.g., spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium and in heart failure patients to increases in serum creatinine.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D [see *Warnings and Precautions (5.1)*].

Valturna contains both aliskiren (a direct renin inhibitor) and valsartan (an angiotensin II receptor blocker). When administered during the second or third trimester of pregnancy, drugs that act directly on the renin-angiotensin-aldosterone system can cause fetal and neonatal morbidity and death. Valturna can cause fetal harm when administered to a pregnant woman. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus.

Angiotensin II receptor antagonists, like valsartan, and angiotensin-converting enzyme (ACE) inhibitors exert similar effects on the renin-angiotensin-aldosterone system. In several dozen published cases, ACE inhibitor use during the second and third trimesters of pregnancy was associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios was also reported, presumably from decreased fetal renal function. In this setting, oligohydramnios was associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus were also reported, although it is not clear whether these occurrences were due to exposure to the drug. In addition, first trimester use of ACE inhibitors, a specific class of drugs acting on the renin-angiotensin-aldosterone system, has been associated with a potential risk of birth defects in retrospective data.

When pregnancy occurs in a patient using Valturna, discontinue Valturna treatment as soon as possible. Inform the patient about potential risks to the fetus based on the time of gestational exposure to Valturna (first trimester only or later). If exposure occurs beyond the first trimester, perform an ultrasound examination.

In rare cases when another antihypertensive agent cannot be used to treat the pregnant patient, perform serial ultrasound examinations to assess the intraamniotic environment. Routine fetal testing with non-stress tests, biophysical profiles, and/or contraction stress tests may be appropriate based on gestational age and standards of care in the community. If oligohydramnios occurs in these situations, individualized decisions about continuing or discontinuing Valturna treatment and about pregnancy management should be made by the patient, her physician, and experts in the management of high risk pregnancy. Patients and physicians should be aware that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Closely observe infants with histories of *in utero* exposure to Valturna for hypotension, oliguria, and hyperkalemia. If oliguria occurs, these infants may require blood pressure and renal perfusion support. Exchange transfusion or dialysis may be required to reverse hypotension or support decreased renal function.

No reproductive toxicity studies have been conducted with the combination of aliskiren and valsartan. However, these studies have been conducted for aliskiren as well as valsartan alone [see *Nonclinical Toxicology (13) in the full prescribing information*].

8.3 Nursing Mothers

It is not known whether aliskiren is excreted in human milk, but aliskiren was secreted in the milk of lactating rats. It is not known whether valsartan is excreted in human milk. Valsartan was excreted into the milk of lactating rats; however, animal breast milk drug levels may not accurately reflect human breast milk levels. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness of Valturna in pediatric patients have not been established.

8.5 Geriatric Use

In the short-term controlled clinical trials of Valturna, 99 (15.9%) patients treated with Valturna were ≥ 65 years and 14 (2.2%) were ≥ 75 years.

No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

10 OVERDOSAGE

Aliskiren

Limited data are available related to overdosage in humans. The most likely manifestation of overdosage would be hypotension. If symptomatic hypotension occurs, provide supportive treatment.

Valsartan

Limited data are available related to overdosage in humans. The most likely effect of overdose with valsartan would be hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. Depressed level of consciousness, circulatory collapse and shock have been reported. If symptomatic hypotension occurs, provide supportive treatment.

Valsartan is not removed from the plasma by hemodialysis.

Valsartan was without grossly observable adverse effects at single oral doses up to 2000 mg/kg in rats and up to 1000 mg/kg in marmosets, except for the salivation and diarrhea in the rat and vomiting in the marmoset at the highest dose (60 and 31 times, respectively, the maximum recommended human dose on a mg/m² basis). (Calculations assume an oral dose of 320 mg/day and a 60-kg patient.)

16 STORAGE

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) in original container. [See USP Controlled Room Temperature.]

Protect from moisture.

Dispense in tight container (USP).

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to a study published in the *Archives of Internal Medicine* in 2009. Researchers at Newton-Wellesley Hospital in Newton, Mass., surveyed 442 doctors across the U.S. for this study. They found that physicians with relatively high numbers of problematic patients were 12 times as likely to report burnout as those with lower numbers of these patients.

Yet these types of patient interactions are not uncommon—physicians describe 15% of their patient-physician encounters as “difficult,” according to a 2007 study in *Family Practice Management*. This chapter provides strategies to better recognize, understand, and cope with difficult patient encounters.

Rethinking Your Response

The first step is to remind yourself that there are no difficult patients, only difficult encounters, Dr. Blackall says. In fact, because even the term “difficult patient” can shade your view of the patient, it should be avoided, he notes.

