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Drug eruptions: 6 dangerous rashes

When to stop the drug immediately and hospitalize your patient

The best intervention for a potentially life-threatening drug rash can happen before you choose a psychotropic. Carefully evaluating your patient's risk for an adverse cutaneous drug reaction (ACDR) will guide safer prescribing. If your patient develops a rash, differentiating serious from benign reactions can help prevent morbidity, which can range from work loss or hospitalization to disfigurement or death.

In the first installment of this 2-part article on drug eruptions, we discussed how to recognize and manage benign rashes.[1] Here we explain how to reduce ACDR risk and identify 6 serious rashes.

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Risk reduction strategies

Although it is impossible to eliminate drug rashes, you may be able to reduce ACDR risk by using sound prescribing methods. Ultimately your choice of a psychotropic comes down to whether the drug's benefits outweigh the risks to your patient. Factors affecting ACDR risk fall into 3 categories:

- historical
- pharmacokinetic
- environmental/other.

Historical factors. Before starting a psychotropic, carefully consider your patient's history. Assess for a personal or family history of an ACDR to the intended drug or another drug in the same class. If the patient experienced a severe drug reaction from a specific medication, never again treat the patient with the same drug.[2]

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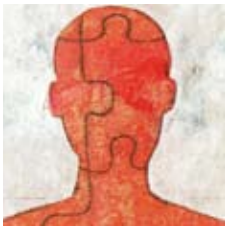

Clinical Point

A patient who has experienced an adverse reaction to a drug may be hypersensitive to other drugs in the same class

Table 1

Steps to reduce ACDR risk

Identify patients at risk
Use lowest effective dosages
Titrate medications according to latest recommendations
Consider the effects of polypharmacy, particularly on drug metabolism
Remain in contact with patients' other providers to stay informed of medication changes
Advise patients that limiting sun exposure may reduce ACDR risk of certain drugs
Educate patients about ACDRs, including how to identify 'red flags' that indicate a serious reaction and when to seek medical attention

ACDR: adverse cutaneous drug reaction

A patient who has had an ACDR also may be hypersensitive to other drugs in the same class. One example is anticonvulsant hypersensitivity syndrome. Phenytoin, carbamazepine, and phenobarbital may be cross-reactive.[3] A patient who is hypersensitive to carbamazepine may have a ≥30% risk of reacting to oxcarbazepine.[4] A major predictor of rash associated with lamotrigine is history of a rash from another antiepileptic.[5] Cross-reactivity also may occur among antidepressants, particularly selective serotonin reuptake inhibitors.[6]

Genetics may play a role in ACDR risk,[7] so inquire about family history of ACDR. In one case report, 4 family members experienced an ACDR to fluoxetine.[8] Knowles et al[3] suggests warning close relatives of a patient with anticonvulsant hypersensitivity syndrome about the risk of using potentially cross-reactive anticonvulsants.

If your patient reports that a relative had an ACDR—particularly a severe reaction—to a drug you are considering prescribing, reduce this patient's risk by choosing an alternate drug or proceeding cautiously by slowly titrating the dosage and monitoring carefully.

Pharmacokinetic factors. In general, ACDRs and dosage are not correlated,[2] but anticonvulsants may be an exception. For example:

- lowering the starting dosage of lamotrigine reduces ACDR risk[9]
- rapid increase in dosages and high serum concentrations of phenytoin and carbamazepine appear to increase the risk of rash.[10]

To reduce ACDR risk, treat patients with the lowest effective anticonvulsant dosage.

Be vigilant for potential interactions between drugs. For instance, valproic acid inhibits lamotrigine metabolism, so when prescribing these 2 medications together, take steps to avoid a serious, life-threatening rash such as Stevens-Johnson syndrome (SJS). For bipolar patients age >12 taking valproic acid, titrate lamotrigine in a special regimen (initially 25 mg every other day, then gradually increased to ≤100 mg/d).[11] Remain in close contact with the patient's other prescribers to ensure that all are aware of potential adverse reactions if the patient's medications are changed.

Environmental /other factors. Psychotropic medications—particularly antipsychotics—are associated with ACDRs related to sun exposure.[12-14] Advise patients to use sunscreen and wear protective clothing, and consider recommending antioxidant supplements to help prevent photosensitive reactions.[15]

Populations at increased risk of developing a drug rash include African-Americans and persons age >70.[7] Women have higher incidence of rash from lamotrigine use compared with men.[9] Underlying diseases, such as human immunodeficiency virus, may increase ACDR risk.[7] Strategies for reducing ACDR risk are summarized in ***Table 1***.

