
Adverse Cutaneous Reactions to Psychotropic Drugs

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This article reviews the adverse cutaneous reactions due to psychotropic medications. The prevalence of skin reactions to these agents is about 5%.

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Psychotherapeutic agents have been in widespread use since the mid-1950's. Antipsychotic drugs, mood stabilizing drugs, antidepressants and anti-anxiety agents account for about 20% of all prescriptions written in the United States. These drugs frequently cause adverse side effects, especially anticholinergic effects such as dry mouth, constipation, sedation and postural hypotension. Among the common side-effects are those involving the skin; it is estimated that skin reactions to psychotropic drugs are twice as frequent as those caused by most other drugs.

ANTIPSYCHOTIC DRUGS

There are two main groups of antipsychotic drugs, phenothiazines and butyrophenones. The neurochemical effect of the phenothiazines depends on their ability to block dopamine receptors. Dopamine-sensitive adenylate cyclase is blocked by a phenothiazine in approximate proportion to its clinical potency, but is affected only slightly by butyrophenones. However, butyrophenones have the same pharmacological effects as phenothiazines and are even more potent. This indicates that these drugs do not act primarily through dopamine receptors linked to adenylate cyclase, designated D1, but through a second type of dopamine receptor – D2. The relative ability of these drugs to compete for D2 dopamine receptors closely parallels their clinical potencies and, as the binding to the receptors increases, their efficacy increases. These antipsychotic drugs also have anticholinergic and antihistaminic activities that are usually weaker than the antidepressant drugs (1, 2).

1. Chlorpromazine (Thorazine, Largactil)

Chlorpromazine (CPZ) is one of a series of alkyl amine derivatives of phenothiazine. It usually exerts a tranquilizing effect in a wide variety of psychiatric states. The drug is widely used in the treatment of schizophrenia, manic-depressive psychosis and in the restless or agitated patient with senile dementia.

Some 5% of patients who take CPZ develop a cutaneous reaction; most appear during the first to eighth week of drug initiation (3).

Contact dermatitis due to touching the drug by patients and medical personnel has been reported (4).

Lichenoid dermatitis: The first report of lichenoid eruption was published by Groth in 1961 (5) in 6 patients, all of whom developed the skin reaction 6 to 9 months after initiation of CPZ treatment. In all cases the dermatitis was localized to the neck, axillae, cubital fossae, and particularly buttocks, groin, and thighs down to the knees. A woman on CPZ (6) developed a bullous eruption on exposed areas that progressed to a lichenoid eruption.

Toxic epidermal necrolysis has been reported in a 21-year-old man (7).

Other eruptions include exfoliative dermatitis (8), Stevens-Johnson syndrome (9), exanthemic reaction (10), and fixed drug eruption (11).

Skin pigmentation: Cases of a purple skin pigmentation have been reported since the introduction of the phenothiazines, especially CPZ. The incidence is low, probably on the order of 0.1–0.2%. Large dosages of CPZ (2000 mg) for at least 14 months can cause pigmentary changes on exposed areas (12), while, paradoxically, lower doses for only a few months have been reported to cause skin pigmentation in both exposed and unexposed areas (13).

Skin pigmentation appears to result from ultraviolet light that reacts with CPZ to produce free radicals (7-hydroxy CPZ, which is purple or blue). The melanin, by its ability to trap free radicals,

further combines with irradiated CPZ or its metabolites to produce a purplish, amorphous material. This has been found in the basal layer of the epidermis, and in the dermis. On post-mortem examination, macrophages laden with this abnormal pigment have been found throughout the body, particularly in the reticulo-endothelial system and in parenchymal cells of internal organs. Histochemical examination of the abnormally pigmented material showed that it was consistent with melanin or melanin-like compound (13).

Zelickson, in his electron microscopy study of patients on CPZ (14) who developed slate-blue skin pigmentation, rejects the theory that it is the result of a melanin or melanin-like substance.

He demonstrated that melanocytes were present in the basal layer as well as dispersed throughout the lower epidermal layers, and that the melanosomes were of normal architecture. The abnormality causing the discoloration was present in the dermis that contained large masses of osmophilic material throughout. These granules were both intracellular and extracellular, extremely dense, and varied in size from 0.2–7 μ or larger. The dense granules were not true melanin, but a drug metabolite, a pseudomelanin, or some other pigment.

