Review Article

Update on Pharmacotherapy in Psychodermatological Disorders

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Abstract

Psychodermatological (PD) conditions encountered in dermatologic practice include primary psychiatric conditions such as delusions of parasitosis or secondary psychiatric conditions such as anxiety and depression due to dermatologic disease. The psychotropics include antipsychotic agents, anti-anxiety agents, antidepressants, and miscellaneous drugs such as anti convulsants. Anti psychotics are further divided into first-generation and second-generation drugs. Currently, second-generation drugs e.g., risperidone are preferred over first-generation drugs e.g., pimozide in delusional infestation owing to the side effect profile of the latter. Anti-anxiety agents include benzodiazepines used in acute anxiety and buspirone in chronic anxiety disorders. They are frequently prescribed along with antidepressants. Although dependence and necessity of tapering is a problem with benzodiazepines, delayed onset of action is a feature of buspirone. The commonly used antidepressants in dermatology include selective serotonin reuptake inhibitors (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline), selective serotonin norepinephrine reuptake inhibitors (venlafaxine, desvenlefaxine, and duloxetine), norepinephrine dopamine reuptake inhibitors (bupropion), tricyclic antidepressants (doxepin, amitriptyline, imipramine, and clomipramine), and tetracyclic antidepressants (mirtazapine). Miscellaneous drugs include anticonvulsants such as gabapentin and pregabalin, naltrexone, and N-acetyl cysteine. The principles of PD treatment are first establish the psychiatric diagnosis, followed by initiating drug treatment. The choice of drugs is dependent on multiple factors such as side-effect profile, drug interactions, and co-morbid conditions. Usually, drugs are started at a low dose and gradually increased. A literature search was done in Pubmed, Google Scholar, and Medline databases, and articles on treatment were analyzed.

Keywords: *Anti-anxiety agents, anti convulsants, antidepressants, anti psychotics, N-acetyl cysteinenaltrexone, pharmacotherapy, psychodermatological disorders*

Introduction

Psychodermatological (PD) conditions are not uncommon in clinical practice. They may present as primary psychiatric disorders such as delusions of parasitosis (DP), dermatitis artefacta etc., or as chronic dermatoses such as atopic eczema or psoriasis, patients of which may have depression or anxiety secondary to their skin disease. In a study from Manipal,[1] 33% of the patients attending a psychodermatology liaison clinic had psychiatric co-morbidity. Since, psychological components contribute to the overall dermatological outcomes, managing them is of importance. It is essential for a clinical dermatologist to have a working knowledge of common psychiatric conditions as well as the use of psychotropic medications. Although DP is infrequently encountered, dysthymia is common in routine practice.[2] Present article addressesrole of psychopharmacotherapy in PD conditions.

Antipsychotics

Antipsychotics are the drugs of choice in delusional disorders such as DP.[3] They are also useful in body focused repetitive behaviors such as trichotillomania (TTM)[4] and skin picking disorder.[5] Owing to their multi-receptor action, they are sometimes used in pruritus[6,7] and hyperhidrosis.[8] They are divided into first-generation antipsychotics (FGAs; neuroleptics, conventional, or typical anti psychotics) and second-generation anti psychotics (SGAs; atypical). The increased incidence of extrapyramidal syndromes (EPS) such as akathisia (feeling of restlessness), Parkinsonism (slow movements, slow speech, tremors, and facial stiffness),

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tardive dyskinesia (irregular jerky movements), and dystonia (spasms and muscle contractions) with FGAs are the main differences between FGAs and SGAs.

All FGAs act by inhibiting the dopamine D2 receptors in the brain and in addition to EPS, hyperprolactinemia is also seen with their use. Of various agents in FGAs, last decades have witnessed the effective and wide usage of pimozide for DP. It is available as 2 mg and 4 mg tablets and may be started at a dose of 0.5 mg/day and up to 6mg daily at 8–12 hourly intervals. Prophylactic anticholinergics (trihexyphenidyl 2 mg tid, benztropine 1–2 mg qid, or diphenhydramine 25–50 mg every 4 to 6 h) can be given to prevent EPS. In a study of 33 patients with DP who were prescribed pimozide,[9] only 18 took it and on follow-up, five had complete remission, four were less symptomatic, five were unchanged, and four died of unrelated causes. Owing to the high incidence of EPS and cardiac effects such as Q-T interval prolongation with pimozide, it has been superseded by Second Generation A ntipsychotics (SGAs). The drug interactions of pimozide such as serious cardiotoxicity with itraconazole and macrolides, the necessity of frequent monitoring with ECG and serum potassium levels, and the occurrence of neuroleptic malignant syndrome (fever, muscle rigidity, confusion, and dysrhythmias) have precluded its use as a first-line treatment in DP.

