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PHOTO-ILLUSTRATED GUIDE helps you identify easily treated reactions, spot 'red flags' of serious conditions

drug eruptions

Is your patient's rash dangerous or benign?

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Your patient who is taking psychotropics suddenly develops a rash. Rapidly identifying the cause is crucial to your decision to either stop the drug and risk decompensation or continue it and deal with the rash.

Adverse cutaneous drug reactions (ACDRs) develop in 2% to 5% of patients taking psychotropics¹ and can occur with all drug classes.² Most “drug eruptions” are benign and easily treated, but they can distress patients and lead to medication nonadherence. Other ACDRs can be disfiguring or life-threatening and require emergent medical treatment.

In this first installment of a 2-part article, we explain how to identify and manage benign ACDRs associated with psychotropics. In part 2, we'll cover serious ACDRs—those that result in persistent or significant disability or are life-threatening³—as well as risk-reduction strategies.

Overall strategy

A psychiatric patient with a suspected drug eruption needs to be examined by you and, if necessary, another physician. Identify the lesion by taking a history and performing a physical examination (**Box 1, page 44**).^{4,5} If you are unable to perform this examination, promptly refer the patient to a primary care provider or dermatologist.

Once a rash is identified, determine its cause. Consider nonpharmacologic origins such as:



Drug eruptions

Clinical Point

Consider any drug as a possible cause of any reaction

Box 1

Is your patient's rash drug-related?

When a patient presents with a suspected adverse cutaneous drug reaction, take a history to determine the rash onset, timing, relationship between symptoms and drug ingestion, associated symptoms, and history of previous drug reactions.

Ask your patient:

- What are your symptoms?
- How did the rash look initially?
- How has it changed?
- Have you used any new soaps, perfumes, cosmetics, medications, or supplements, or been exposed to insects, foliage, or someone with an illness?

Next, perform a physical examination.

In addition to the photos and descriptions in this article (*Table 3*), review up-to-date textbooks, journal articles, and online resources to aid identification. Look for rashes that affect the mucosa and for lymphadenopathy or signs of internal organ involvement. Seek laboratory abnormalities, including elevated creatinine, positive fecal occult blood test, or hematuria. These and other red flags may indicate a serious rash that requires urgent treatment (*Table 2*). Consultation with a dermatologist may be indicated.

- infections
- insect bites
- collagen vascular disease
- neoplasms
- exposure to sun, toxins, etc.

If a medication is the prime suspect, search the literature to determine if the drug has been associated with the observed event. *Table 1* provides examples of psychotropic drugs and classes associated with 8 common benign rashes. Consider any drug as a possible cause of any reaction, however, even if no published reports have associated a specific drug with a particular reaction.⁶

Look for red flags that may indicate a serious reaction (*Table 2*).^{5,7} Treatment of a serious drug reaction may require care by physicians with training and clinical expertise likely to be beyond the scope of psychiatric practice. However, your responsibility is to ensure that the patient

gets a timely—emergent, if indicated—referral so that treatment is not delayed. If an ACDR clearly is benign, follow the guidelines outlined below; otherwise, consult with a dermatologist, infectious diseases clinician, or other appropriate specialist.

Benign rashes

Exanthematous reactions are the most common ACDR.¹ Erythematous macules and papules may initially present on the trunk and spread peripherally within 1 to 2 weeks of a patient's starting psychotropic therapy. Lesions may become confluent and involve the mucosa, hands, and feet. Differential diagnosis includes infections, collagen vascular diseases, and more serious drug rashes.^{1,5,6}

Exanthems usually resolve within 2 weeks after the offending drug is discontinued.^{1,6} Because exanthems may resolve without drug discontinuation,^{1,8} you could continue treatment with the offending agent if other options are not feasible.⁹ Keep in mind, however, that exanthematous reactions may be the presenting symptom of a more serious condition, especially if associated with any of the red flags described in *Table 2*. If the suspect drug has been associated with a severe reaction, discontinue it permanently.⁴ Additional treatments for exanthems include corticosteroids, emollients, and oral antihistamines.⁶⁻⁸