A later study by Zelickson (15) showed by both histology and electron microscopy that the granules were either within macrophages or scattered extracellularly throughout the upper portions of the dermis, or both. Most dense material was located perivascularly. He believed that the combination of melanin and the drug results in the discoloration, with melanin somehow able to attract CPZ from the blood and capillaries. Normally the dense granules are located in close proximity to the capillaries, but in the presence of melanin they leave the capillaries and migrate to the melanin-carrying tissues, where they aggregate into large, dense masses. Exposure to sunlight causes increased melanin production with secondary deposits of melanin in the dermis. Once the melanin is present within the dermis, the CPZ granules that have accumulated vascularly and perivascularly are attracted to the melanin; large masses of CPZ granules in close association with melanin particles are then seen.

The threshold value for the production of skin pigmentation is 800 mg/day (12). Patients maintained for years on 200–600 mg/day of CPZ were

free from pigmentation change, but developed it after the dose was raised to 800–20000 mg/day.

Phototoxic and photoallergic reactions: Photoallergic reactions, either immediate or delayed, can be induced by a lower dose of the drug than phototoxic reactions. The difference between allergic and phototoxic reactions is evident in a patch test. A positive reaction to a concentration of 0.001% CPZ indicates a photoallergic reaction; a negative reaction to 0.001% in the patch test, but a positive reaction to a 0.1% concentration of CPZ, indicates a phototoxic reaction. Exposure of patients injected with 0.0125% CPZ to UV radiation of 300–420 nm caused the immediate appearance of wheals, while phototoxic reaction of erythema was induced by injecting higher concentrations (16, 17). This was demonstrated by applying the substances tested in duplicate on normal back skin thoroughly protected from light to avoid masked photopatch test reactions (16). 24 hours after application one row of test sites was uncovered and irradiated with UV light (300–420 nm) for 10 minutes at a distance of 15 cm. The patient was instructed not to expose himself to direct natural sunlight during the period of irradiation. Immediately after UV light exposure a large wheal developed at the photopatch test site with CPZ, and the peak reaction was reached in about 24 hours. The results of the patch and photopatch tests with 0.001% CPZ were all negative (16).

The cellular mechanism is based on binding among photoproducts of CPZ and nucleic acid. The binding of CPZ to single-stranded nucleic acid is rapid, while the binding to double-stranded nucleic acid is slow. Because most DNA is double-stranded, all phototoxic or photoallergic processes bind to RNA or to single-stranded DNA. There is probably more than one kind of binding between DNA and CPZ. Purines and pyrimidine are responsible for the binding of CPZ and nucleic acid (18), but according to Stanove et al. (13), CPZ induces a phototoxic reaction that leads to melanosis caused by a transference of energy to the tyrosine-tyrosinase system with increased production of melanin.

Lupus-like syndrome: Lupus-like phenomena have been reported in patients taking CPZ. Eight patients of Fabius et al. (19) on phenothiazine treatment had positive antinuclear antibodies (ANA) and LE cell test, and 7 an increased ESR; 4 had hematological abnormalities including leu-

Table I: Cutaneous adverse reactions caused by antipsychotic drugs

Drugs	Effect
<i>Phenothiazines</i>	
Chlorpromazine	contact dermatitis, lichenoid dermatitis, toxic epidermal necrolysis, exfoliative dermatitis, erythema multiforme, Stevens- Johnson syndrome, exanthemic reaction, fixed drug eruption, skin pigmentation, phototoxic and photo – allergic reaction, lupus-like syndrome
Thioridazine	lupus-like syndrome, deep vein thrombosis, skin pigmentation
Trifluoperazine	skin pigmentation
Perphenazine	skin pigmentation, lupus-like syndrome
Fluphenazine	phototoxic reaction
Levomepromazine	lichenoid eruption, lupus-like syndrome
Dixyrazine	alopecia of scalp and axillae, depigmentation of hair, ichthyosis
Hioproperazine	lupus-like syndrome
<i>Butyrophenones</i>	
Haloperidol	photo-sensitive reaction, change in hair texture, depigmentation of hair, folliculitis, ichthyosis
Thiothixene	lupus-like syndrome, erythema multiforme, Stevens-Johnson syndrome, non-thrombocytopenic purpura, urticaria, angioedema
Pimozide	facial swelling, edema of eyelids
Loxapine	flushing

kopenia, thrombocytopenia and splenomegaly, and 4 had rheumatic manifestations. Withdrawal of the phenothiazine derivatives, chlorpromazine, perphenazine, promethazine, perazine, thioridazine, and levomepromazine, coincided with improvement.

