CME ACTIVITY

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CME Objectives

After completing this CME activity, the psychiatrist should be able to:

- Identify the symptomatology and various adverse cutaneous reactions to psychotropic medications
- Recognize and manage the most common cutaneous reactions to psychotropic medications
- Examine the morphology and distribution of the various eruptions of cutaneous lesions resulting from use of psychotropic medications

Statement of Need and Purpose

Physicians responding to articles in *The Journal of Clinical Psychiatry* and its related CME activities have indicated a need to know more about the adverse side effects of psychotropic medications. This CME enduring material presents current information to address that need. There are no prerequisites for participating in this CME activity.

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Critical Overview: Adverse Cutaneous Reactions to Psychotropic Medications

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Background: Adverse cutaneous reactions (ACRs) are common, potentially life-threatening or symptomatically and cosmetically unappealing side effects of psychotropic drugs.

Data Sources: A MEDLINE search of the literature was employed to cite the association of various psychotropic drugs with specific cutaneous reactions.

Data Synthesis: In addition to the common exanthematous eruption, we explore several serious reactions including erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria, angioedema, anaphylaxis, hypersensitivity syndrome, hypersensitivity vasculitis, erythroderma, and drug-induced lupus erythematosus. Other side effects such as alopecia, pigmentary disorders, photosensitivity, lichenoid lesions, fixed drug eruptions, and psoriasiform, acneiform, and seborrheic eruptions are discussed. Attention is paid to the morphology and distribution, systemic findings, diagnosis, and treatment of these conditions.

Conclusion: Awareness of ACRs will allow psychiatrists to deter their continuation or recurrence, educate patients who have them, and diagnose serious instances of them.

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Because adverse cutaneous reactions (ACRs) to psychotropic medications are common, often easily noticed, and potentially serious, psychiatrists should be familiar with common and life-threatening ACRs to medications used in psychiatry. Moreover, since ACRs may cause patients distress and lead to noncompliance, psychiatrists should also be aware of benign and less common ACRs. Although the exact incidence of ACRs due to particular medications is generally unknown and difficult to establish, it has been estimated that approximately 2% to 5% of patients taking psychotropic medications will develop an ACR, and ACRs remain the most common allergic reaction to psychotropic medications.[1,2] This compares with an overall ACR rate of 2% among inpatients taking a variety of medications.[3] Among psychotropic medications, carbamazepine is associated with a uniquely high rate of ACRs (10%–11%).[4,5]

One study[6] found exanthematous and fixed drug eruptions to account for one third of ACRs each and urticaria and angioedema to account for an additional fifth of ACRs. Another study[3] found exanthematous and urticarial eruptions to account for the majority of ACRs. Whereas any drug can cause common adverse reactions such as exanthems and urticaria, epidemiologic data suggest that most serious and rare ACRs are caused by only a limited number of drugs.[7] The exact incidence of these rare reactions is very difficult to ascertain. As a general rule, ACRs are not dose related. ACRs will generally recur more promptly upon rechallenge and may occur with other drugs of the same class that initially caused them.

We discuss ACRs due to psychotropic medications with particular attention to the recognition and management of the most common reactions (i.e., exanthematous) as well as life-threatening cutaneous side effects. In addition, we review various symptomatically and/or cosmetically unappealing side effects of psychotropic drugs. The morphology and distribution of the various eruptions, associated systemic findings, diagnostic workup, and treatment options are discussed. Although any given ACR can

Figure 1. Drug Exanthem Showing a Maculopapular Morbilliform Eruption

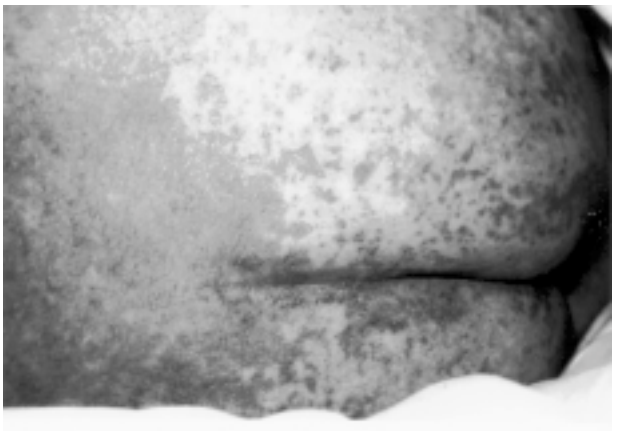


Figure 2. Targetoid Lesions in Erythema Multiforme

be caused by a variety of reported and unreported medications, we list the medications that have been associated with a particular ACR by articles found in a MEDLINE review of the literature. When possible, readers are referred to recent review articles on particular topics related to ACRs.

EXANTHEMATOUS ERUPTIONS

Reference 8 provides an overview of exanthematous eruptions. Morbilliform maculopapular eruptions are the most common type of ACR characterized by erythematous macules and papules distributed symmetrically (Figure 1), often associated with a mild fever. The lesions, thought to be caused by cell-mediated reactions (type IV hypersensitivity), generally start on the trunk and may then generalize. Mucosal and palmoplantar surfaces may occasionally be involved. In general, morbilliform eruptions begin within 1 to 2 weeks of therapy onset and resolve within 2 weeks of discontinuation, although onset within 2 to 3 days may be seen in individuals previously exposed to the drug. The exanthem may or may not recur with rechallenge and may even subside with continued administration. Diagnosis is reached clinically, and the differential diagnosis includes viral exanthems. Skin histopathology may aid in diagnosis but is often nondiagnostic. In cases of mucosal or palmoplantar involvement, abnormal liver or renal function tests or other evidence of systemic involvement, and nonblanching or targetoid lesions, more serious ACRs should be considered and ruled out, and dermatologic consultation should be obtained.

