Clinics in Dermatology (2013) **31**, 101–109

ELSEVIER

Clinics in Dermatology

# Psychiatric medications: Adverse cutaneous drug reactions

**Sarah A. Bliss, MD*, Julia K. Warnock, MD, PhD**

*Department of Psychiatry, University of Oklahoma Health Sciences Center, 4502 E. 41st St, Tulsa, OK 74135-2533*

**Abstract** Psychiatric medications are among the most widely prescribed medications in the United States. Adverse cutaneous drug reactions are associated with psychiatric medications in approximately 2% to 5% of the individuals for whom they are prescribed. Although most adverse cutaneous drug reactions associated with psychotropic medications are benign and easily treated, some can be disfiguring or life-threatening, particularly those associated with the mood stabilizers. Adverse cutaneous drug reactions associated with antidepressants, antipsychotics, and mood stabilizers are reviewed, and important issues that are of concern for the dermatologist who must consider when and how to safely discontinue a psychotropic medication in their patients are presented.


## Introduction

Adverse cutaneous drug reactions (ACDRs) are the most frequent adverse events in patients receiving drug therapy, with higher rates being associated with psychotropic medications.[1] Compounding the concern is that psychotropic medications are among the most highly prescribed medications in the United States. The most recent National Center for Health Statistics report on prescription drug use found that in 2007 to 2008, antidepressants were the most commonly prescribed drugs used by adults in the United States aged 20 to 59 years, surpassing even analgesics in frequency.[2] As these data suggest, the prevalence of psychiatric illness is very high. The most recent National Comorbidity Survey Replication estimated the 12-month prevalence of any *Diagnostic and Statistical Manual of Mental Disorders*, *Fourth Edition, Text Revision* disorder to be 26.2% in the general population, with 22.3% of these being classified as serious.[3]

Although most ACDRs associated with psychotropic medications are benign and easily treated, some can be life-threatening, and particularly those associated with the mood stabilizers. Because it is often necessary to use more than one agent concurrently to obtain remission of severe bipolar mood episodes, this risk is increased in the more severely ill patient who is taking combinations of mood stabilizers.[4-12] In addition, cross-sensitivity between these medications has been noted.[13-15]

The decision to discontinue a psychotropic medication vs symptomatic treatment of a less serious ACDR can be difficult for the dermatologist, because the severity of a patient's psychiatric illness and risk of relapse may not be immediately apparent. With severe ACDRs, the appropriate options for the dermatologist to consider with drug discontinuation can also be challenging, particularly in a patient with a severe mental illness. The decision to remove a possibly offending agent should be weighed carefully, because relapse of mania or severe depression poses a serious risk of morbidity and even mortality. In this contribution, the most common, serious, and general ACDRs associated with antidepressants, mood stabilizers, and antipsychotics will be discussed. Advice concerning when and how to safely discontinue a psychotropic medication will also be presented.

* Corresponding author. Tel.: +1 918 660 3511; fax: +1 918 660 3517.
*E-mail address:* sarah-bliss@ouhsc.edu (S.A. Bliss).

0738-081X/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.clindermatol.2011.11.014

## Special questions and considerations when discontinuing a psychiatric medication secondary to an ACDR

Any time a medication is discontinued secondary to an ADCR, the decision is based on the severity of the skin reaction vs the risk of relapse or exacerbation of the original condition for which the medication was prescribed. When the offending medication is a psychotropic, however, this process can be even more difficult than with other classes of medications. In a busy dermatology practice, it can be time consuming, and perhaps overwhelming, to evaluate a patient's current mental stability to understand fully the severity of their psychiatric condition. Further increasing the difficulty of the decision is the frequent practice in psychiatry of using one psychiatric medication to treat several different disorders or symptoms in the same patient. Also, patients are sometimes unaware of which symptoms each medication may be treating; however, to simplify the decision, the essential duty is to always evaluate the patient's immediate safety. Given that approximately 33,000 people in America die each year by suicide; this is the main risk that must be assessed before the patient leaves your office. It is easy to get overwhelmed or side-tracked when attempting this task, but there are a few high-yield questions that can help you achieve accurate assessments in a short amount of time:

### Have you recently had any thoughts that you should take your own life?

If the answer to this question is yes, this warrants further questioning. Ask if the patient has a plan, means to follow through with that plan (guns in the home or pill stashes), or intent to suicide. Suicidal ideation with intent or with a plan, or both, is a medical emergency. Despite the severity of the ACDR, if the patient is suicidal, then it is the most prudent response to transfer the patient immediately for an assessment for possible admission to an inpatient psychiatric facility. The medication potentially causing the ACDR can then be withdrawn in a safe environment, other medications initiated, and the appropriate follow-up arranged. If the ACDR requires hospitalization in a medical facility, make sure that these suicidal thoughts are communicated with the accepting medical team and a psychiatric consult is obtained.

If the patient is reporting recent vague suicidal ideation without an intent or plan, or if he or she has had previous suicide attempts, the patient remains at high risk if the medication is discontinued. The next level of treatment would depend upon the severity of the ACDR. If the ACDR is severe and, therefore, the drug must be discontinued, then inpatient treatment is the safest choice. If the ACDR is not severe or life-threatening, then immediate referral to a psychiatrist for assessment, preferably before drug withdrawal, is warranted. Remember that it is always best to err on the side of caution and arrange for an emergency assessment for the need for inpatient treatment.