Currently, SGAs are the preferred drugs in DP, among which risperidone is considered as the drug of choice.[10] The other drugs in this class are clozapine, olanzapine, quetiapine, aripiprazole, ziprasidone, and lurasidone. SGAs act by binding to D2 receptors as well as to serotonin 5-HT2 receptors. More binding to the latter and the early dissociation from D2 receptors explains the reduced incidence of EPS with SGAs. SGAs have metabolic side effects (weight gain, diabetes, and hyperlipidemia). In a case series of three DP patients started on risperidone 2mg/day increased upto 4–6mg, good improvement was seen within 3 months.[11] In another study on DP, a good response was reported in three patients with olanzapine at a dose of 5mg/day increased to 10 mg.[12] Aripiprazole, considered as a "third-generation antipsychotic," has also been tried in DP in the dose of 5–10 mg/day.[13] One distinct advantage of aripiprazole over other SGAs is the absence of weight gain.[14]

The principle of treatment is to start with a low dose and gradually titrate upward every 4 weeks depending on the response. During follow-up, all patients on antipsychotics should be questioned about EPS and also get their weight, blood sugars, lipid profile, and blood pressure checked. Elderly patients who are susceptible to side effects such as orthostatic hypertension and neuropsychiatric symptoms should be started with one-fourth to one-half the usual dose and slowly increased.[15] The drug has to be continued till the improvement is maintained for a period of 3–6 months after which it can be tapered or stopped. If there is relapse, the drug can be restarted.

The oral dosing, side effects, and drug interactions of the commonly used anti psychotics are shown in Table 1.[10] Adverse effects, monitoring schedule, management strategies of adverse effects of anti psychotics and strategies in selecting anti psychotics have been mentioned in Table 2,[16] Table 3,[16] Table 4,[16] and Table 5, respectively.

Anti-anxiety agents

Anti-anxiety agents are chiefly used to mitigate anxiety symptoms seen as part of anxiety and/or other emotional disorders, most often in conjunction with antidepressant medications. Commonly encountered anxiety disorders include panic disorder, obsessive-compulsive disorder, specific phobias, social phobia, generalized anxiety disorder (GAD), and anxiety-related to other specific situations such as performance, health anxiety, etc. In a psychodermatology clinic, they are particularly useful in the management of social anxiety which more often than not accompanies chronic and disfiguring skin conditions.

Benzodiazepines

These are the most commonly prescribed class of anxiolytic agents. They exert their anti-anxiety effect by binding to the benzodiazepine (BDZ) receptors at the gamma aminobutyric acid (GABA)-A ligand-gated chloride channel complex. This enhances the inhibitory effects of GABA and also increases chloride conductance through the GABA-regulated channels. These drugs presumably inhibit neuronal activity in amygdala- centered fear circuits to provide therapeutic benefits in anxiety disorders.

The classification of benzodiazepines and the doses of commonly used drugs are given in Table 6.

Adverse effects

The most commonly reported side effect is that of sedation and day time drowsiness, which is partly dose-dependent. Patients also report weakness, giddiness, and impairment of motor performance such as driving, nausea, slight fall in blood pressure, confusion, and anterograde amnesia.[17] Rarely, respiratory depression can occur, especially when taken with central nervous system (CNS) depressants in overdose. Most of these adverse effects usually wane over time. If they persist, dose may be reduced and the largest dose taken at bedtime to avoid day-time drowsiness. The chief concern with long-term use of BDZ is that it is habit-forming and patients may become dependent on the drug. Long-term use of BDZ may also cause tolerance leading to diminished efficacy at the same dose.[18] Hence, short-term treatment is advocated, during which acute or self-limited episodes of anxiety often resolve.[19]

Features of withdrawal include jitteriness, anxiety, palpitations, clamminess, sweating, nausea, confusion,