Drug discontinuation and avoidance of rechallenge, although often not necessary, may be recommended for exanthematous eruptions. Because lesions will generally clear despite drug continuation and usually do not recur on rechallenge, continuation of the drug is permissible if ongoing treatment with the particular agent is necessary and if there is no evidence of a more serious ACR. In the case of medications specifically known to cause more severe ACRs such as Stevens-Johnson syndrome and toxic epidermal necrolysis, it is prudent to discontinue the medication and avoid reexposure. Since morbilliform eruptions occur with almost any drug, the determination of the causative agent is dependent on the timing of the eruption with respect to the initiation of various drugs.

SERIOUS AND LIFE-THREATENING ACRs

Erythema Multiforme, Stevens-Johnson Syndrome, and Toxic Epidermal Necrolysis

Erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal nerolysis constitute one group of serious ACRs.[9,10] Erythema multiforme is an acute, self-limited eruption probably caused by a cell-mediated (type IV hypersensitivity) reaction. It is characterized by fever, a flu-like prodrome, and the development of symmetric polymorphic targetoid lesions favoring the extremities and palmoplantar surfaces (Figure 2) occurring within days of drug initiation. Mucosal involvement, if present, is mild. Erythema multiforme is caused by drugs in 20% of cases, being idiopathic or secondary to herpetic, mycoplasmal, and other infections in the majority of cases. Diagnosis is often reached clinically, but dermatologic consultation for

evaluation of skin histopathology may aid in diagnosis by revealing lymphocytes at the dermoepidermal junction, satellite cell necrosis, vacuolar degeneration of the basal layer, and dermal edema. Management and workup include prompt discontinuation of potential offending medications and a search for causative infections. The eruption is generally self-limited, although recurrences are not uncommon.

Stevens-Johnson syndrome and toxic epidermal necrolysis are acute life-threatening ACRs usually secondary to medications. Stevens-Johnson syndrome is characterized by severe mucositis affecting several mucosal surfaces, particularly the oral and conjunctival surfaces (Figure 3), as well as disseminated discrete dark red cutaneous macules occasionally with a necrotic center. When the skin detachment is extensive, covering greater than 30% to 40% of the skin surface, the condition is called toxic epidermal necrolysis and carries a 30% to 40% mortality rate (Figure 4). This condition leaves behind exposed, red dermis or pale necrotic epidermis that is exquisitely painful. Tracheobronchial or gastrointestinal involvement and permanent ocular damage may occur. There is usually a 1- to 3-day prodrome of flu-like symptoms not associated with an infection that usually starts within 3 to 7 days of drug initiation. The average duration of progression is generally less than 4 days, and skin heals within a few weeks.

Stevens-Johnson syndrome and toxic epidermal necrolysis are often fatal owing to sepsis secondary to loss of the cutaneous barrier, fluid loss causing prerenal azotemia, and diffuse interstitial pneumonitis leading to adult respiratory distress syndrome. Therefore, early recognition and reaction is mandatory. Diagnostic workup should include histopathologic examination of the skin, which reveals subepidermal separation and, in toxic epidermal necrolysis, full-thickness epidermal necrosis. Differentiation from staphylococcal scalded skin syndrome can be made through histologic findings, the presence of mucosal lesions, and negative blood cultures in adult patients with Stevens-Johnson syndrome and toxic epidermal necrolysis. Skin immunofluorescence studies may help exclude other blistering conditions.

Immediate withdrawal of any suspected drug, careful fluid monitoring, nutritional support, antibacterial treatment, pain control, and, if extensive cutaneous involvement is present, transfer to a burn or intensive care unit should be routinely performed. Immunosuppressives such as corticosteroids have either not been proved to help the prognosis or have been shown to worsen the prognosis. As such, these agents should be avoided. Since these conditions may mimic other blistering conditions of the skin, histopathologic and immunofluorescence evaluations are indicated.

Figure 3. Mucositis in Stevens-Johnson Syndrome

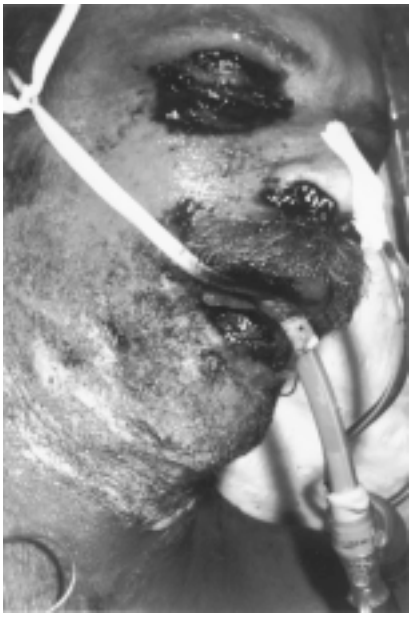
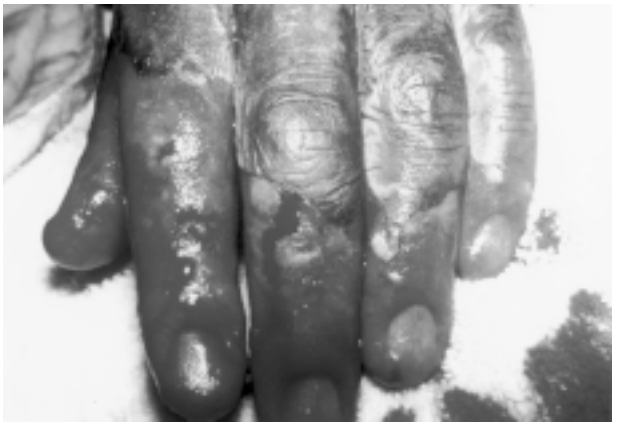