### Have you ever been hospitalized in a psychiatric hospital?

The current standards for inpatient psychiatric treatment are stringent, typically requiring evidence of imminent harm to self or others, or grave deterioration in functioning. Suicide risk is highest in the first few months after inpatient psychiatric treatment than at any other time.[16] It is probably safe to assume that a patient recently discharged from a psychiatric hospital is not fully stable. A recent hospitalization indicates that the patient would be at high risk of exacerbation or relapse if the psychiatric medication is withdrawn. Even a more distant hospitalization is indicative of a higher severity of the patient's illness. In these cases, unless the ACDR is severe, consultation with the patient's psychiatrist or prescribing doctor should be made before drug withdrawal. In the case of a severe ACDR, inpatient withdrawal of the medication may be considered.

### Have you recently had a relapse of your psychiatric disorder?

A recent relapse could indicate a moderate risk of recurrence of psychiatric symptoms if the drug is withdrawn. Recent severe depression or relapse of anxiety would warrant an emergency appointment with the patient's psychiatrist or prescriber for close monitoring during drug discontinuation for a severe ACDR. If the ACDR is not severe, then consultation with a psychiatrist or a cross-taper (decreasing offending agent while slowly starting a drug from another class) is an option, usually depending on the type of drug being discontinued. An antidepressant should be tapered over at least 2 weeks to decrease the risk of relapse of the psychiatric disorder.

Once the immediate safety of the patient has been established, there are also pertinent issues relating to morbidity if a medication is withdrawn due to an ACDR. In general, antipsychotics and mood stabilizers are used for severely debilitating psychotic or manic symptoms, or when the severity of a patient's depression requires augmentation after numerous antidepressant failures. Extreme care should be taken when deciding upon withdrawal of these medications. Medication noncompliance in these patients can be a difficult barrier for treatment, so premature withdrawal of a medication can have a very serious deleterious effect on future compliance. It is also often difficult to elucidate the symptoms for which the drug is prescribed, because patients with chronic schizophrenia or delusional disorders will frequently be hesitant to discuss the reason for their medications.

Owing to these issues, if the eruption is not severe, consulting with the psychiatrist prior to withdrawal is

**Table 1** Common and general acute cutaneous drug reactions associated with frequently used antidepressants[18-48]

| Reaction | Antidepressants | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Flu | Par | Sert | Cit | Fluv | Ven | Bup | Mir | Traz | Nefaz | TCA |
| Pruritus | X | X | X | X | X | X | X | X | X | X | X |
| Exanthematous reactions | X | X | X | X | X | X | X | X | X | X | X |
| Urticaria | X | X | X | X | X | X | X | X | X | X | X |
| Angioedema | X | X | X | X | X | X | X | X | X | X | X |
| Fixed drug eruptions | X | X | X | X | X | X | X | X | X | X | X |
| Photo-sensitivity | X | X | X | X | X | | | | X | | X |
| Drug-induced pigmentation | X | X | X | X | X | X | | | | | X[a] |
| Alopecia | X | X | X | X | X | X | X | X | X | X | X |
| Acneiform eruptions | X | X | X | X | X | X | X | X | | X | X |
| Psoriasiform reactions | X | | | X | | X | | X | | | |
| Seborrheic dermatitis | X | X | | | X | X | | X | | | |
| Hyperhidrosis | | | | | | | X | | | | X[a] |

*Bup,* bupropion; *Cit,* citalopram; *Fluox,* fluoxetine; *Fluv,* fluvoxamine; *Mirt,* mirtazapine; *Nefaz*, nefazodone; *Parox,* paroxetine; *Sert,* sertraline; *TCA*, tricyclic antidepressants; *Traz,* trazodone; *Ven,* venlafaxine.

[a] See text for specific tricyclic antidepressants.

recommended. If this is not feasible, then beginning another antipsychotic with less risk of causing an ACDR while tapering the offending agent is prudent. If the eruption is severe and requires immediate withdrawal of the antipsychotic, then contacting family members or an emergency consultation with the psychiatrist is necessary.

## Most common ACDRS that can occur with psychotropic medications

### Pruritus

Pruritus usually occurs secondary to another drug reaction, but it can be a common primary adverse effect of any of the antidepressants, mood stabilizers, or antipsychotics.[17] Pruritus alone would rarely be a cause of discontinuation of a psychotropic medication when considering the risk of relapse of the patient's disorder. Although pruritus can occur with any psychotropic agent, see Tables1-3 for specific drugs more frequently associated with pruritus.

### Exanthematous reactions

Exanthematous reactions are the most common ACDR with psychotropic medications. Although they can occur with any of the antidepressants, mood stabilizers, or antipsychotics,[17] they are more likely to be an initial symptom of a more severe or life-threatening reaction with the mood stabilizers.

**Table 2** Common and general acute cutaneous drug reactions associated with mood stabilizers [4,7,17,21,49-61]

| Reaction | Mood stabilizers | | | | | | |
|---|---|---|---|---|---|---|---|
| | CBZ | OCBZ | Lithium | GBP | LTG | TPM | VPA |
| Pruritus | X | X | X | X | X | X | X |
| Exanthematous reactions | | | | | | | |
| Reactions | X | X | X | X | X | X | X |
| Urticaria | X | | | | X | X | |
| Angioedema | X | X | X | X | X | | X |
| Fixed drug | | | | | | | |
| Eruptions | X | | X | X | | | |
| Photosensitivity | X | X | | X | | X | X |
| Drug-induced pigmentation | X | | | X | X | X | |
| Alopecia | X | X | X | X | X | X | X |
| Acneiform | | | | | | | |
| Eruptions | | X | X | X | X | X | |
| Psoriasiform reactions | X | X | X | X | | | X |
| Seborrheic dermatitis | X | X | X | X | | | X |
| Hyperhidrosis | X | X | | X | X | X | |

*CBZ,* carbamazepine; *GBP,* gabapentin; *LTG,* lamotrigine; *OCBZ,* oxcarbazepine; *TPM,* topiramate; *VPA,* valproic acid.