Table 1: Pharmacological profile of antipsychotics

Antipsychotic drug	Dosage	Side effects	Drug interactions
Pimozide	1-8 mg/day	Sedation, EPS	Azoles, macrolides, escitalopram, sertraline
Risperidone	0.5-8 mg	Metabolic syndrome (MS), EPS, sedation	Carbamazepine, fluoxetine
Aripiprazole	2-8 mg	MS, EPS, sedation	Azoles, macrolides, fluoxetine, carbamazepine, rifampicin
Olanzapine	2.5-7.5 mg	MS, sedation	Carbamazepine, fluoxetine, fluvoxamine

Table 2: Adverse effects of antipsychotics

Adverse effects	Pim	Ola	Clo	Ari	Risp	Que	Zip	Lur
Anticholinergic effect	++	++	+++	0	0	+/++	0	0
Acute Parkinsonism	++	0/+	0	+	++	0	+	+/++
Akathisia	+++	+	+	++	+	+	+/++	+/++
Tardive dyskinesia	+	0/+	0	0/+	0/+	0/+	0/+	0/+
Diabetes	0	+++	+++	0/+	+	++	0/+	0/+
Weight gain	0/+	+++	+++	0/+	++	++	0/+	0/+
Increased lipids	0	+++	++	0/+	+	++	0/+	0/+
Sialorrhoea	0	0	++	0	0	0	0	0
Neutropenia	0	0/+	+++	0/+	0/+	0/+	0/+	0/+
Orthostatic hypotension	0/+	++	++	0/+	+	++	0	0/+
Hyperprolactinemia	++	++	+	0	+++	0	+	+
Increased QTc interval	+++	0/+	++	0/+	+	+	++	0/+
Sedation	+	+/++	+++	0/+	+	++	+	+/++
Seizures	0/+	0/+	++	0/+	0/+	0/+	0/+	0/+

Ari=Aripiprazole, Clo=Clozapine, Lur=Lurasidone, Ola=Olanzapine, Que=Quetiapine, Ris=Risperidone, Zip=Ziprasidone, 0=None or equivocal, 0/+=Minimal/rare, +=Mild/sometimes occurs, ++=Moderate/occurs frequently, +++=Severe/occurs very often

and heightened sensitivity to sound and light. Seizures are the most worrisome withdrawal symptom, but they are fortunately rare. Patients may experience a rebound of the initial anxiety symptoms, in a more severe form than earlier, however, it is transient, usually lasting about 48–72 h. Hence, it has been advocated that these drugs should always be tapered gradually before discontinuation. One of the rules that have been suggested is to reduce the dose at a maximum rate of approximately 10% every day.

A study on BDZ withdrawal[20] found that withdrawal symptoms on abrupt discontinuation were maximum in patients who had taken the medication for longer than 8 months. As a result of withdrawal, no patient had seizures in this study. Factors associated with a more difficult withdrawal included higher dose, use of a drug with a shorter half-life, longer duration of treatment, and more rapid taper.[21] In the case of long-acting agents such as diazepam, withdrawal symptoms manifest only about 5–7 days after abrupt discontinuation, while they are more quickly evident in case of drugs like lorazepam.[22]

Several medications have been tried in an attempt to alleviate the symptoms of benzodiazepine withdrawal and to make the transition as smooth as possible for the patient. Drugs such as buspirone have been found to be relatively safe, as also melatonin. The antidepressant trazodone relieves anxiety and depression and also promotes sleep while hydroxyzine is an alternative that can be easily procured over-the-counter. However, other medications such as carbamazepine, sodium valproate, lamotrigine, and phenobarbital that have high side-effect profiles and risks of medical complications must be used with caution. The evidence for the use of these drugs as a method of BDZ discontinuation remains poor. Flumazenil, which is used to reverse the effects of benzodiazepines, may precipitate seizures in patients with epilepsy being treated with benzodiazepines. The dosage of anxiolytics would generally need to be reduced in patients with renal, hepatic impairment, and in the pediatric and geriatric population. They are generally not recommended in pregnant and lactating women. A study comparing the efficacy and tolerability of clonazepam with other benzodiazepines in patients with anxiety disorders concluded that all benzodiazepines were equally efficacious in the treatment of anxiety disorders, however, clonazepam exhibited a better adverse effect profile than the other drugs.[23]