Figure 4. Sheet-Like Desquamation of Skin in Toxic Epidermal Necrolysis



Psychotropic drugs that were strongly implicated as causes of Stevens-Johnson syndrome and toxic epidermal necrolysis in a large study include carbamazepine, phenobarbital, and valproic acid.[11] Other psychotropic drugs that have been reported to cause erythema multiforme,

Stevens-Johnson syndrome, and toxic epidermal necrolysis include carbamazepine,[12–14] lamotrigine,[15,16] chlorpromazine,[17] fluvoxamine,[18] propranolol,[19] tiapride,[20] mianserin,[21–23] trazodone,[24] amoxapine,[25] clobazam,[26] and indapamide and sertraline.[27]

Urticaria, Angioedema, and Anaphylaxis

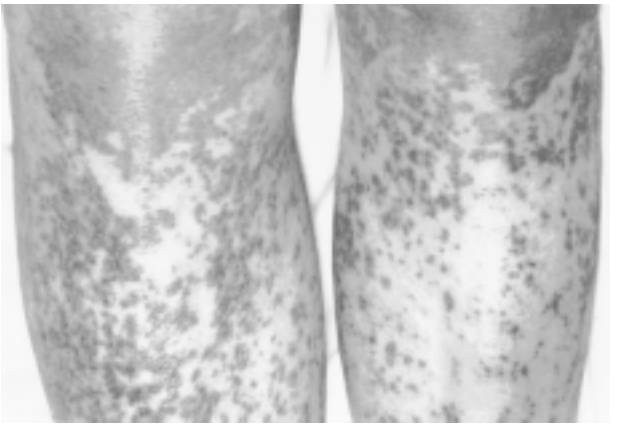
Another group of serious ACRs comprises urticaria (hives), angioedema, and anaphylaxis.[28] Urticaria are erythematous pruritic cutaneous elevations that blanch with pressure, whereas angioedema is edema of the deep dermal and subcutaneous tissues. Anaphylaxis is an acute reaction characterized by diffuse erythema and pruritus, urticaria and angioedema, laryngeal edema, bronchospasm, cardiac arrhythmias, and hypotension. These reactions are secondary to the release of pro-inflammatory modulators, particularly through an IgE-mediated mechanism (type I hypersensitivity reaction), which leads to vascular dilatation and increased vascular permeability resulting in edema. Urticaria may occur anywhere on the skin, whereas angioedema favors the face, tongue, extremities, and genitals and may be fatal when involving the larynx. Diagnosis is generally clinical. Histopathology shows superficial or deep dermal edema in urticaria and angioedema, respectively, with variable mixed infiltrates.

Urticaria and angioedema generally respond to prompt discontinuation of the offending medication and treatment with antihistamines. Histamine-1 (H_1) blockers such as hydroxyzine, cyproheptadine, diphenhydramine, alone or in combination with histamine-2 (H_2) blockers such as ranitidine and cimetidine for more refractory cases, are generally sufficient for the treatment of urticaria and angioedema. Patients who present with laryngeal angioedema, respiratory symptoms, hypotension, or anaphylaxis must be treated immediately with epinephrine and oral prednisone, as these symptoms may forewarn imminent deterioration and death. These reactions may occur with nearly all drugs. However, because the reactions generally start within minutes to hours of drug initiation, determination of the culprit agent is often not difficult. In some instances, skin patch testing by a dermatologist or allergist may aid in confirming that a patient is in fact allergic to a suspected medication.

Hypersensitivity Syndrome

The anticonvulsant hypersensitivity syndrome, which results from an inherited deficiency of epoxide hydrolase (for review, see reference 29), is seen in 1 in 1000 to 1 in 10,000 patients treated with phenytoin, carbamazepine, and phenobarbital. More recently, lamotrigine has been cited as a cause of the hypersensitivity syndrome as well.[30] The syndrome generally develops within a few weeks of initiation of therapy and recurs more severely and promptly with rechallenge. Skin findings, present in 90% of cases, range from exanthematous eruption with or without facial edema, pharyngitis, oral ulcerations, and conjunctivitis to erythroderma, erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis. Systemic findings usually include fever, tender generalized lymphadenopathy with an atypical lymphocytosis, and hepatitis. Less frequently, nephritis, anemia, thrombocytopenia, eosinophilia, diarrhea, myopathy, pseudolymphomas, lymphomas, lymphopenia, aplastic anemia, and pulmonary infiltrates are seen.

Figure 5. Palpable Purpura in Hypersensitivity Vasculitis



Since the exanthem may be indistinguishable from more benign drug exanthems, physicians should be particularly astute in identifying exanthems in the setting of implicated anticonvulsants, ruling out other symptoms of a hypersensitivity syndrome. Death may occur secondary to hepatic necrosis, renal failure, or sepsis from toxic epidermal necrolysis. Prompt discontinuation of the offending agent, administration of oral prednisone, and avoidance of phenytoin, carbamazepine, phenobarbital, and felbamate are obligatory. Other anticonvulsants such as valproate, benzodiazepines, gabapentin, and vigabatrin that do not share the metabolic pathway of these agents are likely to be safe alternatives. Treatment with *N*-acetyl-L-cysteine for hepatitis has been tried, but its efficacy remains unproven. The cutaneous lesions should be treated according to their nature, and dermatologic consultation for management of cutaneous lesions is appropriate.