In another study (20), a significant increase in IgM serum levels and in thromboplastin time was found in 75% of patients who developed a lupus-like syndrome after CPZ treatment for two and a half years; 64% of these patients had high ANA titers. Other findings demonstrated nDNA and nucleoprotein antibodies in 40% and 58%, respectively, of the patients studied (20).

2. Other antipsychotic drugs

Among the antipsychotic drugs, there are many reports of skin eruptions due to phenothiazines

and butyrophenones. Thioridazine (Mellaril, Melleril) (12, 19) has caused the same skin reactions as CPZ, especially lupus-like syndrome, deep vein thrombosis 15–60 days after initiation of the drug (21), and gray-purple pigmentation of the skin (13). The trifluoperazines (Terfluzine, Stelazine, Vesprin) caused skin pigmentation as well as other cutaneous changes typical of phenothiazines (13). Perphenazines (Perphenan, Trilafon) caused similar cutaneous reactions, especially lupus-like syndrome (19) and skin pigmentation (13).

Fluphenazines (Moditen, Modecate, Sediten) caused phototoxic reactions (13), while levomepromazine (Nozinan) caused lichenoid eruptions (5) and lupus-like eruptions (19), as well as other skin reactions typical of phenothiazines.

Dixyrazine caused peculiar skin reactions in 4 patients (22), including diffuse alopecia of scalp and axillae hair, depigmentation of the hair, and ichthyosis on the forehead, neck and extensor surfaces of the limbs.

Thioproperazine (Majeptil) caused lupus-like syndrome and other skin reactions typical of phenothiazine. The same adverse reactions as in CPZ were reported in patients taking sulpiridine (Modal) and ethumine (Clotiapine) (17, 18).

Among the butyrophenones, haloperidol (Haldol, Halidol, Peridol) caused some skin reactions, including a photo-sensitive reaction (23), as well as folliculitis or other skin infections in the groin and on the dorsal surface of the arms and legs. Three weeks after the hair changes were noticed, all head and body hair was shed, although the skin was normal in appearance.

Thiothixene (Navane) caused cutaneous and laboratory findings consistent with lupus-like syndrome, including telangiectatic macules on the palms and the palmar side of the fingers (21). A decrease in the dosage resolved the symptoms and lupus-like laboratory values, and increasing it brought a return of them within a few weeks. Erythema multiforme, Stevens-Johnson syndrome, non-thrombocytopenic purpura, urticaria, and angioedema have also been reported after taking the drug (9).

Pimozide (Orap, Oralep), a drug used by dermatologists for the treatment of delusions of parasitosis, caused facial swelling and edema of the eyelids in chronic schizophrenic patients (24). Loxapine (Loxitane) caused flushing in some patients (17).

Table I summarizes the adverse reactions caused by antipsychotic drugs.

ANTIDEPRESSANT DRUGS

Antidepressant drugs include tricyclic antidepressant agents and related compounds, and MAO (mono amino oxidase) inhibitors. These antidepressant drugs have been classified as heterocyclic because not all have the basic tricyclic nucleus. Other drugs like mono amino oxidase inhibitors and lithium are not first-line drugs for the treatment of depression.

Heterocyclic antidepressant drugs may relieve depression by increasing central nervous system serotonin or norepinephrine. However, this alone does not account for their antidepressant efficacy; their anticholinergic and antihistaminic effects are usually significantly greater than those of the antipsychotic medications. Some antidepressants are significantly more potent H1 receptor antagonists than the commonly used antihistamines.

MAO inhibitors are used most often when tricyclic antidepressants produce unsatisfactory results. Certain neurotic illnesses with depressive features as well as anxiety and phobias may respond especially favorably.

Amitriptyline (Elatrol, Elatrolet, Glavil)

Allergic reactions usually occur within 14 to 60 days of initiation, but have been reported as long as 4 years after first treatment with imipramine (25). Photosensitive reaction (26) and cutaneous hyperpigmentation have been reported (27). The rapidly progressive pigmentation has been attributed to the synergistic effect of amitriptyline with minocycline, potentiating the functional disruption in cellular activity that leads to hyperpigmentation (27).