Urticaria present as pruritic, blanching erythematous wheals of varying size. A single lesion will typically last <1 day, but new lesions may continuously arise. Lesions might develop several days after pharmacotherapy begins. Urticaria may be accompanied by angioedema, which can be life-threatening—particularly if it affects the airway.^{1,5-7,10}

Urticaria usually is treated with antihistamines.^{6,7} A histamine-1 blocker such as hydroxyzine or diphenhydramine—used exclusively or, for severe cases, in combination with a histamine-2 blocker such as ranitidine or cimetidine—may bring relief.¹ Dosage guidelines are based on the severity and distribution of

Table 1

Benign rashes associated with psychotropics*

Rash	Suspect drugs/classes
Exanthematous reactions	Any drug
Urticaria	Any drug
Fixed drug eruption	Any drug
Photosensitivity	Alprazolam, antipsychotics, bupropion, carbamazepine, citalopram, eszopiclone, fluoxetine, oxcarbazepine, paroxetine, sertraline, topiramate, TCAs, valproic acid, zaleplon, zolpidem
Acneiform eruptions	Antidepressants (most), aripiprazole, clonazepam, eszopiclone, lamotrigine, lithium, oxcarbazepine, quetiapine, risperidone, topiramate, zaleplon, zolpidem
Pigmentation changes	Amitriptyline, carbamazepine, citalopram, clomipramine, desipramine, eszopiclone, fluoxetine, lamotrigine, paroxetine, phenothiazines, sertraline, SGAs (most), thioridazine, thiothixene, topiramate, venlafaxine, zaleplon
Alopecia	Aripiprazole, carbamazepine, citalopram, clonazepam, dexamethylphenidate, duloxetine, escitalopram, eszopiclone, fluoxetine, fluvoxamine, haloperidol, lamotrigine, lithium, methylphenidate, mirtazapine, olanzapine, oxcarbazepine, paroxetine, risperidone, sertraline, trazodone, TCAs, valproic acid, venlafaxine, zaleplon, ziprasidone
Psoriaform eruptions	Carbamazepine, fluoxetine, lithium, olanzapine, oxcarbazepine, paroxetine, valproic acid

* Suspect any drug with any reaction
 SGAs: second-generation antipsychotics; TCAs: tricyclic antidepressants
 Source: For reference citations, see this article on CurrentPsychiatry.com

Clinical Point

Though usually benign, an exanthematous reaction may be the presenting symptom of a more serious condition

Table 2

Red flags: Warning signs of a serious drug rash

Constitutional symptoms: fever, sore throat, malaise, arthralgia, lymphadenopathy, cough
Erythroderma
Facial or mucous membrane involvement
Skin tenderness or blistering, particularly if there is full-thickness epidermal detachment
Purpura

Source: References 5,7

the eruption. If these treatments are not effective, discontinuing the offending drug should resolve the condition.^{1,4,11} Resuming the drug can result in anaphylaxis, so warn the patient to never take the offending drug again.⁴

If a patient has unstable vital signs or a rash that affects the airway—or if you believe he or she is at risk for anaphylaxis—emergent treatment is indicated.^{1,6} This may include the use of epinephrine and corticosteroids.

Table 3

Dermatologic glossary

Angioedema: a vascular reaction involving the deep dermis or subcutaneous or sub-mucosal tissue that results in localized swelling
Comedones: noninflammatory acne lesions; also called ‘blackheads’
Effluvium, anagen: hair shedding during the growth phase of the hair cycle
Effluvium, telogen: hair shedding during the resting phase of the hair cycle
Erythema: skin redness
Macule: a discolored skin lesion that is not elevated above the surface
Papule: a small, circumscribed, superficial, solid elevation of the skin <1 cm in diameter
Purpura: red or purple skin discolorations caused by bleeding underneath the skin
Pustule: a visible collection of pus within or beneath the epidermis
Wheal: a smooth, slightly elevated area that appears redder or paler than surrounding skin, is often accompanied by severe itching, and usually disappears within a few hours

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

continued



Drug eruptions

Clinical Point

Discontinue the psychotropic if a patient experiences a fixed drug eruption

Fixed drug eruptions can appear anywhere on the body as single or multiple sharply demarcated, pruritic erythematous macules. They may blister or cause a burning sensation; rarely, a patient may present with constitutional symptoms. Lesions might erupt hours to days after drug exposure. Although this condition usually is benign, consult a dermatologist if the patient exhibits constitutional symptoms or other red flags that may indicate a serious reaction.