**Table 3** Common and general acute cutaneous drug reactions associated with frequently used antipsychotic drugs[17,62-65]

| Reaction | Antipsychotic drugs | | | | | | |
|---|---|---|---|---|---|---|---|
| | Risper | Olanz | Quet | Ziprz | Arip | Cloz | Haldol |
| Pruritus | X | X | X | | | X | |
| Exanthematous reactions | X | X | X | X | X | X | X |
| Urticaria | X | X | | X | | X | |
| Fixed drug eruptions | X | X | X | | | | X |
| Photosensitivity | X | X | X | X | | X | X |
| Drug Induced Pigmentation | X | X | X | | | X | X |
| Alopecia | X | X | | X | X | | X |
| Acneiform Eruptions | X | | X | | X | | X |
| Psoriasiform Reactions | X | | X | | | | |
| Seborrheic Dermatitis | | X | X | | | | |
| Hyperhydrosis | X | X | X | | | | X |

*Arip,* aripiprazole; *Cloz*, clozapine; *Olanz,* olanzapine; *Quet,* quetiapine; *Risper,* risperidone; *Zipr,* ziprasidone.

The initial eruption usually occurs within the first 2 weeks after a patient starts the medication, and a rechallenge reaction may occur within days. Exanthems usually resolve within 2 weeks after an antidepressant has been discontinued; however, in some cases, the eruption may subside without discontinuation of the offending agent.[62,66] The decision to stop the medication should be weighed carefully. Painful skin lesions or fever may indicate a more severe ACDR, such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TENS), or hypersensitivity syndrome. In these cases, the offending agent should be stopped immediately and appropriate steps taken to assure the patient's safety during drug withdrawal (Tables 1-3).

## Urticaria and angioedema

Urticaria is the second most common adverse cutaneous reaction that can occur with any antidepressant, mood stabilizer, or antipsychotic.[62] Wheals of varying size may appear within minutes, a few hours, or even days after the initiation of the drug. Although individual lesions will typically not last more than 1 day, new lesions may continuously arise. After drug discontinuation, lesions can recur within hours after a rechallenge. Urticaria may be accompanied by angioedema, but angioedema alone is rare. Although they can occur with any psychotropic agent, see Tables 1-3 for specific drugs more frequently associated with urticarial eruptions and angioedema.

## Fixed drug eruptions

Fixed drug eruptions are common and may be associated with any of the antidepressants.[62] They can also occur with any mood stabilizer but have been specifically found in patients taking carbamazepine,[49] lithium carbonate,[17] and gabapentin.[62] All antipsychotics have been implicated as well, but notably with olanzapine,[67] quietiapine,[67] risperidone,[67] haloperidol,[68] and prochlorperazine[27,69] (Tables 1-3).

Initial lesions may appear with in hours of drug ingestion and typically resolve within several weeks after drug discontinuation. Reintroduction of the offending agent, or occasionally a similar agent, can cause a recurrence of lesions at the previous sites or even additional lesions, potentially leading to increased hyperpigmentation.[62,66,70,71]

Treatment generally starts with discontinuation of the offending agent, and again, the clinician must consider the severity of the lesions vs risk of relapse of the psychiatric disorder. (See the "Special questions…" section for questions to ask the patient.)

## Photosensitivity

Numerous antidepressants, mood stabilizers, and antipsychotics have been associated with photosensitivity (Tables 1-3). Two types of reactions—phototoxic and photoallergic—can occur with ultraviolet light exposure while patients are taking these medications.[63]

If the photosensitivity reaction is severe, then drug discontinuation may be warranted; however, preventative measures, such as sun avoidance, sunscreen, and appropriate clothing, may allow continued use of the medication if it has been successful in controlling psychiatric symptoms or if the patient is felt to be at high risk for decompensation or relapse.[72]

## Drug-induced pigmentation

Blue, gray, or brown discoloration in sun-exposed areas has been associated with many of the tricyclic antidepres-

sants, including amitriptyline,[18] imipramine,[19-21] desipramine,[22,23] and clomipramine.[24] Hair and nail changes may also be involved. These discolorations generally occur after long-term exposure and can take months or years to resolve after drug discontinuation. Selective serotonin reuptake inhibitors (SSRIs) may rarely cause a more general pigmentation change. Pigmentary changes have also been seen with some mood stabilizers and antipsychotics, most notably with thioridazine[73,74] and chlorpromazine.[74,75] In addition to skin pigmentation changes with chlorpromazine, the cornea and lens may also be involved.[76-78]

Treatment may include drug discontinuation; however, reports have noted successful use of laser treatment on a patient with imipramine-induced slate-gray hyperpigmentation without discontinuing drug therapy.[21]

### Alopecia

Alopecia has been associated with various antidepressants, mood stabilizers, and antipsychotics (Tables 1-3). Because this is a benign condition, the decision to discontinue the drug is based on the level of the patient's distress from the alopecia vs risk of relapse of the psychiatric condition.

