Acta Dermatovenerol Croat 2010;18(1):56-67 REVIEW

Adverse Cutaneous Reactions to Psychopharmaceuticals

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Received: October 29, 2009
Accepted: January 8, 2010

SUMMARY Adverse cutaneous reactions to psychoactive drugs are common. They disturb and interrupt therapy often leading to non-compliance. The majority of adverse cutaneous reactions are benign if they are promptly recognized. Withdrawal of suspected drug is the first step for consequent treatment. As some adverse cutaneous reactions are life threatening, the most important action is to discontinue the drug usage promptly, thus minimizing morbidity. It is very important for physicians to be aware of the potentially serious adverse skin reactions to psychoactive drugs. Patients must be provided with simple information on these adverse effects.

KEY WORDS: adverse cutaneous reactions, psychoactive drugs

INTRODUCTION

An adverse cutaneous reaction caused by a drug is any undesirable change in the structure and function of the skin, its appendages, or mucous membranes (1). Drug reactions encompass all adverse events related to drug administration, regardless of the etiology. The terms “drug allergy”, “drug hypersensitivity” and “drug reaction” are often used interchangeably. Drug hypersensitivity is defined as an immune-mediated response to a drug agent in a sensitized patient. Drug allergy is restricted specifically to a reaction mediated by IgE. Drug reactions can have immune and non-immune etiology. The majority (75 to 80 percent) of adverse drug reactions are caused by predictable, non-immune effects (2). The remaining 20 to 25 percent of adverse drug events are caused by unpredictable effects that may or may not be immune-mediated (1). Immune-mediated reactions account for 5 to 10 percent of all drug reactions and constitute true drug hypersensitivity, with IgE-mediated drug allergies falling into this category (3,4). The Gell and Coombs classification system describes the predominant immune mechanisms that lead to clinical symptoms of drug hypersensitivity. This classification system includes type I reactions (IgE-mediated); type II reactions

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(cytotoxic); type III reactions (immune complex); and type IV reactions (delayed, cell-mediated). However, some drug hypersensitivity reactions are difficult to classify because of the lack of evidence supporting the predominant immune mechanism. These include certain cutaneous drug reactions (i.e. maculopapular rashes, erythroderma, exfoliative dermatitis, and fixed drug reactions) and specific drug hypersensitivity syndromes (5,6). Unpredictable, non-immune drug reactions can be classified as pseudo-allergic, idiosyncratic or intolerance. Adverse drug reactions caused by immune and non-immune mechanisms are a major cause of morbidity and mortality worldwide. They are the most common iatrogenic illness, complicating 5 to 15 percent of therapeutic drug courses (7,8).

ADVERSE CUTANEOUS REACTIONS

The concept of Severe Cutaneous Adverse Reactions (SCARs) has arisen because of difficulties surrounding the definition and differential diagnosis of erythema multiforme, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) (9-13). The acronym SCARs encompasses the continuum between these three conditions, ranging from erythema multiforme at the lower end of morbidity and mortality (mortality approximately 1%) to the much more severe TEN with a mortality of 30%-35% (14-16). SCARs are thought to be T-cell mediated delayed hypersensitivity reactions (13-15). They can be caused by autoimmunity and a number of allergens, including bacteria and viruses. However, drugs are probably the most common cause, particularly of the more severe reactions such as TEN (9). Adverse cutaneous drug reactions (ACDRs) associated with medications have a rate of 2.2 *per* 1000 courses of drug therapy; it has been estimated that approximately 2%-5% of patients taking psychotropic drugs will develop ACDR (1). These rates are higher in patients taking psychotropic drugs (1). The exact incidence of these reactions is very difficult to determine. ACDRs are not dose related and they will generally recur more promptly upon re-exposure and may occur with other drugs of the same class that initially caused them.

PSYCHOACTIVE DRUGS

A psychoactive drug or psychotropic substance is a chemical substance that acts primarily upon the central nervous system where it alters brain function, resulting in temporary changes in perception, mood, consciousness and behavior. The Anatomical Therapeutic Classification code N (Nervous system) includes anesthetics, analgesics, anti-epileptics, anti-parkinsonian drugs, psycholeptics, psycho-analeptics, and other nervous system drugs.