The best way to respond to a difficult patient situation is to consider what’s motivating the patient. Is he or she anxious? Scared? Feeling overwhelmed? Acting out because he or she’s not feeling well? “Knowing that there are reasons for the patient’s behavior makes it less likely that you’ll take their responses personally, thus avoiding defensiveness or confrontational behavior on your part,” Ms. Belzer explains. Having that perspective helps you resist a fight-or-flight response, a typical first reaction to such behavior. “So instead of countering [his or her] every point or folding your arms defensively, make an even greater effort to listen to the patient’s story,” she advises.

Misinformation, fear, or anger is usually at the root of difficult encounters, Dr. Wax says. So you may be able to prevent the problem by being honest and straightforward about the patient’s healthcare issues. “To treat an existing problem, let the patient be heard and let him or her vent and treat the items on his or her agenda before proceeding with your own agenda as a physician, because when you’re mad, you know you want to be heard and possibly validated; and you want changes to be made,” he says.

When Roland Goertz, MD, a family physician in Waco, Tex., and president-elect of the American Academy of Family Physicians, has a patient who will not follow instructions for taking

medicine, he says he looks at possible behavioral issues behind that resistance. Doing so often reveals a logical reason, like inability to afford the prescribed medicine. “Sometimes we for-



“It’s often difficult to get past patients’ anger unless you acknowledge it and then transition to their medical issue. I usually say something like ‘It looks like you’re very angry. Can you tell me why?’”

Roland Goertz, MD

Family physician

Waco, Tex.

President-elect

American Academy of Family Physicians

get how expensive medications are. We need to follow through and find out why [patients] are not taking them,” he says. Only then can a mutually agreeable solution be found. Once that happens, it’s easier to move forward by helping patients save face, even when there’s an impasse. “If a patient has made an unrealistic request or demand, speak slowly and tell them why their request isn’t suitable. Make your response as caring as possible. For example, say, ‘Mrs. J, while that might not be the best treatment, here’s what we can do to make you feel better,’” Ms. Belzer says.

Dr. Blackall says the problem is not the conflict itself. Rather it’s when physicians begin to withdraw from a patient relationship. Shifting a physician-patient relationship from conflict to collaboration means “accepting people where they are, as they are, even if you don’t like them,” he notes. For example, a physician may dread seeing a particular patient and may exhibit subtle behaviors like being slow to return a patient’s phone calls. “Conflict comes up all the time,” Dr. Blackall says. “We have tools to handle it. When we have a difficult encounter with a patient, we withdraw because we feel powerless, and that can create a symptomatic cycle where the harder we try, the worse things get, and we become more entrenched in it.” Often physicians keep doing the same things in their relationship with a

patient, hoping for a different outcome; but when that doesn't work, the relationship "becomes difficult."

Angry Patients

Angry patients are usually not mad at you. They may be carrying their anger about something else—e.g., their medical issues—with them to your office, where the anger may manifest itself in the patients' behavior towards you and your staff. "It's often difficult to get past their anger unless you acknowledge it and then transition to their medical issue. I usually say something like 'It looks like you're very angry. Can you tell me why?'" Dr. Goertz says.

Here are tips for handling an angry patient:

- **Look for signs that a patient is getting angry.** These include changes in body language—a clenched jaw, tense posture, clenched fists, fidgeting, or any other significant change from earlier behavior. Observe the patient for additional signs that his temper is rising. Is his voice raised? Is he demanding excessive attention? If a patient is angry enough to verbally abuse you, remain calm and professional. Keep some distance between you and the patient and do not respond until the verbal barrage is over. If a patient becomes irrational, he's probably trying to intimidate you. He may say something like "I'm calling my lawyer."
- **Use active listening.** Trying to justify the situation or defend your actions will only make things worse. Instead, paraphrase back to the patient what he or she's already told you, while identifying the real feelings behind the words—helplessness or fear, for instance. Keep your statements short and simple. Show accepting body language by letting your arms hang loosely at your sides, rather than standing with your arms crossed or with your hands on your hips.
- **Keep your cool.** If the patient erupts, he or she has lost control and will no longer hear what you say. Your reaction may determine exactly how long this tirade will last. Don't be manipulated by your patient's anger. Never get angry yourself or try to set limits by saying "calm down" or "stop yelling." As the patient's temper explodes, maintain eye contact and just listen. Try to understand the event that triggered this outburst.

Then discuss the situation rationally without reflecting back anger or malice. Sometimes this may need to happen on a different day when everyone has had a chance to cool off, Dr. Ward says, or by involving an office manager who can address the issues in a less clinical manner and may, for example, explain insurance constraints, plan limitations, and even patient non-adherence.



“Usually the difficult situation is related to an illness that isn’t getting better.”