After you discontinue the offending drug, lesions should resolve within several weeks, although there may be residual hyperpigmentation.⁶ Depending on the severity of the eruptions, topical corticosteroids or wound care may be indicated.^{6,12} Resuming the drug typically will cause the eruptions to reoccur at the same site, potentially with more lesions.^{1,5-7}

Photosensitivity describes phototoxic and photoallergic reactions. A phototoxic response resembles sunburn and is distributed in areas exposed to the sun. This can present as erythema, edema, and skin tenderness.

Delayed hypersensitivity response is a photoallergic reaction. This reaction may be pruritic and appear after sunlight exposure as eczematous, bullous, vesicular, or urticarial lesions 1 to 2 weeks after the drug is started. Photoallergic lesions may extend beyond sun-exposed areas. Phototesting can confirm this diagnosis.^{1,5,13,14}

Treat a phototoxic reaction as you would sunburn. Topical soothing agents should bring relief in 1 to 2 days.¹⁵ Instruct patients to use sunscreen and avoid the sun while taking the psychotropic.^{1,15} You may need to discontinue the medication if lesions persist.¹

Managing a photoallergic response entails avoiding the sun or discontinuing the offending agent.^{14,16} For both phototoxic and photoallergic reactions, consider consulting a dermatologist if the above measures do not resolve the rash.¹

Acne lesions present as papules or pustules, typically on the arms, legs, face, chest, or back.¹ Comedones generally are not present.

Treatment options include benzoyl peroxide, antibiotics, and topical retinoids.^{1,12,17} If these measures are insufficient, or if your patient finds the eruption distressing, discontinuing the offending drug usually resolves the condition.¹²

Pigmentation changes. Blue, gray, or brown discoloration resulting from changes in melanin deposition can affect skin, hair, and nails, particularly in sun-exposed areas. Consider in the differential diagnosis other conditions that causes skin pigmentation changes such as:

- hemochromatosis
- Addison's disease.^{1,2,7,12,18-20}

Drug-related pigmentation changes usually resolve once the drug is discontinued, but resolution may take years.¹ Cosmetics may help mask skin discoloration. A dermatologic consultation may not be necessary.¹

Laser treatment has successfully improved pigmentation changes associated with imipramine without the patient discontinuing the offending drug.²¹ Pigmentation changes associated with chlorpromazine have resolved when the drug was replaced by haloperidol²² or phenothiazines, used individually or in combination.²³

Alopecia is diffuse nonscarring hair loss. Anagen effluvium results in rapid hair loss, as seen with chemotherapeutic agents. Telogen effluvium may not occur until months after a drug is started. Frequently, patients experience only partial hair thinning. Differential diagnosis includes:

- infection
- collagen vascular disease
- iron deficiency.^{1,24}

Although alopecia is usually considered benign, patients may find it distressing. Improvement usually occurs within several months after the offending medication is discontinued.^{1,25} The benefits of continuing a medication associated with alopecia may outweigh the risks; discuss this with the patient.

Psoriasis presents as pruritic erythematous patches with scale. Psoriasis may appear at the beginning of drug therapy, or

Box 2

Case study: Is anticonvulsant to blame for painful red lesions?

While visiting the psychiatry clinic to complete paperwork, a patient receiving lamotrigine for bipolar disorder asks the office staff to tell her doctor she has a new rash on her face and in her mouth. Mrs. L, age 52, has been on the same lamotrigine dose (200 mg/d) for >1 year and was also taking lansoprazole (dosage unknown); loratadine, 10 mg/d; bupropion, 300 mg/d; quetiapine, 200 mg/d; clonazepam, 0.5 mg bid; atorvastatin, 10 mg/d; valsartan, 160 mg/d; and gabapentin, 300 mg/d. She has had no recent medication changes. Mrs. L leaves the office after finishing the paperwork.

Because lamotrigine carries an FDA “black-box” warning about serious, potentially life-threatening rashes, the psychiatrist attempts to contact Mrs. L immediately as soon as she learns of her symptoms. By phone, Mrs. L describes painful red lesions on her face and sores in

her mouth that began the day before. She says she isn’t sure if these lesions have gotten worse. She denies having fever, chills, muscle aches, arthralgia, cough, neck stiffness, shortness of breath, or any other constitutional symptoms.