## Severe and life-threatening ACDRs that can occur with psychotropic medications

### Erythema multiforme

Although rare with antidepressants and antipsychotics, fluoxetine,[79] paroxetine,[25] bupropion,[26] clozapine,[25] and risperidone,[25] have been associated with erythema multiformelike eruptions. Erythema multiformelike eruptions have also been found in patients being treated with carbamazepine,[49] valproic acid,[25] lamotrigine,[25] gabapentin,[25] and oxcarbazepine.[25]

Treatment must include immediate discontinuation of the offending drug with inpatient psychiatric or medical hospitalization determined by the severity of the reaction or current psychiatric symptoms. (See the "Special questions…" section for a discussion of safety issues related to psychiatric drug discontinuation.)

### SJS and TEN

Although both conditions are not typically associated with antidepressant use, SJS has rarely been associated with some of the SSRIs,[80] and TEN has in a few instances been reported with amoxapine.[81] With antipsychotics, SJS and TEN have rarely been seen with clozapine and chlorpromazine.[82] The main concern is with the mood stabilizers. SJS has been associated with carbamazepine,[50,83] valproic acid,[25] and significantly with lamotrigine,[5,9-11,25] which has an incidence of 1% in children[4,8] and 0.3% in adults.[4,8] SJS risk is increased further when valproic acid is used in combination with lamotrigine[4-12] or carbamazepine[84,85] (Table 4). Because the patient will require hospitalization, an inpatient psychiatric consult should be obtained to assess the patient's safety after discharge or make recommendations for disposition and also to obtain recommendations concerning future medication management of their psychiatric disorder. The offending drug should never be readministered because symptoms can reoccur rapidly within hours or days of reexposure.

### Drug rash with eosinophilia and systemic symptoms

Drug rash with eosinophilia and systemic symptoms is a potentially life-threatening hypersensitivity syndrome that presents as a triad of fever, rash, and internal organ involvement.[103] Drug rash with eosinophilia and systemic symptoms has almost always been associated with antiepileptic medications, but desipramine,[86] amitriptyline,[104]

**Table 4** Psychotropic medications associated with serious acute cutaneous drug reactions[5,6,9-11,26,31,32,49-51,60-62,86-102]

| Medication | Reaction | | | | | |
|---|---|---|---|---|---|---|
| | EM | SJS/TEN | DRESS | DHV | ED | EN |
| Mood stabilizers | | | | | | |
| Carbamazepine | X | X | X | X | X | X |
| Gabapentin | X | X | | | X | |
| Lamotrigine | X | X | X | X | X | |
| Lithium carbonate | | | | | X | |
| Oxcarbazepine | X | X | X | | | |
| Topiramate | X | X | | | | |
| Valproic Acid | X | X | X | | | |
| Antipsychotics | | | | | | |
| Risperidone | X | | | | X | |
| Olanzapine | | | X | | | |
| Quetiapine | | X | | | X | |
| Ziprasidone | | | | | X | |
| Aripiprazole | | | | | | |
| Clozapine | X | X | | X | | |
| Haldol | | | | X | | |
| Antidepressants | | | | | | |
| Fluoxetine | | X | X | X | X | X |
| Sertraline | X | X | | X | | |
| Paroxetine | X | X | | X | X | X |
| Fluvoxamine | | X | | X | X | |
| Venlafaxine | | | | | X | X |
| Duloxetine | X | X | | | | |
| Bupropion | X | X | | | X | |
| Mirtazepine | | | | | X | |
| Trazodone | X | | | | | |
| TCAs* | | | X | | X | |

*DHV,* drug hypersensitivity vasculitis; *DRESS,* drug rash with eosinophilia and systemic symptoms; *ED,* erythroderma; *EM,* erythema multiforme; *EN,* erythema nodosum; *SJS/TENS,* Stevens-Johnson syndrome/toxic epidermal necrolysis.

imipramine,[86] and fluoxetine have been associated with this severe ACDR. Of the antipsychotics, olanzapine[105] and perphenazine have been implicated. Mood stabilizing agents that have been associated with drug rash with eosinophilia and systemic symptoms are carbamazepine,[87,106-109] lamotrigine,[6] oxcarbazepine, and valproic acid. Because inpatient hospitalization may be necessary for rapid and timely treatment, a psychiatric consult is recommended. (See the "Special questions…" section for a discussion for safety issues related to psychiatric drug discontinuation.)

### Drug hypersensitivity vasculitis

Drug hypersensitivity vasculitis is characterized by inflammation and necrosis of the walls of blood vessels that occurs within a few weeks of drug initiation. It has rarely been associated with clozapine, trazodone,[62] maprotilin,[110] fluoxetine, fluvoxamine, paroxetine, and sertrali. The suspected offending agent should be discontinued immediately, and treatment may include topical anti-inflammatory agents for cutaneous reactions. For systemic involvement, systemic anti-inflammatory or immunosuppressants can be used. (See the "Special questions…" section for a discussion of safety issues related to psychiatric drug discontinuation.)