Hypersensitivity Vasculitis

Drug-induced hypersensitivity vasculitis is a rare condition characterized by inflammation and necrosis of the walls of blood vessels occurring within a few weeks of drug initiation.[8–10] Cutaneous lesions are characterized by palpable purpuric papules, favoring dependent areas but occurring anywhere on the body (Figure 5). Less commonly, hemorrhagic blisters, urticaria, ulcers, nodules, and digital necrosis may be seen. Life-threatening renal, hepatic, gastrointestinal, and central nervous system involvement may occur. Serum sickness is a type III hypersensitivity reaction secondary to deposition of immune complexes in small dermal vessels causing inflammation. This syndrome is characterized by rash, fever, constitutional symptoms, arthralgias, arthritis, and visceral involvement generally starting 1 to 2 weeks after drug initiation. Erythema, typically occurring on the sides of the fingers, toes, and hands, leads to a morbilliform or urticarial eruption.

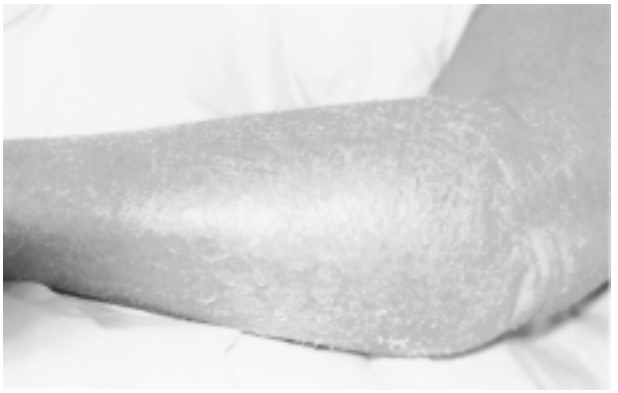
The evaluation of a patient with palpable purpura should include history and physical examination, complete blood count, renal function tests, urinalysis, and fecal occult blood testing. Hypersensitivity vasculitis must be distinguished from other cutaneous vasculitides such as Henoch-Schönlein purpura, cryoglobulinemia, polyarteritis nodosa, Wegener's granulomatosis, infections, and collagen vascular diseases. Histopathologic findings of leukocytoclastic vasculitis affecting small vessels is seen in hypersensitivity vasculitis and other small-vessel vasculitides, and immunofluorescence evaluation of a skin biopsy may aid in differentiation from other conditions. Immediate discontinuation of offending agents is mandatory, and dermatology consultation should be obtained for clinical and histologic confirmation of the diagnosis. Pure cutaneous involvement may require nothing more than monitoring or may require topical agents, or systemic anti-inflammatory agents such as corticosteroids, azathioprine, dapsone, and colchicine. Systemic involvement should be treated with systemic corticosteroids and other immunosuppressive agents such as azathioprine, cyclophosphamide, and methotrexate.

Hypersensitivity vasculitis has been reported with valproic acid,[31] maprotiline,[32] and trazodone,[33] and Henoch-Schönlein purpura secondary to chlorpromazine[34] has been noted.

Erythroderma

Erythroderma, or exfoliative dermatitis, is a rare condition characterized by generalized intensely pruritic erythema, diffuse scaling, and desquamation (Figure 6) often associated with fever, chills, and lymphadenopathy.[10] Erythroderma, the pathophysiology of which remains obscure, often develops weeks after drug initiation and may follow an exanthematous eruption. Erythroderma may lead to high-output cardiac failure due to dilated dermal vasculature and also may lead to hypothermia, hyperpyrexia, and excessive protein loss. Diagnosis is reached clinically, and dermatologic consultation for evaluation of skin histopathology may aid in differentiating drug inducement from other causes of erythroderma such as psoriasis and atopic dermatitis. Treatment includes prompt medication discontinuation, emollients, oral antihistamines, and systemic or topical corticosteroids. Psychotropic drugs noted to cause erythroderma include carbamazepine,[35–37] imipramine,[38] and desipramine.[38]

Figure 6. Diffuse Erythema and Scaling in Erythroderma



Drug-Induced Lupus Erythematosus

Drug-induced lupus erythematosus is characterized by abrupt onset of fever, malaise, myalgias, arthralgias, and arthritis generally several weeks after drug initiation.[39] Cutaneous involvement, which is seen in approximately a quarter of cases, is characterized by erythematous possibly scaling or atrophic eruptions in sun-exposed surfaces. Any of the other features of systemic lupus erythematosus including cytopenias, hemolytic anemias, hypocomplementemia, false-positive syphilis serology, hypergammaglobulinemia, and positive rheumatoid factor and antiphospholipid antibodies may be occasionally seen. Antinuclear antibodies directed at nuclear histone H2B are generally positive in drug-induced lupus erythematosus. Antibodies to double-stranded DNA may be positive. Prompt discontinuation of the offending drug is mandatory in suspected cases of drug-induced lupus erythemato-

sus, and rheumatologists, nephrologists, dermatologists, and other specialists may be necessary in managing the various manifestations of the reaction. In more severe or refractory cases, an oral corticosteroid taper may be necessary. Carbamazepine is the main culprit of drug-induced lupus erythematosus among psychotropic drugs, although various phenothiazines,[40–42] lithium,[43] and thiothixene[44] can also cause drug-induced lupus.

OTHER ACRs

Alopecia

Drug-induced hair loss (alopecia) generally presents as diffuse nonscarring reversible alopecia most commonly affecting the scalp and unaccompanied by other symptoms. Either arrest of mitotic activity (anagen effluvium) or premature entrance of follicles into a resting cycle (telogen effluvium) may be caused by drugs. Anagen effluvium is characteristic of antineoplastic drugs and causes rapid hair loss, whereas telogen effluvium is caused by a variety of medications and generally occurs a few months after medication use is initiated. In either case, alopecia is reversible with discontinuation of medications, although the hazards of medication discontinuation should be carefully considered. Dermatologic consultation is generally unnecessary.