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Table 2

Serious rashes associated with psychotropics*

Rash	Suspect drugs/classes
Erythema multiforme	Bupropion,[a] carbamazepine,[a] clozapine,[b] duloxetine,[a] eszopiclone,[a] fluoxetine,[a,c] lamotrigine,[a] methylphenidate,[b] oxcarbazepine,[a] paroxetine,[a] quetiapine,[d] risperidone,[e] sertraline,[c,f] topiramate,[b] trazodone,[g] valproic acid,[a] venlafaxine[b]
Stevens-Johnson syndrome/toxic epidermal necrolysis	Alprazolam,[b] bupropion,[a] carbamazepine,[a] chlorpromazine,[h] clozapine,[b] duloxetine,[a] fluoxetine,[b] fluvoxamine,[b] lamotrigine,[a] mixed amphetamine salts,[a] oxcarbazepine,[a] paroxetine,[b] quetiapine,[b] sertraline,[b] topiramate,[a] valproic acid,[a] venlafaxine[b]
Hypersensitivity syndrome	Amitriptyline,[i] carbamazepine,[a] clomipramine,[j] desipramine,[k] fluoxetine,[l] lamotrigine,[a] methylphenidate,[b] olanzapine,[m] oxcarbazepine,[a] valproic acid[a]
Vasculitis	Carbamazepine,[a] clozapine,[n] diazepam,[o] fluoxetine,[b] fluvoxamine,[b] haloperidol,[p] lamotrigine,[b] maprotiline,[q,r] paroxetine,[b] sertraline,[b] thioridazine,[s] trazodone[q],[t]
Erythroderma	Aripiprazole,[a] bupropion,[a] carbamazepine,[a] duloxetine,[a] fluoxetine,[b] lamotrigine,[a] lithium,[u] methylphenidate,[a] mirtazapine,[v] paroxetine,[b] phenothiazines,[w] quetiapine,[a] risperidone,[a] TCAs (most),[v] venlafaxine,[b] ziprasidone[a]
Erythema nodosum	Carbamazepine,[a] fluoxetine,[b] paroxetine,[b] venlafaxine[b]

* Suspect any drug with any reaction
TCAs: tricyclic antidepressants

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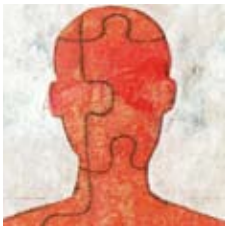
Clinical Point

As the prescriber, you are responsible for ensuring that a patient with a serious rash gets emergent referral and treatment

Serious drug eruptions

Most drug rashes are benign, but some can be life-threatening and require immediate drug discontinuation. Six serious ACDRs associated with psychotropics are listed in ***Table 2***.

As described in part 1 of this article, general strategies for identifying and treat-



Clinical Point

Hypersensitivity syndrome can present like a benign condition, so consider the diagnosis when assessing any rash

Table 3

Managing a serious rash

Discontinue the offending drug immediately
Consult with a dermatologist and other specialists
Hospitalize the patient if indicated for supportive care
Report the case to the FDA and the drug manufacturer if the eruption is atypical or uncommon

ing potential ACDRs include identifying the lesion by taking a history and performing a physical examination (***Box, page 106***). Look for "red flags" that indicate a potentially serious reaction:

- constitutional symptoms (fever, sore throat, malaise, arthralgia, lymphadenopathy, cough)
- facial involvement
- mucous membrane involvement
- skin tenderness or blistering, particularly if there is full-thickness epidermal detachment
- purpura.[16,17]

If you suspect your patient may have a serious ACDR such as those described below, immediately discontinue the psychotropic (***Table 3***). Consult with a dermatologist and other specialists as appropriate, and arrange hospitalization. Although a patient with a serious ACDR typically will require hospitalization and interventions that are beyond the scope of a psychiatrist's practice, as the prescriber you are responsible for ensuring that the patient gets an emergent referral and treatment.

Erythema multiforme (EM) may appear as symmetric erythematous target or iris-like papules and vesicobullous eruptions that present on the extremities and palmoplantar surfaces within days of starting drug therapy (***Photo 1, page 104***). Fever and malaise may accompany this reaction. Mucous membrane involvement is typically mild and limited to oral mucosa, but ocular mucosa also may be affected. Severe EM can cause blindness.