MOST COMMON ADVERSE CUTANEOUS DRUG REACTIONS

Pruritus

Pruritus occurs secondary to most ACDRs and is often primary adverse effect of nearly all antipsychotic, antidepressant and mood stabilizing drugs (17). Pruritus has been reported after using carbamazepine, lithium carbonate, valproic acid, lamotrigine, gabapentin, and oxcarbazepine (18-20). Pruritus is an annoying physical symptom, frequently related to mental states. Dermatologic treatment commonly includes psychotropic medications. The high incidence of itching among psychiatric inpatients necessitates awareness of the psychiatrist of this potential discomfort. Examination, diagnosis and treatment when needed can relieve the physical symptoms, which may also have an emotional effect on the patient (21).

Exanthematous eruptions

Exanthematous eruptions, also known as morbilliform or maculopapular eruptions are the most common form of drug eruptions, accounting for approximately 95 percent of skin reactions (22). Simple exanthemas are erythematous changes in the skin without evidence of blistering or pustulation. The eruption typically starts on the upper trunk and spreads peripherally in a symmetric fashion. Eruption may generalize and include the entire body including palms, soles and mucous membranes. Pruritus is almost always present. These eruptions usually occur within 1 week of therapy initiation and resolve within 7 to 14 days. Resolution occurs with a change in color from bright red to brownish red, which may be followed by scaling or desquamation. This type of reaction is common (1%) and can occur to most mood stabilizers, carbamazepine (23) and lamotrigine (24-26). These two mood stabilizing agents have the highest incidence of exanthematous reactions among the mood-stabilizing agents. Exanthematous reactions are the most common type of ACDR and can occur with any of the antidepressants (27). Eruption usually occurs within the first two weeks of administration with a re-challenge reaction occurring within days. In some cases, the eruption may subside without discontinuation of the drug and

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will not recur on readministration of the drug. Continuation of drug usage is allowed if ongoing treatment with a particular antidepressant is necessary and there is no evidence of a more serious ACDR. Exanthematous reactions have been reported after using various tricyclic antidepressants (TCAs) (28) and selective serotonin reuptake inhibitors (SSRIs) (28-30), especially paroxetine (31,32), fluoxetine (33) and sertraline (28,34). Maculopapular eruptions have been noted after taking lithium (35,36). Antipsychotics can also cause exanthematous reactions, in some cases the eruption may subside without discontinuation of the causative agent and does not recur on readministration (37). Skin rashes are a well known complication of antiepileptic drug (AED) treatment. It has also been recognized that some patients will develop rashes from multiple AEDs (cross sensitivity) (38). The cross sensitivity rate for rashes involving carbamazepine and phenytoin is 40%-58%. If rash develops from either of these AEDs, valproate or clobazam are safe alternatives (39).

Urticaria and edema

Urticaria is characterized by pruritic red wheals of various sizes. Individual lesions generally last for less than 24 hours, although new lesions can commonly develop. When deep dermal and subcutaneous tissues are also swollen, the reaction is known as angioedema. Angioedema is frequently unilateral and non-pruritic and lasts for 1 to 2 hours, although it may persist for 2 to 5 days (40). Urticaria and angioedema, when associated with drug use, are usually indicative of an immunoglobulin E (IgE)-mediated immediate hypersensitivity reaction. Signs and symptoms of IgE-mediated allergic reactions typically include pruritus, urticaria, cutaneous flushing, angioedema, nausea, vomiting, diarrhea, abdominal pain, nasal congestion, rhinorrhea, laryngeal edema, and bronchospasm or hypotension, or both. Urticaria is the second most common cutaneous adverse effect (17). Urticaria and/or angioedema have been reported after administration of clomipramine (41), paroxetine (42), ziprasidone (43), clozapine (44) and bupropion (45).

Fixed drug reactions

Fixed drug reactions (FDR) usually appear as solitary, erythematous, bright red or dusky red maculae that may evolve into an edematous plaque; bullous-type lesions may be present. FDRs are most commonly found on the genitalia and in the perianal area, although they can occur anywhere on the skin surface. Some patients may complain of burning or stinging, and others may have fever, malaise, and abdominal symptoms. FDR can develop from 30 minutes to 8-16 hours after ingestion of the medication. After the initial acute phase lasting for days to weeks, residual grayish hyperpigmentation develops. On rechallenge, not only do the lesions recur in the same location, but often new lesions also appear. FDRs can develop in patients using any antidepressant, mood stabilizer, antipsychotic or antiepileptic. They have been specifically found in patients taking carbamazepine (23), lithium carbonate (20), gabapentin (20), olanzapine (19), quetiapine (19), risperidone (19), haloperidol (19), and prochlorperazine (19).