Buspirone

It is a 5-HT1A partial agonist, administered orally. The starting dose is 5 mg twice daily, increased upto 20–30 mg/day in divided doses. The major drawback of the drug is the delayed onset of action (2–4 weeks), which precludes its use on an as needed basis. It remains inappropriate for the treatment of acute situational stress because the therapeutic effect may not become evident until after the stressful event has been resolved.[24] Side effects include dizziness, headache, nervousness, sedation, excitement, nausea, and restlessness. It has an advantage over benzodiazepines in that it is not habit-forming, hence does not require tapering before discontinuation. Side effects are time-limited. However, the dose may be reduced if they continue to be troublesome. Buspirone is primarily metabolized by CYP450 3A4, hence, dose needs to be adjusted when used along with inhibitors e.g., fluoxetine or inducers e.g., carbamazepine of the enzyme. A lower dose is also recommended in patients with hepatic and renal impairments and in the elderly. It is safer than benzodiazepines in pregnant and lactating women.

Anti-anxiety drugs are usually prescribed along with antidepressants, at the lowest effective dose. This dose is often continued for a period of 4–6 weeks until the anti-depressant drugs begin to act, following which it is gradually tapered and discontinued. Buspirone may be used for longer periods and does not require taper before discontinuation. The use of concomitant psychological

Table 3: Suggested monitoring schedule for antipsychotics

	Baseline	During titration	At 3 months	At 6 months	Annually
Weight	X	X			
Tardive dyskinesia	X	X		X	
Akathisia, Parkinsonism	X	X			X
FBS, HbA1C	X		X		X
FLP	X		X		X
PR, BP	X		X		X
Sexual function	X	X			X
Sedation	X	X	X	X	X
ECG (Based on symptoms)	X				
Prolactin		If symptoms of hyperprolactinemia appear			

BP=Blood Pressure, ECG=Electrocardiogram, FBS=Fasting Blood Sugar, FLP=Fasting Lipid Profile, PR=Pulse Rate

Table 4: Management strategies of adverse effects of antipsychotics

Adverse effects	Option 1	Option 2	Option 3
Parkisnosim (tremor, rigidity, bradykinesia)	Dose reduction	Change antipsychotic	Add anticholiergic agent
Akathisia	Dose reduction	Change antipsychotic	Use beta blocker
Sedation	Dose at night	Lower the dose	Change to non-sedating antipsychotic
Hyperprolactinemia, sexual dysfunctions	Dose reduction	Change to prolactin sparing antipsychotic	Add aripiprazole
Weight gain, dyslipidemia	Lifestyle modification	Change antipsychotic	Metformin
Orthostatic hypotension	Dose/scheduling titration	Adequate hydration	Change antipsychotic
QT prolongation	Change antipsychotic		

Table 5: Clinical practice points for use of antipsychotics

In general, SGAs are preferred over FGAs.

FGAs carry risk of EPS and SGAs can cause metabolic disturbance (clozapine and olanzapine have the highest risk).

Newer SGAs may carry less of a risk of metabolic disturbances.

Baseline and periodic monitoring of BMI, waist circumference, HbA1c, fasting plasma glucose, and fasting lipids for SGAs is recommended.

If abnormalities are found in any of these parameters, following strategies can be tried: switching to an SGA that is less risky; titrating dose or discontinuing the agent; lifestyle modifications; seeking dietician and endocrinologist's opinion

Monotherapy when appropriate to decrease the risk of side effects.

SGA=Second-generation antipsychotic, FGA=First-generation antipsychotic, EPS=Extra Pyramidal Syndrome, BMI=Body Mass Index, HbA1c=Glycated Hemoglobin

interventions can also help in reducing the duration of treatment with anti-anxiety agents.

Antidepressants

Depression can be an underlying, co-existing, or a consequence of the dermatological condition. When features of depression start manifesting and form part of or major component of the skin disease in course of dermatosis, antidepressants are indicated.