### Erythroderma (exfoliative dermatitis)

Erythroderma, also known as exfoliative dermatitis, has been associated with a number of antidepressants. Most of the tricyclic antidepressants have been implicated including desipramine, protriptyline, nortriptyline, amitriptyline, doxepin, trimipramine, clomipramine, and imipramine.[88] In addition, fluvoxamine, fluoxetine, sertraline, bupropion, venlafaxine and mirtazapine have also been associated with exfoliative dermatitis. Of the mood stabilizers, carbamazepine,[49,89] lithium carbonate, and gabapentin have been implicated. Antipsychotics are rare causes of this disorder, but it has been reported with quetiapine, risperidone, ziprasidone, and the phenothiazines. Symptoms typically appear in the first few weeks of drug initiation, and the dermatitis may appear abruptly or be a progression of another benign skin eruption. Treatment includes medication discontinuation, antihistamines, and topical corticosteroids. (See the "Special questions…"section for a discussion of safety issues related to psychiatric drug discontinuation)

### Erythema nodosum

Erythema nodosum is an acute inflammatory immunologic reaction to a medication consisting of painful, bright to dark-red deep-seated nodules. Erythema nodosum has rarely been associated with paroxetine and venlafaxine. Like the other serious ACDRs, immediate drug discontinuation is necessary. (See "Special questions…" for a discussion of safety issues related to psychiatric drug discontinuation.)

## General conditions associated with psychotropic medications

### Acneiform eruptions

Acneiform eruptions have been associated with almost all antidepressants. Lithium,[17] topiramate, lamotrigine, gabapentin, and oxcarbazepine are the mood stabilizers that are associated with acne, and the antipsychotics of note are quetiapine and haloperidol.[66] Typically occurring on the face, chest, and upper back, the eruption consists of folliculocentric pustules, usually without comedones. Discontinuation of the agent will lead to improvement, but is not necessary as antibiotics with topical benzoyl peroxide can manage the eruption. Retinoids are often less helpful due to the lack of comedones.

### Psoriasiform reactions

Antidepressants associated with psoriasiform reactions are fluoxetine,[27] citalopram, venlafaxine, and trazodone.[28] The mood stabilizers are carbamazepine,[52,53] lithium carbonate,[17,54] valproic acid,[81] gabapentin,[66] and oxcarbazepine.[66] Of the antipsychotics, quetiapine[66] and risperidone[66] are implicated. The severity of the psoriasis compared with the severity of the patient's psychiatric disorder should be weighed carefully when considering drug discontinuation. (See "Special questions…"section.)

### Seborrheic dermatitis

Seborrheic eruptions have been caused by paroxetine, fluvoxamine, fluoxetine, mirtazapine, and venlafaxine.[66] Of the mood stabilizers, carbamazepine,[81] lithium carbonate,[61,66] valproic acid,[53] gabapentin, and oxcarbazepine have been implicated. Seborrheic dermatitis can also be a very common ACDR in patients undergoing long-term treatment with phenothiazines. In addition to the phenothiazines, ACDR has been reported with olanzapine, quetiapine, and loxapine.

### Hyperhidrosis

An increase in perspiration has been noted with clomipramine, nortriptyline, phenelzine, bupropion, and maprotiline. Hyperhidrosis has also been noted in patients taking carbamazepine, topiramate, lamotrigine, gabapentin, and oxcarbazepine. Of the antipsychotics, it has been noted with olanzapine, quetiapine, and pimozide. Treatment options include the various aluminum chloride compounds.

## Conclusions

Although ACDRs are frequent with psychotropic medications, most of the skin lesions are benign and easily

managed. When serious ACDRs occur, care must be taken to assess safety before withdrawal of the medication. In addition, consideration of the potential for severe morbidity when a drug is withdrawn should not be underestimated. Because many patients with debilitating psychiatric illnesses have almost always had numerous medication trials before an effective regimen is found, a thorough assessment of the necessity of drug withdrawal should always be undertaken. Of the psychotropic medications frequently used by physicians today in the United States, it is the mood-stabilizing agents that have the highest incidence of severe and potentially life-threatening ACDRs. Patients who are taking mood stabilizers must be assessed carefully, and when necessary for safety reasons, the drug should be withdrawn in an inpatient psychiatric or hospital setting. Immediate attention will hopefully reduce the risk of the ACDRs developing into serious lesions.