Amoxapine

Amoxapine often causes dryness of the mouth (28). Erythema multiforme, and later toxic epidermal necrolysis, have been reported (29).

Desipramine (Deprexan, Norpramin)

Desipramine caused icterus, pruritus and a confluent, erythematous, maculopapular and desquamating eruption on the entire body in a woman taking 100 mg/day of the drug (30); the eruption disappeared when the drug was discontinued.

Doxepin (Sinequan, Gilex, Adepin)

This drug was reported to cause a bad after-taste and pain and soreness of the tongue, palate and gums in one patient; these completely resolved upon discontinuation of the drug (31). It also has been reported to cause photosensitive reactions (26).

Imipramine (Tofranil, Primonil)

The most common cutaneous adverse reaction to imipramine is cutaneous photosensitivity. Dry mouth and marked glossitis with or without stomatitis have been reported. Allergic reactions are uncommon and mostly affect the skin. Urticaria and angioneurotic edema occur, and the former occasionally clears without withdrawal of the drug. Retention of fluid with edema of the legs has been noted. Photosensitivity reactions are far less common than with the phenothiazines. Occasionally, exfoliative dermatitis develops (26, 32). A purplish skin pigmentation that resembles that seen with long-term high-dose CPZ has been reported. It resolved completely a few weeks after discontinuation of therapy (33, 34).

Maprotiline (Ludiomil, Melodil)

Maculopapular rash with areas of urticaria, and persistent acne are the cutaneous reactions reported to tricyclic and tetracyclic antidepressants like maprotiline. Discontinuation of these drugs resulted in disappearance of the reactions (35, 36).

Clomipramine (Anafranil, Maronil)

This drug has caused rash with photosensitivity (37), while other heterocyclic antidepressants such as protriptyline, trimipramine maleate, and tranylcypromine have not been reported to cause adverse cutaneous reactions.

Phenelazine sulphate (Nardil), Isocaboxazid

These mono amino oxidase inhibitors may cause dry mouth, peripheral edema of extremities, and skin rashes (27, 38). A lupus-like reaction with no cutaneous manifestation has been reported (39).

Trazodone (Piperazine, Desyrel)

Trazodone, available since 1982, has been extensively documented in the dermatological literature since 1984 as a drug causing cutaneous reactions. The reactions include generalized urticarial eruption and generalized, erythematous, maculo-papular

eruption. These reactions cleared when the drug was discontinued (40).

Mianserin (Bolvidin, Tolvon)

Mianserin has been reported to cause two severe cutaneous reactions – erythema multiforme and toxic epidermal necrolysis. The former disappeared with drug discontinuation, as did glossitis which was also reported (41, 42, 43).

Lithium

Lithium salts were introduced into psychiatry in 1949 for the treatment of manic-depressive psychoses. The general biology and pharmacology of the lithium ion has been known since 1957. The mechanism of action of lithium as a mood-stabilizing agent remains unknown, although effects on biological membranes are suspected. Therapeutic concentrations of lithium have almost no discernible psychotropic effects in normal man (3).

Acne: The first cutaneous manifestations caused by lithium carbonate were acneiform, reported by Kusumi (44) in 1971. Several features in the lithium-induced acneiform eruptions make it possible to distinguish them from acne vulgaris. Firstly, the acneiform lesions in lithium toxicity are found in areas not usually affected by acne vulgaris – particularly the forearms and legs. Areas usually affected in acne vulgaris may be less severely or not at all affected. Secondly, the lithium-associated acneiform lesions tend to be uniform, most of them beginning as pustules on an erythematous base rather than evolving in cycles as in acne vulgaris. Thirdly, comedones and cystic lesions, reported in acneiform eruptions, are not a feature of lithium-induced eruptions (45, 46).

Acne vulgaris exacerbated by lithium carbonate has been treated by topical preparations and tetracycline, separately and in combination. These drugs, previously effective in controlling acne vulgaris, were inadequate after the administration of lithium. Tretinoin, the topical form of retinoic acid, was added as an adjunct to the tetracycline, and the acne diminished to cosmetic degree (47).