Fred Ralston, Jr., MD, FACP
 Fayetteville Medical Associates
 Fayetteville, Tenn.
 President
 American College of Physicians

Try to identify the underlying reason the patient is uncooperative. A patient who balks when a type of therapy or test is suggested, for example, may actually be anxious about an upcoming procedure or test results. After you listen to the concerns, reassure the patient that you take them seriously. Empathize by saying something like this: “I understand how upsetting this must be for you.” Calmly explain the consequences of a refusal to have a test or procedure that you recommend. You may need to elaborate on the reason you recommend the new test or procedure and explain that the patient’s unwillingness to cooperate may delay recovery, according to the Healthcare Providers Service Organization (<http://www.hpso.com/resources/article/3.jsp>).

- **Be willing to refer to another physician.** Dr. Ralston says that referral can often mollify a tense situation. “Usually the difficult situation is related to an illness that isn’t getting better,” he says, and a second opinion will usually offer the patient the peace of mind that can reduce the emotional stress. Dr. Blackall agrees that it’s okay to refer patients you can’t connect with to a colleague. He suggests saying something like this: “I feel ill-equipped to work with you, but I know

someone who might be a better fit, and we can set up an appointment for you to meet her.”

- **Say you’re sorry.** There’s nothing like an apology to defuse a situation. For example, you could say; “I’m sorry for my part in any miscommunication between us,” which will go a long way towards repairing the damage caused by misunderstandings, Dr. Epstein says. Hear out patients who are angry because they feel you have missed a diagnosis or haven’t been responsive to their needs, and be willing to apologize if they feel they didn’t get the best care from you, Dr. Stubbs says.

Breaking Bad News

The very reason you entered medicine—compassion for others, caring about people—can make you uncomfortable delivering bad news, Ms. Belzer says. Conveying bad news is particularly difficult when there’s a long-term doctor-patient relationship. In those cases you treat not only the patient, but often the patient’s entire family, and that makes the emotional connection even stronger. But Dr. Ehrmann says you can make this unpleasant experience easier for yourself and your patient by doing the following:

- Always deliver the bad news in person.
- Always have a plan ahead of your discussion.
- Never deliver bad news through a third party.
- Never deliver bad news on a Friday if it’s life threatening (unless something helpful can be done over the weekend).
- Never take away hope.

Dr. Ehrmann applied these rules for a patient who was recently diagnosed with breast cancer. He called her, asked her to come in to review test information, and told her the difficult news in person: “When my 50-year-old patient of 20 years came in Monday evening (I try to do this at the end of the day just in

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case I need to answer more questions and do not want to move to another patient room), she came in with her husband since she felt there was something wrong (her mother had breast cancer). I sat in a chair next to her and then proceeded to tell her that her biopsy came back as cancer. I told her the next step was that it had to be staged and I already had arranged a consultation with a cancer specialist, locally the next day. While they both started to cry, I told her that she would get the best care possible, also if requested they could always get a second opinion at one of the nearby cancer centers, and I would be there to help and answer questions in the future every step of the way. After 30 minutes of answering questions, the office visit concluded; and while it was a difficult encounter, I hoped that I was able to ease the pain somewhat of the bad news.”

Dr. Ralston says that there are some times when delivering news by phone may be the “less bad” way. He cites the example of a biopsy or test report that shows cancer; then one is faced with calling a patient to schedule an appointment to discuss the

Finding the Right Words

The following is a six-step outline for delivering bad news as developed by Robert Buckman, MD, in his book *Breaking Bad News: A Guide for Health Care Professionals*:

- 1. Get started:** The physical setting should be private, with comfortable seating for both you and your patient. Ask the patient who else should be present and let the patient decide. Dr. Buckman recommends asking a question like “How are you feeling right now?” to show the patient that this conversation will be a two-way one.
- 2. Find out how much the patient knows:** In order to understand how much the patient already knows, ask, “What have you already been told about your illness?” This can also help you learn about the patient’s level of technical sophistication, as well as his or her emotional state.
- 3. Find out how much the patient wants to know:** Ask patients what level of detail you should cover. You could say, “Some patients want me to cover every medical detail, but others want only the big picture—what would you prefer now?” This establishes that there is no right or wrong answer, and it establishes that a patient may want a different level of detail during the next discussion.

result when the patient will know that this means the test was not normal: “You would have passed along the good news if it was normal. “The longer the time between the phone call and the appointment, the more opportunity [the patient has] to worry about results far worse than those actually to be given. In those cases it may be necessary to have that discussion by phone,” Dr. Ralston says.

Dr. Multack notes that one strategy is to remind the patients of original expectations. “If the patient has end-stage or terminal disease, the fantasy of a cure may still exist in the family. We must during care be direct and honest in explaining the likely outcome without dispelling hope,” he says.