Mood stabilizers are common causes of alopecia.[45] Lithium was found to cause hair loss in 17% of 99 patients,[46] and valproic acid causes alopecia in as many as 10% of patients.[47] Alopecia has also been reported with the use of fluoxetine,[48–53] carbamazepine,[54,55] sertraline,[56,57] imipramine,[58] desipramine,[58] fluvoxamine,[59] haloperidol,[60] and propranolol.[61,62] Alopecia areata-like lesions characterized by focal areas of potentially permanent heavy hair loss have been reported with the use of imipramine[63] and zotepine.[64] Change in hair color due to valproic acid has also been reported.[65] Although some psychiatrists have been using zinc and selenium supplementation, we are unaware of any studies that confirm their effectiveness in drug-induced alopecia.

Pigmentary Disorders

Drugs may cause variable discoloration of skin, mucosae, hair, and nails.[66] Pigmentary abnormalities are particularly common among phenothiazines. A total of 1.7% of 768 hospitalized schizophrenic patients were found to have skin pigmentary abnormalities.[67] Chlorpromazine and, less commonly, other phenothiazines cause a tan, blue-gray, or slate-gray pigmentation that is particularly prominent on sun-exposed surfaces, as well as pigmentary deposits in the lens and cornea.[68–77] The cutaneous discoloration is most likely secondary to dermal granules containing melanin bound to the drugs or their metabolites.[78] Black galactorrhea secondary to phenothiazines has also been reported.[79] In the case of chlorpromazine hyperpigmentation, it appears that the pigmentation generally reverses within months to years of discontinuing therapy; that use of other neuroleptics, including other phenothiazines, does not cause pigmentary disorders; and that lenticular changes persist, whereas corneal changes may slowly resolve.[80–82]

Slate-gray pigmentation has been noted with desipramine[83] and imipramine,[84] which is structurally related to chlorpromazine. Blue-gray pigmentation has been reported with stelazine[85] and desipramine,[86] and clomipramine has been noted to cause a pseudocyanotic discoloration.[87] Hyperpigmentation has also been reported with oxprenolol[88] and minocycline-amitriptyline combinations.[89] Chronic pigmented purpura has been noted secondary to chlordiazepoxide.[90] Vitiligo-like hypopigmentation secondary to fluphenazine enanthate has also been reported.[91]

These pigmentary changes generally occur with long-term exposure, resolve months or years after drug discontinuation, and have a proclivity for sun-exposed areas. Unless other causes of hyperpigmentation such as melanoma, hyperthyroidism, hemochromatosis, and Addison's disease are considered, dermatologic consultation may be unnecessary, although skin histopathology may aid in determination of potential etiologies. Treatment includes potential drug discontinuation or the use of topical agents to mask the pigmentary changes.

Photosensitivity

There are 2 types of photosensitive ACRs: phototoxicity and photoallergy.[92] Phototoxic reactions are secondary to alterations in the drug caused by sun exposure resulting in more pronounced cutaneous response to ultraviolet light. Phototoxicity presents as erythema, edema, desquamation, and hyperpigmentation resembling a severe sunburn that may be seen within the first day of therapy. Photoallergic reactions are caused by immunologic reactions to cutaneous proteins that bind haptens formed by exposure of drugs to light. The lesions are generally eczematous, lichenoid, bullous, or urticarial and occur 1 to 2 weeks after drug initiation. Clinically, phototoxic and photoallergic reactions may be difficult to distinguish. Treatment should include sun avoidance, use of topical sunscreens, and medication discontinuation if these measures fail or in the case of severe phototoxicity.

Dermatologic consultation is necessary only if the photosensitivity fails to respond to these measures. The use of various other topical and oral agents may be indicated in some instances. Phototoxicity has been demonstrated with practically all neuroleptics.[92,93] Other psychopharmacologic agents anecdotally associated with photosensitivity include amitriptyline,[94] protriptyline,[95] clomipramine,[96] fluoxetine,[97] alprazolam,[98] clorazepate,[99] phenelzine,[100] fluvoxamine,[101] and chlordiazepoxide.[102] Moreover, chlordiazepoxide has been noted to worsen porphyria.[103,104]

Lichenoid Drug Eruptions

Lichen planus is an idiopathic skin disease characterized by violaceous flat-topped papules and plaques with scant scales and white lacy lines called Wickham's striae.[105] A clinically and histologically similar eruption caused by a cell-mediated (type IV) hypersensitivity reaction is seen after exposure to drugs. Whereas idiopathic lichen planus has a predilection for the flexoral surfaces of the forearms and legs and orogenital mucosae, lichenoid drug eruptions occur symmetrically on the trunk and extremities, often in a photosensitive distribution, and generally sparing mucosae. Follicular involvement leading to severe alopecia and sweat duct atrophy leading to decreased sweat production may be seen. Lichenoid drug eruptions generally occur months after initiation of drug therapy, may take months to clear after discontinuation of the offending agent, and may either continue, disappear, or remit and recur with continuation of the offending agent. The lesions as well as associated post-inflammatory hyperpigmentation may be of cosmetic significance to many patients. Diagnosis is reached clinically and may be confirmed histopathologically. Dermatologic consultation is necessary for histologic confirmation. Treatment includes drug discontinuation and topical steroids. Lichenoid drug eruptions have been reported with carbamazepine,[106,107] phenothiazines,[108,109] propranolol,[110,111] lithium,[112] and lorazepam.[113]