Folliculitis: Folliculitis has been reported in patients treated with lithium carbonate for a period of one to 12 months. The eruption was asymptomatic in all cases. Microscopic examination revealed a dilated hair follicle filled with keratin and parakeratotic material. The upper dermis contained a mixture of in-

flammatory cells localized around small blood vessels and hair follicles. In most cases the rash remitted when lithium carbonate therapy was discontinued, although partial remission occurred in some of the patients who continued to take the drug. Some patients responded well to steroid cream while taking the drug. The gradual onset of the eruption and the fact that it is frequently seen in patients receiving lithium carbonate suggest that this reaction to lithium carbonate was toxic rather than allergic (48, 49).

Psoriasis: Lithium can induce chronic psoriasis in individuals without previous history (50), while some such individuals may have a family tendency for such a cutaneous response (51). Some authors recommend routine inquiry about family history of psoriasis prior to initiating the drug. Patients have been found to respond to different kinds of treatment: topical anti-psoriatic therapy (dithranol, tar, potent topical corticosteroids), Ingram treatment (tar bath, UV radiation and dithranol), and discontinuation of the lithium therapy and frequent PUVA treatment (52, 53, 54).

The mechanism by which lithium exacerbates psoriasis remains an enigma. Some theories invoke the cyclic AMP model. It is well known that drugs that cause a decrease in cyclic AMP can exacerbate psoriasis. Lithium has been shown to have an inhibitory effect *in vitro* on adenyl cyclase, and thus to decrease cyclic AMP, causing a reduction of epidermal cyclic AMP to such an extent that florid psoriasis occurs. Other evidence indicates that lithium's chemotactic effect on neutrophils may offer an alternate explanation for its psoriatic effect. Psoriasis is a disease of increased epidermal cell division and decreased cell differentiation. Hyalases within polymorphonuclear cells have been shown to increase epidermal cell division and decrease differentiation. Therefore, the increased neutrophilic migration in the dermis induced by lithium may cause increased cell division, exacerbating pre-existing psoriasis or inducing it in normal populations (55).

Maculopapular erythematous eruption and ulcerations: Nonspecific rashes including maculopapular erythematous rashes, exfoliative eruptions and generalized maculopapular rash with periorbital edema have been reported with lithium. The cutaneous manifestations appeared within two weeks of initiation of the drug and cleared after its discontinuation (56). Lithium was also responsible for what ap-

Table II: *Cutaneous adverse reactions caused by anti-depressants*

Drugs	Effect
Amitriptyline	erythema multiforme, angioneurotic edema, hyperpigmentation
Amoxapine	dryness, erythema multiforme, toxic epidermal necrolysis
Desipramine	icterus, pruritus, erythematous desquamating eruption
Doxepin	stomatitis, photosensitive reaction
Imipramine	glossitis, stomatitis, urticaria, angioneurotic edema, peripheral edema, pruritus, photosensitive reaction, exfoliative dermatitis, skin pigmentation
Maprotiline	maculopapular rash, urticaria, acneiform eruption
Clomipramine	photosensitive reaction
Phenelazine sulphate	dry mouth, peripheral edema, lupus-like syndrome
Trazodone	urticaria, exfoliative dermatitis, erythroderma, icterus, leukonychia, leukocytoclastic vasculitis, erythema multiforme, Stevens-Johnson syndrome
Mianserin	erythema multiforme, toxic epidermal necrolysis, glossitis
Lithium	acne, folliculitis, psoriasis, erythematous eruption, ulcerations, stomatitis, ichthyosis, xerosis, peripheral edema, lupus-like syndrome hair loss, nail pigmentation

peared to be a delayed hypersensitivity to a single dose of the drug in the form of a diffuse, erythematous, maculopapular and pruritic eruption on the upper chest and neck, which cleared without treatment within 3–4 days (57).

The drug has also been reported to cause a severe cutaneous reaction, most probably Stevens-Johnson syndrome, although the authors considered it to be exfoliative dermatitis (58). The skin cleared spontaneously when the drug was discontinued. Fixed drug eruption (11) and a papular, intensely pruritic dermatitis resembling dermatitis herpetiformis (59) have also been reported.

Stomatitis: Contact stomatitis (62), nonspecific stomatitis and lichenoid stomatitis are other adverse reactions to lithium carbonate. Like other heavy metals (gold, mercury, bismuth, chromium, nickel, copper and zinc), lithium can also cause contact stomatitis. While the tablet preparations appear to

be particularly problematic (60), stomatitis can also develop with the capsule preparation (61).