Photosensitivity

Photosensitivity induced by exogenous agents can be divided into phototoxicity and photoallergy. Phototoxicity is the result of direct tissue injury caused by the phototoxic agent and radiation. It can occur in all individuals exposed to adequate doses of the agent and activating wavelengths of radiation. Acute phototoxicity usually occurs within hours of exposure to the phototoxic agent and UV radiation. Symptoms are drug-dose and UV-dose dependent, but at sufficient doses, the patient complains of a burning and stinging sensation on exposed areas such as forehead, nose, V area of the neck, and dorsa of the hands. Erythema and edema may appear within hours of exposure; in severe cases, vesicles and bullae may develop. Protected areas such as nasolabial folds, postauricular, submental areas, and areas covered by clothing are spared. In contrast, photoallergy is a type IV delayed hypersensitivity response to a molecule that has been modified by absorption of light energy. It has a sensitization phase, occurs only in sensitized individuals, and requires only a minimal concentration of the photoallergen. In sensitized individuals, exposure to the photoallergen and sunlight results in the development of a pruritic, eczematous eruption within 24 to 48 hours after exposure. Although the morphology is clinically indistinguishable from that of allergic contact dermatitis, the distribution of the eruption in photoallergy is predominantly confined to sun-exposed areas; however, in severe cases it may spread to the covered areas, at a lower intensity. There are many reports of photosensitivity caused by antipsychotic and antidepressant agents. Although the majority of the research was focused on the photosensitizing potential of chlorpromazine, other antipsychotics and antidepressants have been

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shown to cause cutaneous photosensitivity. In order to properly diagnose photosensitivity to systemic drugs it is important to prove photosensitivity by phototesting and to rule out other causes of systemic photosensitivity such as systemic lupus erythematosus and porphyria cutanea tarda (46).

Drug induced pigmentation

Pigmentation disorders of the skin can be either hypomelanotic or hypermelanotic, or may present with a pattern of mixed hypo- and hypermelanosis. Among antipsychotics, phenothiazines are most frequently associated with pigmentary changes, especially chlorpromazine, thioridazine and haloperidol (19). Chlorpromazine and related phenothiazines can produce bluish-gray pigmentation, especially in sun-exposed areas, and pigmentations of the conjunctivae (17). Pigmentary changes have been observed with amitriptyline, imipramine, desipramine and clomipramine (18). Among mood stabilizers, pigmentary changes have been associated with carbamazepine (20), topiramate (20), lamotrigine (20) and gabapentin (20). Cutaneous discoloration is secondary to dermal granules containing melanin bound to the drugs or their metabolites. In most cases, discoloration slowly fades with discontinuation of the offending agent. Treatment options include drug discontinuation or use of cosmetic agents to mask skin discoloration.

Alopecia/hair changes

Drug induced alopecia is characterized as a diffuse, non-scarring alopecia with localized or generalized hair loss, which commonly affects the scalp (37). Hair loss generally occurs when normal telogen hairs are shed, typically several months after the drug administration or rapidly in anagen effluvium. The hair loss is reversible upon discontinuation of the offending agent. Drug induced alopecia has been reported with numerous antipsychotics, antidepressants and mood stabilizing drugs. Hirsutism and hypertrichosis have been reported with various antidepressants and rarely with mood stabilizers (see Table 1).