Fixed Drug Eruptions

Fixed drug eruptions are characterized by solitary or occasionally multiple lesions that start as pruritic erythematous macules that evolve into erythematous, pruritic, burning plaques that may occasionally blister or become hemorrhagic.[114] The lesions, which develop within days to weeks of initial drug exposure, subside after drug discontinuation, leaving post-inflammatory hyperpigmentation. However, within hours of drug reintroduction, the lesions recur at the same sites that were previously involved and leave more intense post-inflammatory hyperpigmentation. Reintroduction may also lead to the development of new lesions. Cross-reactivity with similar agents may occasionally be seen. The lesions may be found on any mucocutaneous site and have a predilection for lips, sacral regions, and genitalia. Diagnosis is reached clinically and may be confirmed by histopathologic findings consistent with an erythema-multiforme–like eruption. Antihistamines are ineffective in relieving the symptoms of fixed drug eruptions, but adrenocorticotropic hormone (ACTH) and corticosteroids may diminish the intensity of the reaction. Drug discontinuation is generally necessary to prevent progression of the lesions, and dermatologic consultation is helpful in ruling out other skin conditions. Psychotropic medications causing fixed drug eruptions include chlorpromazine,[108] chlordiazepoxide,[115] carbamazepine,[116] prochlorperazine,[117] hydroxyzine,[118,119] oxazepam,[120] lormetazepam,[121] and temazepam.[122]

Psoriasiform Eruptions

Psoriasis is a disease of unknown etiology characterized by erythematous, sharply defined plaques with copious silvery-white scale and has a predilection for extensor surfaces, the scalp, and nails, although palmoplantar and flexoral involvement is also seen.[123] Drugs may cause exacerbation of preexisting psoriasis or induce psoriasis in someone without the disease. Lithium and β-blocking agents such as propranolol, when used chronically, are the drugs most commonly associated with psoriasiform eruptions, causing the development or exacerbation of various forms of psoriasis including limited plaque, generalized severe, generalized pustular, palmoplantar pustular, nail, scalp, and erythrodermic psoriasis.[123] Drug withdrawal results in improvement, and rechallenge results in psoriatic flare. Drug-induced or aggravated psoriasis is more refractory to treatment than primary idiopathic psoriasis. As the incidence of these exacerbations is not clear, preexisting psoriasis is not a contraindication for lithium therapy. Flares of psoriasis due to lithium can be managed by lithium discontinuation or dose reduction or by more aggressive treatment of the psoriasis through the use of topical steroids and other antipsoriatic agents, such as calcipotriene, psoralens plus ultraviolet A radiation, and methotrexate.[123] Other psychotropic medications causing psoriasiform eruptions include fluoxetine,[124] trazodone,[125] nitrazepam,[126] sodium valproate, and carbamazepine.[127]

Acneiform and Seborrheic Eruptions

Acneiform eruptions are characterized by papules and pustules on the face, chest, and upper back. Acneiform

Table 1. Adverse Cutaneous Reactions

Reaction Type	Major Clinical Features	Major Etiologic Agents	Complications	Management
Exanthem	Erythematous maculopapular eruptions	Any drug	May be an indicator of a more serious reaction	Consider drug discontinuation, antihistamines, topical corticosteroids
Erythema multiforme	Targetoid lesions	Carbamazepine, phenobarbital, valproate	May evolve into Stevens-Johnson syndrome	Dermatology consultation, discontinue drug
Stevens-Johnson syndrome	Mucositis, targetoid lesions	Carbamazepine, phenobarbital, valproate	Sepsis, death	Discontinue drug, dermatology consultation
Toxic epidermal necrolysis	Diffuse desquamation	Carbamazepine, phenobarbital, valproate	Sepsis, death	Discontinue drug, dermatology consultation, burn unit care
Urticaria	Erythematous edematous plaques	Any drug	May progress to angioedema	Discontinue drug, antihistamines
Angioedema	Tissue swelling	Any drug	Laryngeal involvement may cause respiratory failure	Discontinue drug, dermatology consultation, antihistamines, oral corticosteroids
Anaphylaxis	Urticaria, angioedema, bronchospasm, hypotension, arrhythmias	Any drug	Death	Epinephrine, oral corticosteroids, discontinue drug
Hypersensitivity syndrome	Fever, exanthem, lymphadenopathy, hepatitis	Carbamazepine, phenobarbital, phenytoin	Hepatic and renal failure, death	Discontinue drug, oral corticosteroids
Hypersensitivity vasculitis	Palpable purpura, renal, hepatic, gastrointestinal vasculitis	Valproate, trazodone, maprotiline	Organ failure, death	Discontinue drug, dermatology consultation, biopsies, immunosuppressive agents
Erythroderma	Diffuse erythema and scaling	Carbamazepine	High-output cardiac failure, negative nitrogen balance	Discontinue drug, dermatology consultation, topical corticosteroids, consider immunosuppressive agents
Drug-induced lupus	Fever, arthritis	Carbamazepine, phenothiazines	Renal failure, cytopenias	Discontinue drug, dermatology consultation, consider oral corticosteroids and immunosuppressive agents
Alopecia	Hair loss	Lithium, valproate, carbamazepine, fluoxetine	None	Consider drug discontinuation
Pigmentary disorders	Blue, brown, gray pigmentation	Phenothiazines	None	Consider drug discontinuation
Photosensitive reactions	Exaggerated sunburn reaction or eczematous plaques	Neuroleptics	Severe sunburns	Topical sunscreens, consider drug discontinuation
Lichenoid eruptions	Violaceous papules	Carbamazepine, phenothiazines, propranolol	Residual hyperpigmentation	Topical corticosteroids, consider drug discontinuation
Fixed eruptions	Erythematous plaques	Any drug	Residual hyperpigmentation	Discontinue drug
Psoriasiform eruptions	Erythematous scaly plaques	Lithium	None	Dermatology consultation, topical corticosteroids, antipsoriatics, consider drug discontinuation
Acneiform eruptions	Facial papules and pustules	Amineptine, lithium	None	Topical benzoyl peroxide, oral antibiotics, consider drug discontinuation
Seborrhea	Erythematous plaques with yellow greasy scales	Neuroleptics	None	Topical corticosteroids and topical antifungals