Ichthyosis, Xerosis: Ichthyosis accompanied by palmo-plantar hyperkeratosis (63) and xerosis (64) due to lithium carbonate therapy have been reported.

Peripheral edema due to fluids and electrolytes balance: Lithium was found to produce an increase in total body water and intracellular water and a trend towards increased extracellular water, with no significant reduction in exchangeable sodium in extracellular space (65).

Lupus-like syndrome: There have been several reports on the possible association between lithium carbonate and drug induced SLE. Johnstone et al. (66) compared 100 unselected patients with acute psychiatric disease to 112 osteoarthritic controls matched for age and sex. At a titer of 1:64 or higher, 8 of the psychiatric patients had weakly positive and 17 had strongly positive sera, 10 of the osteoarthritis patients had weakly positive and 6 had strongly positive sera, and 7 of the psychiatric group had positive sera. The control group showed no positive reactions at titers higher than 1:16 ($P < 0.002$). Seven of the 100 psychiatric patients were on lithium carbonate; 4 of these were found to have ANA, and in three of them the titer was 1:64 or greater. This tendency to higher titers of ANA in patients on lithium was statistically significant ($p < 0.01$).

Other authors reported 18% incidence of ANA or SLE in patients on lithium carbonate therapy. The absence of anti-DNA antibodies in these patients indicates that they did not have true SLE. None of the control group were positive for ANA (67). A dermatological manifestation of lupus with a positive ANA titer has been reported (68).

Hair and nail changes: Munitz et al. (69) reported the first case of hair loss on lithium carbonate in 1982 in a woman who developed diffuse scalp hair loss. A hair sample from the nape of the neck revealed 0.03 mg/dl of lithium (normal 0.0009–0.0228). In another series (71) only 12 out of 100 patients attending a lithium clinic complained of hair loss. Three had hypothyroidism and two had regrowth of hair with thyroxine. The only man with hypothyroidism and hair loss still complained of hair loss while taking thyroxine. Some regrowth occurred when lithium

was reduced and thyroxine continued, and a full head of hair grew one year after discontinuation of lithium. A woman who developed bald patches showed regrowth of hair two years after stopping lithium. Three of the 12 patients complained of loss of body hair. One with alopecia areata since the age of 5 developed alopecia totalis at 37 when she started lithium therapy, and within two years had alopecia universalis. Months after discontinuing lithium her hair regrew for the first time in several years.

It can be summarized that hair loss can occur after only a few months of lithium treatment, and withdrawal of the drug will usually lead to regrowth of hair (70). Thyroid function tests are essential in such cases since hypothyroidism may contribute to the alopecia (72).

Hooper noted a very clear demarcation line of rich gold color on the toenails of a patient on lithium (73).

Table II summarizes adverse reactions caused by antidepressant drugs.

ANTIANXIETY DRUGS

Benzodiazepines are used mainly in treating anxiety, but also as sedatives, muscle relaxants and anaesthetics, and in the treatment of alcohol withdrawal (74). Studies have proven that they are effective antianxiety agents, and are clearly more effective than a placebo (75).

Chlordiazepoxide (Librium, Servium)

Skin reactions to chlordiazepoxide are uncommon. Most are allergic in nature, including urticaria and angioneurotic edema. Generalized macular erythematous rashes of mild degree occur more frequently, with no pathognomonic features.

A photoallergic reaction was reported in one case (75), and 7 cases of lupus-like syndrome were described (76). Only a few cases of erythema multiforme and erythema nodosum have been noted (32), and one case of non-thrombocytopenic purpura (77).

Three experimental studies with chlordiazepoxide were reported. Two studies on porphyria demonstrated an exacerbation of the condition in rats (78, 79). A third study on phototoxicity of the drug showed that the N4-oxide group is responsible for the systemic effects reported for phototoxic chlordiazepoxide (80).

Diazepam (valium)

Diazepam is one of the most widely used antianxiety drugs.