Diseases such as alopecia areata and vitiligo have been found to have a bidirectional relationship with depression in large scale cohort studies.[25,26] A systematic review of 35 studies found that chronic pruritus that is unresponsive to topical treatment and oral antihistamines will benefit from oral antidepressants (fluoxetine, fluvoxamine, paroxetine, sertraline, amitriptyline, nortriptyline, doxepin, and mirtazapine).[27] Indications for antidepressants are outlined in Table 7.[28,29]

Table 6: Classification and doses of various benzodiazepines

Long-acting	Intermediate-acting	Short-acting
Chlordiazepoxide 15-40 mg in 3-4 doses	Alprazolam 1-4 mg/day	Midazolam
Clorazepate	Bromazepam	Triazolam
Diazepam 5-40 mg/day	Clobazam	
Flurazepam	Clonazepam 0.5-2.0 mg/day	
	Lorazepam 1-6 mg/day	
	Nitrazepam	
	Oxazepam 15-120 mg	
	Temazepam	

Classification

Antidepressants commonly used in a dermatologic setting are classified as selective serotonin reuptake inhibitors (SSRIs), selective

Table 7: Indications of antidepressants

I. Primary psychiatric disorders related to skin	1. Dermatitis artefacta
	2. Dermatitis para-artefacta: skin picking syndrome (neurotic excoriations), acne excoriee
	3. Compulsive disorders: Eczema due to hand washing, Trichotillomania
	4. Psychogenic pruritus
	5. Somatoform disorders: somatoform pain disorders/cutaneous dysesthesias, itching, paresthesias, burning
2. Secondary psychiatric disorders due to dermatoses	Depression and anxiety secondary to chronic dermatosesEg: Atopic dermatitis, Prurigo, Psoriasis, Alopecia areata, Chronic urticarial
3. Treatment ofpsychiatric manifestations secondary to treatment	Isotretinoin: depression, suicidality
	Estrogen: depression, panic attacks
	Antiretrovirals: depression, suicidal thoughts
	Corticosteroids: depression, psychosis
	Dapsone: depression
	H2 antihistaminics: depression
	Acyclovir: depression (in high doses)
	Fluoroquinolones: depression

serotonin-norepinephrine reuptake inhibitors (SNRIs), norepinephrine-dopamine reuptake inhibitors (NDRIs), tricyclic antidepressants (TCAs), and tetracyclic antidepressants (TeCAs). Others such as serotonin modulators and stimulators (SMSs), monoamine oxidase inhibitors (MAOIs), and norepinephrine reuptake inhibitors (NRIs) are rarely used. Table 8 describes the dose, indications and side effects of antidepressants.[30-32] Table 9[33] mentions monitoring recommendations for antidepressants and Table 10 describes about choosing the right antidepressant.

Selective serotonin reuptake inhibitors

These increase levels of serotonin in the synaptic cleft by inhibiting its reuptake into presynaptic cells. They are preferred as first-line antidepressants due to their better tolerability and favorable side effects profile.

A study to determine if psoriasis was affected by the use of SSRIs showed that the risk of switching from non-systemic to systemic psoriasis treatments was significantly decreased in the SSRI-exposed group.[34] In a retrospective study of 51 patients suffering from primary burning mouth syndrome, SSRIs appeared to be effective and well-tolerated.[35]

Citalopram/Escitalopram

Escitalopram is an S-stereoisomer of its predecessor citalopram and has the highest affinity for serotonin receptors among all SSRIs and more cost-effective.[36]

In a double-blind RCT of citalopram (20 mg/day, over 4 weeks) in 45 patients with pathological skin picking, there was a significant improvement with citalopram compared to placebo.[37] In an open-label trial of escitalopram for 18 weeks in 29 patients with pathological skin picking, 44.8% showed full remission and 27.6% showed partial response.[38]

Fluoxetine

It is useful in neurotic excoriations, pathologic skin picking, and body dysmorphic disorder.[39,40] In an open-label double-blind study to check the usefulness of fluoxetine in pathological skin picking, of 15 recruited eight responded by 6 weeks. On randomization, four patients on fluoxetine maintained improvement, the other four patients on placebo, returned to baseline symptom level.[39]

Fluvoxamine

Its antidepressant property is enhanced by its affinity (maximum among SSRIs) for the σ1 receptor.[41] It is useful in patients with neurotic excoriations, chronic pruritus, body dysmorphic disorder and trichotillomania (TTM).