SEVERE AND LIFE-THREATENING ADVERSE CUTANEOUS DRUG REACTIONS (SCARs)

Erythema multiforme

Erythema multiforme-like eruptions occur within days of the drug initiation. The reaction is characterized by typical target lesions that are variable in size, configuration and appearance. The typical eruption is acute, polymorphous, and sharply demarcated. Distribution is symmetrical on dorsal surface extremities and palmoplantar surfaces. Mucous membranes can be severely involved in some episodes and spared in others. Erythema multiforme-like eruption can precede a more severe reaction such as SJS or TEN. In most cases, erythema multiforme-like eruption involves well under 10 percent of the body surface area (17). In 88 hospital cases of erythema multiforme-like eruption prospectively included in the Severe Cutaneous Adverse Reactions study, the median involvement was 1 percent of the body surface area (9). Erythema multiforme-like eruptions do not occur frequently with antidepressants and antipsychotics, but have been observed with fluoxetine (18), paroxetine (18) and bupropion (18); and among antipsychotics with clozapine (19) and risperidone (19). Erythema multiforme-like eruption occurs more frequently with mood stabilizing drugs such as carbamazepine (20,47), valproic acid (20,47), lamotrigine (20), gabapentin (20) and oxcarbazepine (20). The acronym EMPACT is suggested (E: erythema; M: multiforme; associated with P: phenytoin; A: and; C: cranial, radiation; T: therapy) to best describe erythema multiforme-like lesions that develop particularly in the radiation field. EMPACT should be classified as a specific entity among the erythema multiforme-like drug reactions as it only appears after radiotherapy and seizure prophylaxis with the anticonvulsant phenytoin (48,49).

Stevens-Johnson syndrome and toxic epidermal necrolysis

SJS and TEN (Lyell's syndrome) are rare and life-threatening, mainly drug induced reactions characterized by confluent purpuric and erythematous maculae evolving to flaccid blisters and epidermal detachment predominating on the trunk and upper limbs and associated with mucous membrane involvement. Early identification and withdrawal of suspect drugs are essential for good patient outcome. The suspected medication should never be readministered. Treatment is mainly symptomatic (17). Antipsychotics are rarely the cause of SJS and TEN, but they have been observed with clozapine (19), chlorpromazine (19) and flurazepam (50). Among antidepressants, bupropion (18) has been observed to cause SJS, while fluoxetine (30,51,52), fluvoxamine (30), paroxetine (53) and amoxapine (18) were in rare instances associated with TEN. Mood stabilizers are often the cause of SJS and TEN, life-threatening reactions

Table 1. Most common ACDRs

MOST COMMON ACDRs	DRUGS	REFERENCE(S)
Pruritus		
	All antipsychotics	17, 82
	All antidepressants	17, 82
	All mood stabilizers	17, 18, 19, 20, 82
Exanthematous reactions		
	All phenothiazines	82
	Chlorprothixene	82
	Clozapine	82
	Haloperidol	82
	Loxapine	82
	Olanzapine	82
	Risperidone	82
	Ziprasidone	82
	All antidepressant	28, 29, 30
	Carbamazepine	23, 82
	Gabapentin	82
	Lamotrigine	24, 25, 26
	Lithium carbonate	82
Urticaria and edema		
	All phenothiazines	82
	Clozapine	44, 82
	Olanzapine	82
	Risperidone	82
	Ziprasidone	43, 82
	All antidepressant	18, 41, 42, 45
	Carbamazepine	82
	Gabapentin	82
	Lamotrigine	82
	Lithium carbonate	82
Fixed drug reactions		
	Haloperidol	82
	Olanzapine	82
	Quetiapine	82
	Risperidone	82
	Haloperidol	82
	All antidepressant	82
	Carbamazepine	23, 82
	Lithium carbonate	82
	Gabapentin	82
Photosensitivity		
	All phenothiazines	82
	All TCAs	82
	All SSRIs	82
	Carbamazepine	82
	Gabapentin	82
	Oxcarbazepine	82
	Topiramate	82
	Valproic acid	82
Drug induced pigmentation		
	All phenothiazines	19, 82
	Clozapine	82
	Haloperidol	82
	Olanzapine	82
	Quetiapine	82
	Risperidone	82
	All SSRIs	18, 82
	Carbamazepine	20, 82
	Gabapentin	20, 82
	Lamotrigine	20, 82
Alopecia/hair changes		
	Haloperidol	19, 82
	Olanzapine	19, 82
	Risperidone	19, 82
MOST COMMON ACDRs	**DRUGS**	**REFERENCE(S)**
	Ziprasidone	19, 82
	Desipramine	18
	Imipramine	18
	Nortriptyline	82
	Clomipramine	18, 82
	Maprotiline	18, 82
	Amoxapine	18, 82
	All SSRIs	18, 82
	Bupropion	18, 82
	Nefazodone	18, 82
	Venlafaxine	18, 82
	Mirtazapine	18, 82
	Trazodone	18, 82
	Carbamazepine	20, 82
	Gabapentin hirsurtism	20, 82
	Lamotrigine hirsutism	20, 82
	Lithium carbonate	20, 82
	Valproic acid	20, 82