Table 2. Psychotropic Drugs and Resulting Adverse Cutaneous Reactions

Agent	Adverse Cutaneous Reactions
Drug class	
Phenothiazines	Drug-induced lupus erythematosus, pigmentary disorders, lichenoid eruptions, phototoxicity
Neuroleptics	Phototoxicity, seborrheic dermatitis
Individual drug	
Alprazolam	Phototoxicity
Amineptine	Acneiform eruption
Amitriptyline	Pigmentary disorder, phototoxicity
Amoxapine	Toxic epidermal necrolysis
Carbamazepine	Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, hypersensitivity syndrome, erythroderma, alopecia, drug-induced lupus erythematosus, lichenoid eruption, fixed drug eruption, psoriasiform eruption
Chlordiazepoxide	Pigmented purpura, phototoxicity, fixed drug eruption
Chlorpromazine	Toxic epidermal necrolysis, hypersensitivity vasculitis, pigmentary disorders, fixed drug eruption, acneiform eruptions
Clobazam	Toxic epidermal necrolysis
Clomipramine	Pigmentary disorder, phototoxicity
Clorazepate	Phototoxicity
Desipramine	Erythroderma, alopecia, pigmentary disorder
Fluoxetine	Alopecia, phototoxicity, psoriasiform eruption
Fluphenazine	Hypopigmentation
Fluvoxamine	Toxic epidermal necrolysis, alopecia, phototoxicity
Haloperidol	Alopecia
Hydroxyzine	Fixed drug eruption
Imipramine	Erythroderma, alopecia, alopecia areata, pigmentary disorder
Indapamide	Erythema multiforme
Lamotrigine	Hypersensitivity syndrome, Stevens-Johnson syndrome, toxic epidermal necrolysis
Lithium	Alopecia, psoriasiform eruption, acneiform eruption, lichenoid eruption, drug-induced lupus erythematosus
Lorazepam	Lichenoid eruption
Lormetazepam	Fixed drug eruption
Maprotiline	Hypersensitivity vasculitis, acneiform eruption
Mianserin	Erythema multiforme, toxic epidermal necrolysis
Nitrazepam	Psoriasiform eruption
Oxazepam	Fixed drug eruption
Oxprenolol	Pigmentary disorder
Phenelzine	Phototoxicity
Phenobarbital	Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, hypersensitivity syndrome
Phenytoin	Hypersensitivity syndrome
Prochlorperazine	Fixed drug eruption
Propranolol	Lichenoid eruption, Stevens-Johnson syndrome, alopecia
Protriptyline	Phototoxicity
Sertraline	Erythema multiforme, alopecia
Stelazine	Pigmentary disorder
Temazepam	Fixed drug eruption
Thiothixene	Drug-induced lupus erythematosus
Tiapride	Erythema multiforme
Trazodone	Hypersensitivity vasculitis, erythema multiforme, psoriasiform eruption
Valproate	Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, hypersensitivity vasculitis, alopecia, psoriasiform eruption
Zotepine	Alopecia areata

eruptions have been reported with lithium,[128] amineptine,[129–131] chlorpromazine,[132] and maprotiline.[133] Diagnosis is reached clinically, and drug discontinuation, although not necessary, leads to improvement. Oral and/or topical antibiotics in combination with topical benzoyl peroxide may be effective in managing the cutaneous symptoms.

Seborrheic dermatitis is a cutaneous eruption of erythematous plaques with yellowish greasy scale generally involving the scalp, ears, face, and chest. It is well-known to occur in the setting of parkinsonism, although the reason for this remains unknown.[134] A recent study[135] has shown that 60% of patients with drug-induced parkinsonism suffer from seborrheic dermatitis versus 15% of a psychiatric inpatient control group. Seborrheic dermatitis is restricted to patients with chronic as opposed to acute neuroleptic-induced parkinsonism.[136] The diagnosis is reached clinically, and treatment of seborrheic dermatitis includes topical antifungals and topical low-potency corticosteroids. Dermatologic consultation is usually unnecessary for acneiform and seborrheic lesions.

CONCLUSIONS

ACRs to psychotropic medications are common, important, and potentially serious complications of pharmacotherapy for psychiatric disorders. As such, psychiatrists should be aware of these reactions to help avoid their continuation or recurrence, to educate patients with ACRs about the significance of their reactions, and to properly diagnose serious and life-threatening ACRs. In cases where there is suspicion of a serious or life-threatening eruption, prompt dermatologic consultation may be necessary. It is important for patients to be aware of the risk of developing common ACRs. Exanthematous and urticarial eruptions may be seen with relative frequency with any medication, whereas some reactions are commonly seen in association with a particular drug (e.g., alopecia with lithium). Moreover, patients should be warned of the risks of more serious drug reactions when medications specifically associated with those reactions are prescribed. In such cases, patients should be instructed to promptly notify a health care professional if suspicious skin lesions are noted.