In a 12 weeks uncontrolled study of flexible-dose of fluvoxamine (25–50 mg/day - 300 mg/day) over 12 weeks in skin picking, all 14 patients showed significant reduction in behaviors involving the skin (e.g., scratching, picking, gouging, or squeezing), increased control over skin behavior and a significant improvement in the presence of skin sensations, skin appearance, and lesions.[42]

Paroxetine

It has been used successfully in patients with TTM and pathologic picking.[43] In a case series of eight adolescents with acne and depression, paroxetine was beneficial in improving both depression and acne.[44] In a double-blind, randomized, placebo-controlled trial with paroxetine in 13 patients (eight-paroxetine and five placebo) with alopecia aerate and psychiatric comorbidity, complete regrowth of hair was seen in two patients on paroxetine, while four showed partial regrowth. Only one in placebo group had an almost complete hair regrowth.[45] It can cause weight gain, memory impairment, paresthesias and reproductive risks, as it may cause sperm DNA fragmentation.[46]

Table 8: Antidepressants-pharmacological profile

Drug	Recommended dose	Psychiatry indication	Side effects
Selective Serotonin Reuptake Inhibitors (SSRI)			
Citalopram	20-60 mg/d at night Begin with 20mg/d Hike by 20 mg after 2-4 weeks in partial responders, maximum 60 mg/d	Depression, OCD, Panic disorder, Social Phobia	Nausea, sleep disturbances, sexual dysfunctions, appetite changes, headache, dry mouth
Escitalopram	10-30 mg/d at night Start with 10mg/d and to increase by 5 mg after 2-4 weeks in partial responders, maximum 30m/d	Depression, Anxiety disorders, OCD	
Fluoxetine	10-80 mg/d in morning Begin with 10mg/d and can be increased by 20mg after 4 weeks up to 80mg/d	Depression, Anxiety disorders, OCD, Premature ejaculation, Bulimia nervosa	
Fluvoxamine	100-300 mg/d at night or BD Start with 50mg/d, and to increase by 50-100mg every 2-4 weeks up to 300 mg/day	OCD, Depression, Post traumatic stress disorder	
Paroxetine	12.5-37.5 mg/d in morning Start with 12.5mg/d and to increase by 12.5 mg every 2 weeks up to 37.5 mg/d	Depression, Anxiety disorders, OCD, Premature ejaculation, Premenstrual dysphoric disorder	
Sertraline	50-200 mg/d at night Start with 50 mg/d, hike by 50 mg/day every 2 weeks in partial responders, up to 200 mg/d	Depression, Anxiety disorders, OCD, Premenstrual dysphoric disorder	
Serotonin Norepinephrine Reuptake Inhibitor (SNRI)			
Venlafaxine	37.5-300mg at night or BD Start with 37.5 mg/d and to increase by 37.5 mg/d every 2-4 weeks up to 300 mg/d	Depression, generalized anxiety disorder, panic disorder	Hypertension, tachycardia, nausea, sleep disturbances, sexual dysfunctions, appetite changes, headache, dry mouth
Desvenlafaxine	50-100 mg/d at night Start with 50mg/d and increase by 50 mg after 4 weeks in partial responders	Depression	
Duloxetine	20-60 mg/d twice daily Start with 20mg/d and increase by 20mg every 2 weeks	Depression, generalized anxiety disorder, diabetic neuropathy, fibromyalgia, chronic pain	
Norepinephrine-Dopamine Reuptake Inhibitor (NDRI)			
Bupropion	150-450 mg/d in morning Start with 150mg/d and increase by 150 mg/d after 4 weeks in partial responders	Depression, smoking cessation	Seizures, headache, insomnia
Tricyclic Antidepressant (TCA)			
Amitriptyline	25-150 mg/d at night Start with 25 mgd and to increase by 25 mg every 2 weeks	Depression, migraine, neuropathic pain, fibromyalgia	Dry mouth, dizziness, blurred vision, constipation, sedation, orthostatic hypotension, tachycardia
Clomipramine	25-250 mg/d at night	OCD, depression, panic disorder, body dysmorphic disorder, Trichotillomania, enuresis, chronic pain, premature ejaculation	
Doxepin	25-150 mg/d at night	Depression, anxiety disorder, chronic hives	
Imipramine	25-150 mg/d	Depression, nocturnal enuresis	
Tetracyclic Antidepressant (TeCA)			
Mirtazapine	7.5-30 mg/d at night Start with 7.5 mg/d and increase by 7.5mg every 2 weeks	Depression	Drowsiness, increased appetite, weight gain, hypercholesterolemia, cardiac disturbance