are caused by carbamazepine (47,54-59), valproic acid (47,54), lamotrigine (47,54-60), gabapentin (56), phenytoin (47,55,56), phenobarbital (47,55,56) and oxcarbazepine (56). Valproic acid in combination with lamotrigine increases the risk of SJS and TEN (61). Patients that undergo therapy with antiepileptic drugs (AEDs), particularly new users of these agents, should be informed of and monitored for possible systemic and cutaneous adverse effects of AEDs. Concomitant use of lamotrigine and aripiprazole possibly increases the risk of SJS (62). Recently, the USA Food and Drug Administration (FDA) has made a labeling change to the drug information contained in carbamazepine. Owing to recent data implicating the HLA allele B*1502 as a marker of carbamazepine-induced SJS and TEN in Han Chinese, the FDA recommends genotyping of all Asians for the allele (63-68).

Drug hypersensitivity syndrome/ reaction

An exanthematous eruption in conjunction with fever and internal organ involvement (e.g., liver, kidney, central nervous system) signifies a more serious reaction, known as the hypersensitivity syndrome reaction (HSR). HSR occurs most frequently on first exposure to the drug, with initial symptoms starting 1 to 6 weeks after exposure. Fever and malaise are often the presenting symptoms. Atypical lymphocytosis with subsequent eosinophilia may occur during the initial phase of reaction in some patients. Although most patients have an exanthematous eruption, more serious cutaneous manifestations may be evident. Internal organ involvement can be asymptomatic (17). The formation of toxic metabolites by aromatic anticonvulsants may play a pivotal role in the development of HSR (69). In most individuals, the chemically reactive metabolites that are produced are detoxified by epoxide hydroxylases. If detoxification is defective, however, one of the metabolites may act as a hapten and initiate an immune response, stimulate apoptosis, or cause cell necrosis directly. Approximately 70 percent to 75 percent of patients that develop anticonvulsant HSR in response to one aromatic anticonvulsant show cross-reactivity to other aromatic anticonvulsants. In addition, *in vitro* testing shows that there is familial occurrence of HSR induced by anticonvulsants (69). Mood stabilizing agents that have been associated with HSR are carbamazepine (59,70-72), lamotrigine (73-75), oxcarbazepine (76) and valproic acid (20). Antipsychotics and antidepressants that have been associated with HRS are listed in Table 2. Prompt withdrawal of the offending drug is the first step in the treatment of HRS.

Drug hypersensitivity vasculitis

The clinical hallmark of cutaneous vasculitis is palpable purpura, classically found on lower extremities. Urticaria can be a manifestation of small vessel vasculitis, with individual lesions remaining fixed in the same location for more than 1 day. Other features include hemorrhagic bullae, ulcers, nodules, Raynaud disease, and digital necrosis (77). The same vasculitic process may also affect internal organs such as the liver, kidney, gut, and central nervous system and can be potentially life-threatening. Drug induced vasculitis can be difficult to diagnose and is often a diagnosis of exclusion. Clozapine is the drug of choice for schizophrenia patients with persistent residual symptoms. Clozapine-induced allergic vasculitis is a rare but serious complication that should be added to the adverse reactions caused by clozapine therapy (78). Paroxetine (32,42), fluoxetine (79), maprotiline (80), and trazodone (81) have been reported to cause urticarial vasculitis.

Exfoliative dermatitis

Exfoliative dermatitis is diffuse erythema and scaling of the skin involving more than 90 percent of total body skin surface area. Systemic complications include fluid and electrolyte imbalance, thermoregulatory disturbance, fever, tachycardia and high output failure, hypoalbuminemia, and peripheral edema. It may appear abruptly or may manifest as progression of a benign drug induced skin eruption (17). Exfoliative dermatitis has been reported with quetiapine (82), risperidone (82), ziprasidone (82) and phenothiazines (82). It has been associated with most TCAs (82) and a number of other antidepressants (Table 2). Among mood stabilizers, exfoliative dermatitis has been reported with carbamazepine (82), lithium (82), and gabapentine (82).