We have summarized the clinical features, major etiologic agents, and management of various ACRs in Table 1. In Table 2, a list of psychotropic medications and medication classes is listed along with corresponding ACRs that have been reported in the English-language MEDLINE literature. Although this list is not necessarily

representative of all possible drug reactions to a particular agent, it is helpful in determining which reactions have been previously reported with any given psychotropic drug. It should be noted that as exanthematous eruptions as well as urticaria and angioedema may be seen with any drug, these reactions have not been specifically placed in the table.

Drug names: alprazolam (Xanax and others), amitriptyline (Elavil and others), amoxapine (Asendin and others), azathioprine (Imuran and others), calcipotriene (Dovonex), carbamazepine (Tegretol and others), chlordiazepoxide (Librium and others), chlorpromazine (Thorazine and others), cimetidine (Tagamet and others), clomipramine (Anafranil and others), clorazepate (Tranxene), colchicine (ColBENEMID), cyclophosphamide (Cytoxan), cyproheptadine (Periactin), desipramine (Norpramin and others), diphenhydramine (Benadryl and others), felbamate (Felbatol), fluoxetine (Prozac), fluvoxamine (Luvox), gabapentin (Neurontin), haloperidol (Haldol and others), indapamide (Lozol and others), lamotrigine (Lamictal), lorazepam (Ativan and others), methotrexate (Rheumatrex and others), minocycline (Dynacin, Minocin and others), oxazepam (Serax and others), phenelzine (Nardil), phenytoin (Dilantin and others), prochlorperazine (Compazine), propranolol (Inderal and others), protriptyline (Vivactil), ranitidine (Zantac), sertraline (Zoloft), temazepam (Restoril and others), thiothixene (Navane), trazodone (Desyrel and others), valproic acid (Depakene).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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Instructions

Psychiatrists may receive 1 hour of Category 1 credit toward the American Medical Association Physician's Recognition Award by reading the article starting on page 714 and correctly answering at least 70% of the questions in the posttest that follows.

1. Read each question carefully and circle the correct corresponding answer on the Registration form.
2. Type or print your full name and address and Social Security, phone, and fax numbers in the spaces provided.
3. Mail the Registration form along with a check, money order, or credit card payment in the amount of $10 to: Physicians Postgraduate Press, Office of CME, P.O. Box 752870, Memphis, TN 38175-2870.
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All replies and results are confidential. Answer sheets, once graded, will not be returned. Unanswered questions will be considered incorrect and so scored. Your exact score can be ascertained by comparing your answers with the correct answers to the posttest, which will be printed in the *Journal* issue after the submission deadline. The Physicians Postgraduate Press Office of Continuing Medical Education will keep only a record of participation, which indicates the completion of the activity and the designated number of Category 1 credit hours that have been awarded.

1. Which of the following is true of adverse cutaneous reactions to psychotropic medications?
- a. Most patients chronically taking psychotropic medications will at some point develop an adverse cutaneous reaction.
- b. Most types of adverse cutaneous reactions are dose related.
- c. Exanthematous, urticarial, and fixed drug eruptions are the most common types of adverse cutaneous reactions.
- d. Clinically, it is difficult to distinguish benign from life-threatening adverse cutaneous reactions.

2. Which of the following represents an inappropriate pairing between an adverse cutaneous reaction and the class of psychotropic drugs most likely to cause it?
- a. Seborrheic dermatitis: neuroleptics
- b. Toxic epidermal necrolysis: anticonvulsants
- c. Hypersensitivity syndrome: anticonvulsants
- d. Alopecia: phenothiazines

3. You are concerned that a patient taking carbamazepine has developed the anticonvulsant hypersensitivity syndrome. Which set of features is most characteristic for this condition?
- a. Fever, rash, arthritis, and nephritis
- b. Fever, rash, hepatitis, and lymphadenopathy with lymphocytosis
- c. Fever, rash, altered mental status, and glomerulonephritis
- d. Fever, rash, rhabdomyolysis, and acute tubular necrosis

4. Which of the following is true of hyperpigmentation induced by psychotropic drugs?
- a. Its etiologic mechanism is similar to that of drug-induced phototoxicity.
- b. Chlorpromazine and structurally related drugs are the prime causes.
- c. Dermatologic consultation is necessary to make a proper diagnosis.
- d. The lens and cornea are rarely affected.

5. Which of the following patients has the highest likelihood of mortality?
- a. A patient taking phenobarbital who develops diffuse skin desquamation affecting 50% of the body surface area
- b. A patient taking carbamazepine who develops fever, lymphadenopathy, and elevated transaminases
- c. A patient taking trazodone who develops non-blanching purpuric papules on the legs associated with increased serum creatinine
- d. A patient who develops urticaria, swelling of the lip and tongue, and wheezing within half an hour of the first dose of clozapine

6. Which of the following is true of hair loss caused by psychotropic drugs?
- a. The hair loss is likely to be initially noticed in the first 6 weeks of therapy.
- b. The hair loss is often associated with scarring and may be permanent.
- c. Lithium and valproic acid are the prime causes of alopecia induced by psychotropic drugs.
- d. Oral zinc and selenium supplementation have been found to be effective in drug-induced alopecia.

7. A patient with severe bipolar disorder treated with lithium and valproic acid presents with oral and conjunctival erosions as well as desquamation of approximately half of the patient's skin surface. Which of the following is true of this patient's condition?
- a. The most likely diagnosis is Stevens-Johnson syndrome.
- b. The patient should receive systemic corticosteroids.
- c. The patient should be admitted to a dermatology or medicine inpatient service.
- d. The patient has a 40% chance of mortality from this condition.

Answers to the April 1999 CME posttest

1. b 2. b 3. d 4. c 5. d 6. e 7. b