## References


1. Svensson CK, Cowen EW, Gaspari AA. Cutaneous drug reactions. Pharmacol Rev 2001;53:357-79.
2. Gu Q, Dillon CF, Burt VL. Prescription drug use continues to increase: U.S. prescription drug data for 2007-2008. NCHS Data Brief 2010;42: 1-8.
3. Kessler RC, Chiu WT, Demler O, et al. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 2005;62:617-27.
4. Culy CR, Goa KL. Lamotrigine. A review of its use in childhood epilepsy. Paediatr Drugs 2000;2:299-330.
5. Messenheimer JA, Giorgi L, Risner ME. The tolerability of lamotrigine in children. Drug Saf 2000;22:303-12.
6. Schaub N, Bircher AJ. Severe hypersensitivity syndrome to lamotrigine confirmed by lymphocyte stimulation in vitro. Allergy 2000;55:191-3.
7. Yalçin B, Karaduman A. Stevens-Johnson syndrome associated with concomitant use of lamotrigine and valproic acid. J Am Acad Dermatol 2000;43:898-9.
8. Guberman AH, Besag FM, Brodie MJ, et al. Lamotrigine-associated rash: risk/benefit considerations in adults and children. Epilepsia 1999;40:985-91.
9. Schlienger RG, Shapiro LE, Shear NH. Lamotrigine-induced severe cutaneous adverse reactions. Epilepsia 1998;39:S22-6.
10. Page II RL, O'Neil MG, Yarborough III DR, et al. Fatal toxic epidermal necrolysis related to lamotrigine administration. Pharmacotherapy 1998;18:392-8.
11. Sachs B, Rönnau AC, von Schmiedeberg S, et al. Lamotrigine-induced Stevens-Johnson syndrome: demonstration of specific lymphocyte reactivity in vitro. Dermatology 1997;195:60-4.
12. Li LM, Russo M, O'Donoghue MF, et al. Allergic skin rash with lamotrigine and concomitant valproate therapy: evidence for an increased risk. Arqu Neuropsiquiatr 1996;54:47-9.
13. Troost RJ, Van Parys JA, Hooijkaas H, et al. Allergy to carbamazepine: parallel in vivo and in vitro detection. Epilepsia 1996;37:1093-9.
14. Dam M. Practical aspects of oxcarbazepine treatment. Epilepsia 1994;35:23-5.
15. Beran RG. Cross-reactive skin eruption with both carbamazepine and oxcarbazepine. Epilepsia 1993;34:163-5.
16. Qin P, Nordentoft M. Suicide risk in relation to psychiatric hospitalization: evidenced based on longitudinal. Arch Gen Psychiatry 2005;62:427-32.
17. Srebrnik A, Hes JP, Brenner S. Adverse cutaneous reactions to psychotropic drugs. Acta Derm Venereol Suppl (Stockh) 1991;158: 1-12.
18. Basler RS, Goetz CS. Synergism of minocycline and amitriptyline in cutaneous hyperpigmentation. [letter]. J Am Acad Dermatol 1985;12:577.
19. Ming ME, Bhawan J, Stefanato CM, et al. Imipramine-induced hyperpigmentation: four cases and a review of the literature. J Am Acad Dermatol 1999;40:159-66.
20. Hashimoto K, Joselow SA, Tye MJ. Imipramine hyperpigmentation: a slate-gray discoloration caused by long-term imipramine administration. J Am Acad Dermatol 1991;25:357-61.
21. Atkin DH, Fitzpatrick RE. Laser treatment of impramine-induced hyperpigmentation. J Am Acad Dermatol 2000;43:77-80.
22. Steele TE, Ashby J. Desipramine-related slate-gray skin pigmentation. [letter]J Clin Psychopharmacol 1993;13:76-7.
23. Narurkar V, Smoller BR, Hu CH, et al. Desipramine-induced blue-gray photosensitive pigmentation. Arch Dermatol 1993;129:474-6.
24. Tunca Z, Tunca MI, Dilsiz A, et al. Clomipramine- induced pseudocyanotic pigmentation. Am J Psychiatry 1989;146:552-3.
25. MacMorran WS, Krahn LE. Adverse cutaneous reactions to psychotropic drugs. Psychosomatics 1997;38:413-22.
26. Lineberry TW, Peters Jr GE, Bostwick JM. Bupropion-induced erythema multiforme. Mayo Clin Proc 2001;76:664-6.
27. Hemlock C, Rosenthal JS, Winston A. Fluoxetine-induced psoriasis. Ann Pharmacother 1992;26:211-2.
28. Barth JH, Baker H. Generalized pustular psoriasis precipitated by trazodone in the treatment of depression. Br J Dermatol 1986;115: 629-30.
29. Skonicki JJ, Warnock JK. Drug Eruptions. Curr Psychiatry 2008;7: 43-51.
30. Gaufberg E, Ellison JM. Photosensitivity reaction to fluoxetine [letter]. J Clin Psychiatry 1995;56:486.
31. Gillet-Terver MN, Modiano P, Tréchot P, et al. Fluvoxamine photosensitivity. Australas J Dermatol 1996;37:62.
32. Epstein JH, Wintroub BU. Photosensitivity due to drugs. Drugs 1985;30:42-57.
33. Cooper GL. The safety of fluoxetine: an update. Br J Psychiatry Suppl 1988;3:77-86.
34. Miller LG, Bowman RC, Mann D, et al. A case of fluoxetine-induced serum sickness. Am J Psychiatry 1989;146:1616-7.
35. Warnock JK, Sieg K, Willsie D, et al. Drug-related alopecia in patients treated with tricyclic antidepressants. J Nerv Ment Dis 1991;179: 441-2.
36. McCollom RA, Elbe DH, Ritchie AH. Bupropion-induced serum sickness-like reaction. Ann Pharmacother 2000;34:471-3.
37. Peloso PM, Baillie C. Serum sickness-like reaction to bupropion [letter]. JAMA 1999;282:1817.
38. Yolles JC, Armenta WA, Alao AO. Serum sickness induced by bupropion. Ann Pharmacother 1999;33:931-3.
39. Tripathi A, Greenberger PA. Bupropion hydrochloride induced serum sickness-like reaction. Ann Allergy Asthma Immunol 1999; 83:165-6.
40. Taniguchi S, Hamada T. Photosensitivity and thrombocytopenia due to amitriptyline. Am J Hematol 1996;53:49-50.
41. Ljunggren B, Bojs G. A case of photosensitivity and contact allergy to systemic tricyclic drugs, with unusual features. Contact Dermatitis 1991;24:259-65.
42. Case JD, Yusk JW, Callen JP. Photosensitive reaction to phenelzine: a case report. Photodermatol 1988;5:101-2.
43. Ogilvie AD. Hair loss during fluoxetine treatment [letter]. Lancet 1993;342:1423.
44. Gupta S, Major LF. Hair loss associated with fluoxetine. Br J Dermatol 1991;159:737-8.
45. Seifritz E, Hatzinger M, Müller MJ, et al. Hair loss associated with fluoxetine but not with citalopram [letter]. Can J Psychiatry 1995;40:362.