OCD=Obsessive compulsive disorder

Table 9: Monitoring recommendations for antidepressants

Monitoring parameter	Agent	Frequency	Remarks
ECG for QT prolongation	TCAs	Baseline, After initial dose titration and at dose changes	More caution is indicated in children, elderly, and at higher doses
Liver function test	Agents with hepatic liability	Baseline and at 6, 12, and 24 months and when indicated	Specially in people with liver dysfunctions
BMI, Waist circumference	Agents with known weight gain liability	Baseline and 6 monthly	More caution with Mirtazapie, TCAs
Electrolytes for hyponatremia	SSRIs, SNRIs, TCAs, Mirtazapine	Baseline and after 1 month if indicated in high-risk groups, especially in >65 years age group	More frequent monitoring in renal impairment or existing hyponatremia patients
Blood Pressure monitoring	Venlafaxine, TCAs	Baseline, during titration and 3 monthly	Closer monitoring in initial periods
Sexual functioning	SSRIs	Baseline, 3 monthly	Decreased libido, premature/delayed ejaculation

BMI=Body Mass Index, ECG=Electrocardiogram, SNRI=Serotonin norepinephrine reuptake inhibitor, SSRI=Selective serotonin reuptake inhibitor, TCA=Tricyclic antidepressant

Table 10: Choosing an antidepressant

Clear indication definition: Unequivocal diagnosis of the primary disorder andsecondary symptoms
Determination of target symptoms
Desired effect: Selection of the substance depending on its mode of action
Consideration of undesired side effects
Clear performance and long-term control strategy (advance information about side effects, delayed onset of action, and dose titration)
Some unique points of antidepressant treatment to consider
Same antidepressant may act differently in different patients
Antidepressant from the same group may act differently in the same patient
Antidepressant dose differs from patient to patient
Selection and indications of antidepressant may be made on basis of the side effects profile
The off-label use of antidepressants in dermatology is sometimes due to a lack of studies
A foresighted treatment plan and patient motivation are necessary to an extent, especially because the onset of effect is often evident only after couple of weeks
Antidepressant initial therapy is administered for 2-3 weeks before an optimal therapeutic dose range is found. Maximal-dose therapy should be administered for 6 weeks before efficacy is rated (or the substance changed)
The duration of therapy for the first appearance of disease is 6-9 months on average

Sertraline

It can be used in the treatment of neurotic excoriations and chronic pruritus.[27] With a response rate of 68% in an open-label trial using flexible-dose of sertraline, it also emerged as a promising agent for reducing skin-picking.[47]

Discontinuation syndrome[48] if SSRIs are abruptly stopped, patients may experience nausea, weakness, dizziness, insomnia, anxiety, irritability and headache. It is seen with paroxetine and fluvoxamine which have short half-lives and less with fluoxetine, which has a longer half-life. Usually, the symptoms tend to resolve within a week and can be prevented by slowly tapering SSRIs over a few weeks.

Serotonin Norepinephrine Reuptake Inhibitors

This group includes drugs that inhibit serotonin and norepinephrine reuptake.

Venlafaxine

It is considered to be superior to SSRIs and TCAs.[49] It may be particularly useful in patients who have mixed symptoms of depression and anxiety because it has anxiolytic properties.

Duloxetine: Although useful in depression, diabetic neuropathy and somatoform disorders, it has been successfully tried in burning mouth syndrome.[50]

Norepinephrine dopamine reuptake inhibitor

Bupropion is a NDRI and a nicotinic and acetylcholine receptor antagonist.It does not cause sexual dysfunction. It can lower the seizure threshold and can unmask underlying psychosis.[51] Ten patients with psoriasis and ten patients of atopic dermatitis, without depression were studied in a single track open-label treatment with bupropion – sustained release (SR) with 150 mg/day and 300 mg/day doses, given sequentially for 3 weeks with a

washout period of 3 weeks. In atopic dermatitis group, six of ten subjects showed a reduction in affected body surface area by the end of 6 weeks of bupropion treatment, with affected area increasing toward the pre-study baseline in all responders following bupropion discontinuation. Eight of ten patients improved after 6 weeks of treatment in psoriasis group. Average reduction in the affected area in the responders at week 6 of treatment was approximately 50% in both groups.[52]