The psychiatrist tells Mrs. L she may be having a serious skin reaction to lamotrigine and instructs her to stop taking the drug and visit the ER immediately. She also explains that abruptly stopping lamotrigine might cause a relapse of Mrs. L’s bipolar disorder.

The ER physician examines Mrs. L, diagnoses herpes zoster, and prescribes the antiviral famciclovir, 500 mg tid for 7 days, and hydrocodone/acetaminophen, 7.5 mg/500 mg, as needed for pain. Three days later, Mrs. L sees the psychiatrist for a follow-up visit and resumes taking lamotrigine. She has no further complications.

pharmacotherapy may worsen preexisting disease.^{2,26}

You can treat psoriasis by withdrawing the offending drug. Ultraviolet light has been used to treat drug-related psoriasis;²⁷ other treatments include topical corticosteroids and antipsoriatics. Consultation with a dermatologist is recommended.¹

Restarting a medication

By accurately identifying a rash and quickly determining its cause, you may avoid unnecessarily discontinuing a patient’s stabilizing medication (Box 2). If you need to discontinue a drug that is causing an ACDR, try to wait 2 weeks before initiating another drug. If this is not possible, cross-tapering a different medication from another class may diminish the risk of drug-rash relapse. To decrease the risk of drug-related rash, follow the manufacturer’s dosing recommendations²⁸ and use the lowest effective dose.

Explain to patients the potential risks of new medications. Teach them how to identify the red flags that indicate a seri-

ous rash and what to do if they appear.³

Educate office and hospital staff about specifics pertaining to drug rashes to help ensure that:

- vital information gets to you immediately
- evaluation and treatment can start promptly.

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Clinical Point

Treat a phototoxic rash with topical soothing agents and advise patients to use sunscreen and avoid the sun



Drug eruptions

Clinical Point

After discontinuing the offending medication, drug-related pigmentation changes may take years to resolve

Related Resources

- Dermatology Image Atlas. www.dermatlas.org.
- American Academy of Dermatology. www.aad.org.

Drug Brand Names

Alprazolam • Xanax	Hydroxyzine • Atarax
Amitriptyline • Elavil	Imipramine • Tofranil
Aripiprazole • Abilify	Lamotrigine • Lamictal
Atorvastatin • Lipitor	Lansoprazole • Prevacid
Bupropion • Wellbutrin	Loratadine • Claritin
Carbamazepine • Tegretol	Methylphenidate • Ritalin
Chlorpromazine • Thorazine	Mirtazapine • Remeron
Cimetidine • Tagamet	Olanzapine • Zyprexa
Citalopram • Celexa	Oxcarbazepine • Trileptal
Clomipramine • Anafranil	Paroxetine • Paxil
Clonazepam • Klonopin	Quetiapine • Seroquel
Desipramine • Norpramin	Ranitidine • Zantac
Dexmethylphenidate • Focalin	Risperidone • Risperdal
Diphenhydramine • Benadryl	Sertraline • Zoloft
Duloxetine • Cymbalta	Thioridazine • Mellaril
Escitalopram • Lexapro	Thiothixene • Navane
Eszopiclone • Lunesta	Topiramate • Topamax
Famciclovir • Famvir	Trazodone • Desyrel
Fluoxetine • Prozac	Valproic acid • Depakote
Fluvoxamine • Luvox	Valsartan • Diovan
Gabapentin • Neurontin	Venlafaxine • Effexor
Haloperidol • Haldol	Zaleplon • Sonata
Hydrocodone/acetaminophen	Ziprasidone • Geodon
• Vicodin	Zolpidem • Ambien

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Bottom Line

Discontinuing a medication that is causing a rash is generally an appropriate step but might not always be necessary and may exacerbate psychiatric illness. Look for red flags that indicate a serious reaction such as constitutional symptoms, facial or mucous membrane involvement, and skin tenderness or blistering. Try to wait 2 weeks before restarting pharmacotherapy in a patient who has developed a rash, or cross-taper a different medication from another class.