46. Bourgeois JA. Two cases of hair loss after sertraline use. J Clin Psychopharmacol 1996;16:91-2.
47. Bhatara VS, Gupta S, Freeman JW. Fluoxetine associated paresthesias and alopecia in a woman who tolerated sertraline. [letter]. J Clin Psychiatry 1996;57:227.
48. Parameshwar E. Hair loss associated with fluvoxamine use. Am J Psychiatry 1996;153:581-2.
49. Alanko K. Patch testing in cutaneous reactions caused by carbamazepine. Contact Dermatitis 1993;29:254-7.
50. Welykyj S, Gradini R, Nakao J, Massa M. Carbamazepine-induced eruption histologically mimicking mycosis fungoides. J Cutan Pathol 1990;17:111-6.
51. Dooley J, Camfield P, Gordon K, et al. Lamotrigine-induced rash in children. Neurology 1996;46:240-2.
52. Roberts DL, Marks R. Skin reactions to carbamazepine. Arch Dermatol 1981;117:273-5.
53. Brenner S, Wolf R, Landau M, et al. Psoriasiform eruption induced by anticonvulsants. Isr J Med Sci 1994;30:283-6.
54. Ghadirian AM, Lalinec-Michaud M. Report of a patient with lithium-related alopecia and psoriasis. J Clin Psychiatry 1986;47:212-3.
55. Hyson C, Sadler M. Cross sensitivity of skin rashes with antiepileptic drugs. Can J Neurol Sci 1997;24:245-9.
56. Wong IC, Mawer GE, Sander JW. Factors influencing the incidence of lamotrigine-related skin rash. Ann Pharmacother 1999;33:1037-42.
57. Wong IC, Mawer GE, Sander JW. Adverse event monitoring in lamotrigine patients: a pharmacoepidemiologic study in the United Kingdom. Epilepsia 2001;42:237-44.
58. Richens A. Safety of lamotrigine. Epilepsia 1994;35:S37-40.
59. Sander JW, Trevisol-Bittencourt PC, Hart YM. The efficacy and long term tolerability of lamotrigine in the treatment of severe epilepsy. Epilepsy Res 1990;7:226-9.
60. Srebrnik A, Bar-Nathan EA, Ilie B, et al. Vaginal ulcerations due to lithium carbonate therapy. Cutis 1991;48:65-6.
61. DeToledo JC, Minagar A, Lowe MR, et al. Skin eruption with gabapentin in a patient with repeated AED-induced Stevens-Johnson's syndrome. Ther Drug Monit 1999;21:137-8.
62. Kimyai-Asadi A, Harris JC, Nousari HC. Critical overview: adverse cutaneous reactions to psychotropic medications. J Clin Psychiatry 1999;60:714-25.
63. Harth Y, Rapoport M. Photosensitivity associated with antipsychotics, antidepressants, and anxiolytics. Drug Saf 1996;14:252-9.
64. Gold MS, Sweeney DR. Perphenazine-induced systemic lupus erythematosus-like syndrome. J Nerv Ment Dis 1978;166:442-5.
65. Eberlein-König B, Bindl A, Przybilla B. Phototoxic properties of neuroleptic drugs. Dermatology 1997;194:131-5.
66. Nigen S, Knowles SR, Shear NH. Drug eruptions: approaching the diagnosis of drug-induced skin diseases. J Drugs Dermatol 2003;2: 279-99.
67. Korkij W, Soltani K. Fixed drug eruption. A brief review. Arch Dermatol 1984;120:520-4.
68. Hamann GL, Egan TM, Wells BG, et al. Injection site reactions after intramuscular administration of haloperidol decanoate 100mg/mL. J Clin Psychiatry 1990;51:502-4.
69. Reilly GD, Wood ML. Prochlorperazine—an unusual cause of lip ulceration. Acta Derm Venereol 1984;64:270-1.
70. Shear NH, Knowles SR, Sullivan JR, et al. Cutaneous reactions to drugs. In: Freedbury IM, Eisen AZ, Wolff K, Austen KF, Goldsmith LA, Katz S, editors. Fitzpatrick's dermatology in general medicine. 6th ed. New York: McGraw-Hill; 2003. p. 1330-7.
71 Chosidow OM, Stern RS, Wintroub BU. Cutaneous drug reactions. In: Kasper DL, Braunwald E, Fauci AS, et al, editors. Harrison's principles of internal medicine. 16th ed. New York: McGraw-Hill; 2005. p. 318-24.
72. Moore DE. Drug-induced cutaneous photosensitivity: incidence, mechanism, prevention and management. Drug Saf 2002;25:345-72.
73 Berger H. Pigmentation after thioridazine [letter]. Arch Dermatol 1969; 100:487.
74. Ban TA, Guy W, Wilson WH. Neuroleptic-induced skin pigmentation in chronic hospitalized schizophrenic patients. Can J Psychiatry 1985;30:406-8.
75. Zelickson AS. Skin pigmentation and chlorpromazine. JAMA 1965;194:670-2.
76. Garnis-Jones S. Dermatologic side effects of psychopharmacologic agents. Dermatol Clin 1996;14:503-8.
77. Bond WS, Yee GC. Occular and cutaneous effects of chronic phenothiazines therapy. Am J Hosp Pharm 1980;37:74-8.
78. Wolf ME, Richer S, Berk MA, et al. Cutaneous and ocular changes associated with the use of cholorpromazine. Int J Clin Pharmacol Ther Toxicol 1993;31:365-7.
79. Wernicke JF. The side effect profile and safety of fluoxetine. J Clin Psychiatry 1985;46:59-67.
80. Gales BJ, Gales MA. Erythema multiforme and angioedema with indapamide and sertraline. Am J Hosp Pharmacy 1994;51:118-9.
81. Camisa C, Grines C. Amoxapine: a cause of toxic epidermal necrolysis? Arch Dermatol 1983;119:709-10.
82. Simpson GH, Pi EH, Sramek JJ. Neuroleptics and anti-psychotics. In: Dukes MNG, editor. Meyer's side effects of drugs. Amsterdam: Elsevier; 1982. p. 95-108.
83. Friedmann PS, Strickland I, Pirmohamed M, et al. Investigation of mechanisms in toxic epidermal necrolysis induced by carbamazepine. Arch Dermatol 1994;130:598-604.
84. Herbert AA, Ralston JP. Cutaneous reactions to anticonvulsant medications. J Clin Psychiatry 2001;62:22-6.
85. Yoon Y, Jagoda A. New antiepileptic drugs and preparations. Emerg Med Clin North Am 2000;18:755-65.
86. Panuska JR, King TR, Korenblat PE, et al. Hypersensitivity reaction to desipramine. J Allergy Clin Immunol 1987;80:18-23.
87. Cullinan SA, Bower GC. Acute pulmonary hypersensitivity to carbamazepine. Chest 1975;68:580-1.
88. Powell Jr WJ, Koch-Weser J, Williams R. Lethal hepatic necrosis after therapy with imipramine and despipramine. JAMA 1968;206:642-5.
89. Troost RJ, Oranje AP, Lijnen RL, et al. Exfoliative dermatitis due to immunologically confirmed carbamazepine hypersensitivity. Pediatr Dermatol 1996;13:316-20.
90. Miranda-Romero A, Pérez-Olivia N, Aragoneses H, et al. Carbamazepine hypersensitivity syndrome mimicking mycosis fungoides. Cutis 2001;67:47-51.
91 Schlienger RG, Shear NH. Antiepileptic drug hypersensitivity syndrome. Epilepsia 1998;39:S3-7.
92. Tennis P, Stern RS. Risk of serious cutaneous disorders after initiation of use of phenytoin, carbamazepine, or sodium valproate: a record linkage study. Neurology 1997;49:542-6.
93. Scerri L, Shall L, Zaki I. Carbamazepine-induced anticonvulsant hypersensitivity syndrome—pathogenic and diagnostic considerations. Clin Exp Dermatol 1993;18:540-2.
94. Okuyama R, Ichinohasama R, Tagami H. Carbamazepine induced erythroderma with systemic lymphadenopathy. J Dermatol 1996;23:489-94.
95. Sarzi-Puttini P, Panni B, Cazzola M, et al. Lamotrigine-induced lupus. Lupus 2000;9:555-7.
96. De Vriese AS, Philippe J, Van Renterghem DM, et al. Carbamazepine hypersensitivity syndrome: report of 4 cases and review of the literature. Medicine (Baltimore) 1995;74:144-51.
97. Sterker M, Berrouschot J, Schneider D. Fatal course of toxic epidermal necrolysis under treatment with lamotrigine. Int J Clin Pharmacol Ther 1995;33:595-7.
98. Chaffin JJ, Davis SM. Suspected lamotrigine-induced toxic epidermal necrolysis. Ann Pharmacother 1997;31:720-3.
99. Fogh K, Mai J. Toxic epidermal necrolysis after treatment with lamotrigine (Lamictal). Seizure 1997;6:63-5.
100. Pavlidakey GP, Hashimoto K, Heller GL, et al. Chlorpromazine-induced lupus-like disease: case report and review of the literature. J Am Acad Dermatol 1985;13:109-15.
101. McNevin S, MacKay M. Chlorprothixene-induced systemic lupus erythematosus. J Clin Psychopharmacol 1982;2:411-2.