Although many patients take the drug, only a few cases of cutaneous side effects have been reported in the medical literature, and most were due to an overdose (3). Varma et al. (81) reported a young man who developed a widespread skin eruption, localized mainly to pressure points on the left side of the body, after ingesting 400 mg of diazepam tablets. Three types of lesions were distinguished: blisters surrounded by an erythematous border, seen mostly on bony prominences of the left shoulder, forearm, wrist, hand, chest wall, achilean area, and right foot and forearm; dark brown and black scabs on the left temple and penis (fixed drug eruption?); and erythematous patches and plaques. Many of the lesions in these three groups had irregular shapes and angular, geometrical or circinate borders. A biopsy specimen showed eccrine sweat gland and sweat gland duct necrosis. These findings are important for the dermatologist, since hyperhidrosis triggered by emotional stress responds to diazepam. Dobson (82) reported that 5 mg of valium at bedtime for a week or two can stop emotional sweating before anticipated periods of stress.

Some of the benzodiazepines, such as oxazepam (Sera, Vagen), lorazepam (Activan, Louvan, Bonton) and midazolam (Versed, Dormicum), are also used as antianxiety drugs and as sedative hypnotics. These benzodiazepines are post hepatic metabolites with shorter half-lives and are alternates to the diazepam and chlorodiazepoxide. Only lorazepam and midazolam are known to have cutaneous manifestations. Lichenoid reaction of the gingiva to lorazepam was informed in the dental literature (83).

Midazolam, a sedative drug used also in anaesthetics, was reported to cause intense pruritus involving the head, neck and trunk (84). The pruritus resolved after several hours.

Barbiturates

Barbiturates, once used extensively as sedative-hypnotic drugs, have been largely replaced by the much safer benzodiazepines. The barbiturates reversibly depress the activity of all excitable tissues. The central nervous system is extremely sensitive, and when barbiturates are administered in sedative or hypnotic doses, there is very little effect on skeletal, cardiac or smooth muscle. Even in anaesthetic concentra-

Table III: Cutaneous adverse reactions caused by anti-anxiety drugs

Drugs	Effect
Chlordiazepoxide	urticaria, angioneurotic edema, erythematous eruption, photoallergic reaction, lupus-like syndrome, erythema multiforme, erythema nodosum, non-thrombocytopenic purpura, fixed drug eruption, porphyria, eczematous dermatitis
Flurazepam	swelling of tongue
Lorazepam	porphyria, lichenoid eruption
Diazepam	blisters, erythematous eruption, fixed drug eruption
Midazolam	pruritus
Barbiturates	maculopapular eruption, exfoliative dermatitis, urticaria, photosensitive reaction, purpura, angioneurotic edema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, lupus-like syndrome
Phenobarbitone	erythema multiforme, Stevens-Johnson syndrome, thrombophlebitis

tions, direct effects on peripheral excitable tissues are minor and do not create difficulties if the anaesthesia is not prolonged. However, if depression is extended, as in acute barbiturate intoxication, serious defects in cardiovascular and other peripheral functions occur (85).

Rashes due to barbiturates appear frequently. Long-term acting barbiturates are generally believed to cause more rashes than the more freely excreted short-acting barbiturates.

The most common reactions to barbiturates are allergic, the most typical being a maculopapular eruption which may be preceded by pruritus, accompanied by fever and lymphadenitis. Less commonly, a scarletiform rash occurs. Exfoliative dermatitis has also been reported. Urticaria and serum sickness occur, but are reported less frequently with the long-acting barbiturates.

Photosensitivity is not common after barbiturate therapy, but has been noted. Purpura, a punctate purpuric rash, erythema multiforme and especially Stevens-Johnson syndrome with severe mucosal involvement are well known (84).

Phenobarbitone, Phenobarbital

Allergic reactions affecting the skin were reported in individuals taking phenobarbitone (86, 87). Acute

cutaneous reactions caused by the drug include erythema multiforme and Stevens-Johnson syndrome. A case (87) was described in a two-day-old neonate on 9 mg phenobarbitone for 10 days because of right-sided focal seizures. He developed maculopapular lesions and pustules on the arms, legs and trunk accompanied by speared soles and palms, red peeling penis and perineum, dry scaling skin around the lips and periorbital areas, congested nose with boggy mucosa and bullous lesions, erythema of the eye lid and conjunctiva. The skin lesions improved one day after the drug was discontinued, and 6 days later only a faint erythematous rash was noted. Three cases of thrombophlebitis were reported in intravenous phenobarbitone treatment (88). Barbiturates with short and ultra-short half-life now used in some outpatient anaesthetic procedures are safe and have no known cutaneous side-effects.

Table III summarizes adverse reactions caused by antianxiety drugs.

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