The patient might present with detachment of the epidermis from the dermis. If this consider SJS spectrum disease (see below).[2,13,18,19]

Because EM may be a harbinger of a more severe skin reaction, consult a dermatologist and—if the rash involves the eyes—an ophthalmologist.[12] Antihistamines and topical corticosteroids may be used to treat EM.[18] Depending on the severity of the reaction, hospitalization might be indicated.

Stevens-Johnson syndrome/toxic epidermal necrolysis (TEN) are considered a spectrum of reactive skin disorders; TEN is the more severe variant. Patients may present with a prodrome of fever, cough, and malaise. Oral lesions—such as mucosal blistering (***Photo 2***)—may precede skin lesions. Look for widespread distribution of flat, atypical target lesions characterized by blisters on purpuric macules.[2] Compared with EM, SJS/TEN lesions are more far-reaching, and the more extensive mucous membrane involvement can affect the mouth, esophagus, and genitalia. Ocular involvement might lead to blindness.[20-23]

Epidermal detachment also may be widespread. SJS and TEN are differentiated by the extent of skin detachment:

- <10% of body surface area is SJS
- 10% to 30% detachment is SJS/TEN
- >30% is TEN.[2]

Arrange for the patient with signs of SJS/TEN to be admitted to an ICU or burn unit.[20] There, clinicians will implement aggressive supportive measures such as temperature control, nutritional support, fluid balance, and pain management.[2,24] Treatments for SJS/TEN include hemofiltration, IV immunoglobulin, plasmapheresis, and cyclosporine. Corticosteroids are not recommended.[25]

Advise patients who have had TEN to alert relatives that they also may be at increased risk of an ACDR to the offending drug.[22] Because SJS/TEN can cause blindness, an ophthalmologist typically will be involved in the patient's care.[20]

Hypersensitivity syndrome—known as drug rash with eosinophilia and systemic symptoms (DRESS)—is a potentially life-threatening syndrome that presents as a

triad of fever, rash, and internal organ involvement.[26] These symptoms typically present 2 to 6 weeks after the patient starts the offending drug.

Early symptoms may include fever, malaise, pharyngitis, and lymphadenopathy.[2] Cutaneous manifestations range from relatively benign exanthematous eruptions to more serious eruptions such as erythroderma or TEN.

Laboratory findings might show abnormalities of the liver, kidneys, lungs, or thyroid. Atypical lymphocytes and eosinophilia may be present.

Because hypersensitivity syndrome may present like a benign condition, consider the diagnosis when assessing any drug rash, particularly if the patient is receiving an anticonvulsant.[20,22,27] Appropriate, timely care may be best delivered in an inpatient setting, so hospitalization might be indicated. Laboratory tests to assess organ function may include complete blood count (CBC), urine analysis (UA), creatinine, liver function tests, and thyroid stimulating hormone (TSH).

Treatment is supportive. Note that unlike those with SJS/TEN, patients with hypersensitivity syndrome may be treated with systemic corticosteroids.[27] As with TEN, patients should alert relatives to a possible increased risk of a severe reaction to the offending drug.[22]

Vasculitis may present with palpable purpura, fever, and rash generally in dependent areas (***Photo 3***). Patients often develop morbilliform or urticarial eruptions, and the condition might affect internal organs. Differential diagnosis includes:

- Henoch-Schönlein (allergic) purpura
- Wegener's granulomatosis
- infections
- collagen vascular diseases.[2]

Perform a complete history and physical in patients with suspected vasculitis. Because vasculitis can affect the blood vessels of any organ,[20] laboratory tests such as CBC, UA, and fecal occult blood test to assess organ involvement are indicated.[2]

Pharmacotherapy depends on the severity of presentation and ranges from topical agents to immunosuppressants.[2]

Box

Dermatologic glossary

Desquamation: skin falling off in scales or layers; exfoliation
Erythema: redness of the skin
Macule: a discolored lesion on the skin that is not elevated above the surface
Morbilliform: resembling measles
Nodule: a small lump, swelling, or collection of tissue
Papule: a small circumscribed, superficial, solid elevation of the skin <1 cm in diameter
Purpura: red or purple discolorations on the skin caused by bleeding underneath the skin
Urticaria: a vascular reaction in the upper dermis characterized by pruritic hives
Vesicobullous: denoting an eruption of fluid-containing lesions of various sizes

Source: *Dorland's illustrated medical dictionary.* 30th ed. Philadelphia, PA: Saunders; 2003.