Still it can be hard to find the right words (see “Finding the Right Words”). “I’ll never forget how an attending [physician] told my brother that he had inoperable brain cancer,” Ms. Belzer says. “Flanked by a group of residents, the attending came in and without even a few words of welcome, said, ‘We have the results and it’s bad. It’s really bad. I mean, it’s the worst news

4. **Share the information:** Decide on your agenda before sitting down with the patient so you have relevant information at hand. Topics to consider in planning an agenda are diagnosis, treatment, prognosis, and support. Give information in small bits, then ask the patient between each bit of information if he or she understands or has questions. Long lectures are confusing and overwhelming. Translate medical terms into plain English.
5. **Respond to the patient’s feelings:** You will miss an opportunity to be a caring physician if you don’t understand your patient’s reaction to the news, and you would leave a lot of unfinished business if you ignored or did not respond to his or her reaction.
6. **Outline a plan and prepare to follow-through:** You need to integrate the medical issues and the patient’s concerns into a plan that can be carried out in the patient’s healthcare system. The best way to do this is to outline a step-by-step plan, explain it to the patient, and explain your next contact with him or her (“I’ll see you back in the clinic in two weeks”). Be sure the patient has a phone number to contact the relevant medical caregiver in case something comes up before the next appointment.

you could expect to hear.’ He then described the cancer as a spider that had extended its arms into all parts of my brother’s brain. A spider? What an unfortunate choice of metaphor. What’s more, the doctor stood several feet from my brother’s hospital bed, raising his voice to deliver the message across the room. The eye contact, the compassion, consideration for appropriate wording, even a kind touch—all were missing.”

End-of-life Discussions

Empathy and honesty to the point of transparency are keys to any end-of-life discussions, says Dr. Multack. “It would be inappropriate to look at someone and say, ‘Your mom is going to die, and there is nothing I can do about it’; rather, ‘I need to be honest with you. The health of your mom is deteriorating, as you can see. I know we all wish that we could change that, but we can’t. I want you to know that we did everything we could do. I feel your pain and sadness.’”

If possible, end-of-life discussions with patients should be held when the individual is still in good health. Dr. Ralston says the questions should be raised honestly and compassionately when the potential need for intervention appears closer. For example, he might say, “I hope we can help you get better without machines, but if the current treatment does not work and if you stop breathing, would you want to be placed on a breathing machine? If your heart stops, would you want to be shocked?” Dr. Ehrmann recommends holding such conversations in person, not over the telephone. A family member should be present, whether or not the patient is of sound mind and body. He encourages all of his patients to file a living will with an attorney and to have a copy placed in their medical chart.

Arthur L. Caplan, Ph.D., director of the Center for Bioethics at the University of Pennsylvania in Philadelphia, Pa., recommends that physicians discuss end-of-life issues routinely as part of every medical history with “no big fanfare” as well as with very ill patients. “Don’t be blunt—but don’t be shy about raising the subject of [end-of-life],” he says. Ask next of kin and friends if they have discussed these issues with your patient or if there has been any discussion with a religious advisor, he suggests. “Ask if the patient has an advance directive or medical

durable power of attorney. When was it last updated? These are good ways to get into these topics,” he says.

Discussing Depression

Talking to your patients about depression includes finding a way to address the stigma often associated with this diagnosis. Dr. Ralston acknowledges to his patients that depression is a real physical condition that medication, exercise, and counseling can help. He points out that there are many others in their community who are being treated for depression, that there is nothing to be ashamed of, and that it is an illness like high blood pressure, often with a good prognosis.

It’s important to affirm that the symptoms of the patient are real and address patient’s concerns that their symptoms may be related to a serious underlying condition like cancer, Dr. Stubbs says. “I will then stop and ask them what they think, and often this leads to a discussion of misperceptions of what depression is. If I can get buy-in from the patient that this could be depression, then we discuss possible medications to treat it and an appropriate follow-up plan.”

Dr. Epstein says physicians can address concerns that mental illness is a character weakness, is the patient’s own fault, or is embarrassing by emphasizing the following points:

- Depression is common.
- Anyone can be affected by depression.
- There is a biological component to depression (e.g., not enough or too much of certain chemicals in the brain).
- Patients do not cause their own depression.
- Treatment is usually effective.

When Strategies Fall Short

At times the strategies for dealing with difficult patients or delivering bad news don’t work. There will always be some patients whom physicians can’t work with, for one reason or another. Dr. Ehrmann says he can detect such circumstances as early as the first office visit during which he establishes a patient’s goals. If he feels the patient’s objectives are inappropriate, he may say, “I understand where you’re coming from and respect how you feel, but I may not be the right doctor for you.”