OTHER ADVERSE CONDITIONS

Acneiform eruptions

The eruption consists of monomorphic, diffuse folliculocentric pustules, usually without comedones, on the face, chest and upper back (17). Acneiform eruptions have been associated with most TCAs and all SSRIs as well as with other antidepressants (82) (Table 3). Among

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Table 2. Severe and life threatening ACDRs

SCARs	DRUGS	REFERENCE(S)
Erythema multiforme		
	Clozapine	19
	Risperidone	19
	Fluoxetine	18
	Paroxetine	18
	Bupropion	18
	Carbamazepine	18, 47
	Gabapentin	20
	Lamotrigine	20
	Oxcarbazepine	20
	Valproic acid	20, 47
SJS and TEN		
	Clozapine	19
	Chlorpromazine	19
	Flurazepam	51
	Bupropion	18
	Fluoxetine	31, 51, 52
	Fluvoxamine	30
	Paroxetine	53
	Amoxapine	18
	Carbamazepine	47, 54, 55, 56, 57, 58, 59
	Gabapentin	57
	Lamotrigine	47, 54, 55, 60
	Oxcarbazepine	56
	Valproic acid	47, 54
	Phenytoin	47, 55, 56
	Phenobarbital	47, 55, 56
Drug hypersensitivity syndrome		
	Aromatic anticonvulsant	69
	Olanzapine	19
	Perphenazine	19
	Desipramine	18
	Amitriptyline	18
	Imipramine	18
	Carbamazepine	59, 70, 71, 72
	Lamotrigine	73, 74, 75
	Oxcarbazepine	76
	Valproic acid	20
Drug hypersensitivity vasculitis		
	Clozapine	78
	Paroxetine	32, 42
	Fluoxetine	79
	Maprotiline	80
	Trazodone	81
	Carbamazepine	20
Exfoliative dermatitis		
	All phenothiazines	82
	Risperidone	82
	Quetiapine	82
	Ziprasidone	82
	Most TCAs	18, 82
	Most SSRIs	18, 82
	Carbamazepine	20, 82
	Gabapentin	20, 82
	Lithium carbonate	20, 82

antipsychotics, quetiapine (82) and haloperidol (82) have been observed to cause acneiform eruptions. Topiramate (82), lamotrigine (82), gabapentin (in >1% of patients) (20), lithium carbonate (35,36), and oxcarbazepine (in 2% of patients) (20) cause acneiform eruptions. Acneiform eruptions were observed in patients on lithium therapy that were administered tetracyclines (83).

Psoriasiform reactions

Psoriasiform eruption is typically composed of scaly pink papules and plaques, sharply demarcated by silvery-white scales. The eruption may be localized, regional, or generalized. The lesions are often bilaterally distributed with a predilection for elbows, knees and scalp. Psoriasiform reactions have been reported in association with quetiapine

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Table 3. Other adverse conditions

OTHER ADVERSE CONDITIONS	DRUGS	REFERENCE(S)
Acneiform eruptions		
	Haloperidol	19, 82
	Quetiapine	19, 82
	Desipramine	18, 82
	Protriptyline	18, 82
	Amitriptyline	18, 82
	Doxepine	18, 82
	Trimipramine	18, 82
	Clomipramine	18, 82
	Imipramine	18, 82
	Maprotiline	18, 82
	All SSRIs	18, 82
	Bupropion	18, 82
	Nefazodone	18, 82
	Venlafaxine	18, 82
	Mirtazapine	18, 82
	Carbamazepine	18, 47
	Gabapentin	20
	Topiramate	20, 82
	Lamotrigine	20
	Oxcarbazepine	20
	Lithium carbonate	20, 35, 36, 83
Psoriasiform reactions		
	Quetiapine	19, 82
	Haloperidol	19, 82
	Fluoxetine	18, 82
	Citalopram	18, 82
	Venlafaxine	18, 82
	Trazodone	18, 82
	Carbamazepine	20, 82
	Gabapentin	20, 82
	Oxcarbazepine	20, 82
	Valproic acid	20, 82
Seborrheic eruptions		
	All phenothiazines	19, 82
	Olanzapine	19, 82
	Loxapine	19, 82
	Quetiapine	19, 82
	Fluoxetine	82
	Fluvoxamine	82
	Paroxetine	82
	Mirtazapine	82
	Venafaxine	82
	Gabapentin	82
	Lamotrigine	82
	Topiramate	82
	Valproic acid	82
Hyperhidrosis		
	Olanzapine	82, 84
	Pimozide	82
	Quetiapine	82, 84
	Risperidone	82, 84
	Nortriptyline	18
	Clomipramine	18
	Maprotiline	18
	Phenelzine	18
	Bupropion	18
	Carbamazepine	20
	Gabapentin	20
	Lamotrigine	20
	Oxcarbazepine	20
	Topiramate	20