Table 4

3 'As' to protect patients after a life-threatening ACDR

Allergy. Add the offending drug to the patient's allergy list to ensure it is not given again
Alert. Tell the patient he or she should wear a medical alert bracelet to prevent being given the drug
Advise. Inform the patients' close relatives that they may be at risk for a similar reaction to the same drug or drugs from the same class

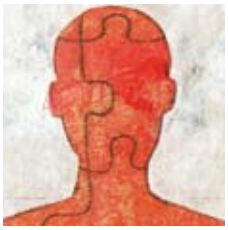
ACDR: adverse cutaneous drug reactions

Other treatments are rest, elevation, support stockings, and antihistamines.[28]

Erythroderma, also known as exfoliative dermatitis, can present as sudden, pruritic erythema that can generalize (***Photo 4***). Scaling will appear, followed by desquamation. Patients typically complain of irritation, feeling cold, and a sensation of tightness. Dilated dermal vessels can result in high-output cardiac failure. This potentially life-threatening condition

Clinical Point

Laboratory tests to assess internal organ involvement are indicated for any patient you suspect might have vasculitis



Drug eruptions

can develop within 1 week of starting a drug.[2,29]

Pharmacotherapy includes emollients, antihistamines, and corticosteroids.[2] Erythroderma is best treated in a hospital, where patients typically receive supportive care, with special attention to nutritional and hydration status.[29]

Erythema nodosum may present as painful erythematous nodules—usually in the lower extremities (***Photo 5, page 105***)—that are the result of fat necrosis.[13,30] Treatment typically involves best rest, nonsteroidal anti-inflammatory drugs, and potassium iodide.[30] Systemic corticosteroids also may be used.[31]

Clinical Point

Erythema nodosum presents as painful erythematous nodules, usually in the lower extremities

Resuming psychiatric treatment

Although medically necessary for patients with a serious rash, abruptly discontinuing a psychotropic might place them at risk for rapid psychiatric decompensation. Whenever possible, wait 2 weeks before restarting psychopharmacotherapy in a patient who has been treated for an ACDR. If that is not feasible because (for example) the patient is psychotic and agitated, you can cross-taper with a different medication from another class.

If your patient has experienced a serious ACDR, follow the 3 "A's" to protect against recurrence (***Table 4***).

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Related Resources

- Knowles SR, Shear NH. Recognition and management of severe cutaneous drug reactions. *Dermatol Clin* 2007;25(2):245-53.
- Dermatology Image Atlas. www.dermatlas.org.
- American Academy of Dermatology. www.aad.org.

Drug Brand Names

Alprazolam • Xanax
Amitriptyline • Elavil
Aripiprazole • Abilify
Bupropion • Wellbutrin
Carbamazepine • Tegretol
Chlorpromazine • Thorazine
Clomipramine • Anafranil
Clozapine • Clozaril
Cyclosporine • Neoral, Sandimmune
Desipramine • Norpramin
Diazepam • Valium
Duloxetine • Cymbalta
Eszopiclone • Lunesta
Fluoxetine • Prozac
Fluvoxamine • Luvox
Haloperidol • Haldol
Lamotrigine • Lamictal
Lithium • Lithobid, Eskalith
Maprotiline • Ludiomil
Methylphenidate • Ritalin
Mirtazapine • Remeron
Olanzapine • Zyprexa
Oxcarbazepine • Trileptal
Paroxetine • Paxil
Phenytoin • Dilantin
Phenobarbital • Luminal
Quetiapine • Seroquel
Risperidone • Risperdal
Sertraline • Zoloft
Thioridazine • Mellaril
Topiramate • Topamax
Trazodone • Desyrel
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Venlafaxine • Effexor
Ziprasidone • Geodon

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Bottom Line

Reduce the incidence of adverse cutaneous drug reactions (ACDRs) by evaluating patients' historical, pharmacokinetic, and environmental risk factors. Constitutional symptoms, facial or mucous membrane involvement, skin tenderness or blistering, and purpura indicate a potentially serious ACDR. If your patient develops a serious ACDR, immediately discontinue the offending drug and obtain expert consultation.

Clinical Point

Whenever possible, wait 2 weeks before resuming psychotropics in a patient who has had a serious drug rash