102. Scuderi S, Gift TE. Thiothixene induced edema. Psychiatr Med 1986;4:249-52.
103. Bachot N, Roujeau JC. Differential diagnosis of severe cutaneous drug eruptions. Am J Clin Dermatol 2003;4:561-72.
104. Milionis HJ, Skopelitou A, Elisaf MS. Hypersensitivity syndrome caused by amitriptyline administration. Postgrad Med J 2000;76: 361-3.
105. Raz A, Bergman R, Eilam O, et al. A case report of olanzapine-induced hypersensitivity syndrome. Am J Med Sci 2001;321:156-8.
106. Vittorio CC, Muglia JJ. Anticonvulsant hypersensitivity syndrome. Arch Intern Med 1995;155:2285-90.
107. Scerri L, Shall L, Zaki I. Carbamazepine-induced anticonvulsant hypersensitivity syndrome: pathogenic and diagnostic considerations. Clin Exp Dermatol 1993;18:540-2.
108. Horneff G, Lenard HG, Wahn V. Severe adverse reaction to carbamazepine: significance of humoral and cellular reactions to the drug. Neuropediatrics 1992;23:272-5.
109. Robbie MJ, Scurry JP, Stevenson P. Carbamazepine-induced severe systemic hypersensitivity reaction with eosinophilia. Drug Intell Clin Pharm 1988;22:783-4.
110. Oakley AM, Hodge L. Cutaneous vasculitis with maprotiline. Aust N Z J Med 1985;15:256-7.