(82), risperidone (82), fluoxetine (18), citalopram (18), venlafaxine (18), trazodone (18), carbamazepine (20), lithium carbonate (20), valproic acid (20), and oxcarbazepine (20).

Seborrheic dermatitis

The affected skin is pink, edematous, and covered with yellow-brown scales and crusts, often associated with increased sebum production (seborrhea) of the scalp and the sebaceous follicle rich areas of the face and trunk (17). Antidepressants that have been associated with seborrheic eruptions are fluoxetine (82), fluvoxamine (82), paroxetine (82), mirtazapine (82), and venlafaxine (82). Among mood stabilizers, carbamazepine (20), lithium carbonate (20), valproic acid (20), gabapentin and oxcarbazepine (20) have been associated with seborrheic eruptions (83). Seborrheic eruptions were observed in patients treated with atypical antipsychotics (84), olanzapine (82),

quetiapine (82), and loxapine (82). Seborrheic eruptions are very common ACDRs in patients taking phenothiazines for a longer period (19). Sixty percent of patients with chronic neuroleptic induced parkinsonism also had comorbid seborrheic dermatitis (19).

Hyperhidrosis

An increase in perspiration has been noted in patients treated with carbamazepine (82), topiramate (82) (in 1% of patients), lamotrigine (82) (in 2% of patients), gabapentin (82), and oxcarbazepine (82) (in 3% of patients). Among antipsychotics, hyperhidrosis has been noted in patients treated with olanzapine (82), quetiapine (82), and pimozide (82). Clomipramine, nortriptyline, phenelzine, bupropion and maprotiline have been noted to cause an increase in perspiration. Hyperhidrosis as part of the serotonin syndrome has been reported as a side effect of citalopram use (85).

CONCLUSION

Psychotropic drugs are frequently used in both psychiatric and general medical practice. The knowledge of common side effects and their management may help psychiatrists in the selection of drugs to suit individual patient needs. Although most adverse dermatologic reactions to drugs follow a benign course after drug discontinuation, more serious effects are known to occur with certain agents (86). However, these adverse events may have an impact on compliance, so discussing strategies with the patient to avoid potential adverse cutaneous effects will improve compliance. The most important step in minimizing morbidity is prompt recognition of severe drug reactions with withdrawal of the causative medication. If skin eruption occurs in an outpatient setting, it is generally advisable to discontinue the drug and to consider switching to another class agent. If the reaction is mild and therapeutic benefits exceed by far the risks of symptomatic treatment, then the agent may be continued. There are certain characteristics that place an individual at a higher risk of ACDR, such as female sex, increasing age, African-American ethnicity, use of multiple medications and presence of a serious illness. Treatment of the ACDR should be symptomatic if the patient shows no other significant signs of reaction. If other signs are present, however, dermatology consultation should be obtained. Since the diagnosis of ACDR is often tentative, and the exanthema is likely to be benign, the physician treating a patient with a mood or anxiety disorder must weigh the risk of developing these potential problems against the possibility of relapse of the psychiatric disorder should the medication be discontinued. Of all the psychotropic medications currently available, the mood-stabilizing agents have the highest incidence of severe and life-threatening ACDRs. An exanthematous eruption in a patient treated with a mood-stabilizing agent should be viewed as possibly being the initial symptom of a severe and life-threatening ACDR, such as hypersensitivity reaction, SJS or TEN. A combination of mood-stabilizing agents may increase the risk of such reactions. Patients should also be advised to seek medical attention if they suspect a drug-induced skin reaction.

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