Tricyclic and tetracyclic antidepressants

Both groups of drugs inhibit serotonin and norepinephrine reuptake, in addition they block histamine, muscarinic acetylcholine, and noradrenergic receptors, which account for their antidepressant effects and adverse effects. When imipramine was compared with placebo in a double-blind study of 13 patients for 6 months, five of seven patients receiving imipramine showed significant regrowth of hair, whereas no change was noticed in placebo group.[53]

Doxepin

This is the most relevant and commonly used TCA in dermatology because of its H1 and H2 histamine-blocking activity. It can be considered as first-line "off-label" treatment for neurotic excoriations, generalized pruritus, and chronic urticaria.[54] It is available in the topical cream formulation also for pruritus. In a retrospective, cross-sectional study over a 20-year period (1998-2017) of 36 patients with chronic urticaria who had poor antihistamine responses and received doxepin therapy, 16 (44.4%) patients showed a complete response and it was effective in 27 (75%) patients with a short onset time.[55] In a double-blind cross-over study of 50 patients with chronic idiopathic urticaria, doxepin (10 mg TDS) with diphenhydramine (25 mg TDS), 43% of the patients on doxepin had a complete response (total clearance of pruritus and urticarial lesions), whereas only 5% of patients receiving diphenhydramine had responded; partial or total control of urticaria and itch was found in 74% of patients receiving doxepin and only in 10% of patients on diphenhydramine.[56]

In a case series of 11 patients with scalp dysesthesia, nine benefitted with antidepressants, eight patients experienced improvement/complete resolution with low-dose doxepin or amitriptyline and one patient completely responded to sertraline and hydroxyzine hydrochloride but then experienced a relapse.[57]

Mirtazapine

It is a tertracyclic antidepressant (TeCA) as well as noradrenergic and specific serotonergic antidepressant that antagonizes adrenergic α2-auto- and α2-heteroreceptors as well as 5-HT2 and 5-HT3 receptors.[58] It is useful for pruritus in patients with malignancy, cholestasis, renal failure, atopic dermatitis, and neurotic excoriations.

In a case series of four cases mirtazapine was found effective for pruritus associated with advanced cancer, cholestasis, and hepatic and renal failure.[59] In an open, uncontrolled pilot study of three non-depressed patients with inflammatory skin diseases and severe nocturnal pruritus, after treatment with mirtazapine, all showed improvement in itching.[60]

Antidepressant medications such as paroxetine (20–50 mg/day), sertraline (25–200 mg/day), fluoxetine (10–60 mg/day), escitalopram (10–20 mg/day), low-dose doxepin (50 mg/day or less), and venlafaxine extended-release (75–150 mg/day) have also been shown to be useful for the treatment of chronic anxiety.[24] Occasionally, use of SSRI's may be associated with a worsening of anxiety symptoms in the initial days of treatment.[61] Ameta-analytic review of studies that compared the use of benzodiazepines and serotonergic antidepressants in patients with generalized anxiety disorder (GAD) concluded that benzodiazepines are a viable treatment option for adults with GAD, particularly in the initial treatment phases. The review, however, did not minimize the role of antidepressant agents as treatment for the same and suggested that the combined use of the two could yield optimum risk-benefit ratio of both the medications.[62]

Cutaneous side effects associated with antidepressants include pruritus, exanthematous rash, urticarial, angioedema, fixed drug reactions, photosensitive reactions, pigmentation, alopecia, psoriasiform reactions, acneiform reaction, seborrheic dermatitis, and hyperhidrosis. Serious reactions such as erythema multi for me, Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), vasculitis, erythroderma, and erythema nodosum have also been reported.[63]

Choosing the right antidepressant: The choice depends on side-effect profile, drug interactions, and comorbid conditions. First-line drugs are generally SSRIs such as escitalopram or sertraline.In those with disturbed sleep, mirtazapine or TCAs are preferred. In overweight patients, bupropion may be tried. It also aids in smoking cessation. SSRIs are safe in pregnancy and lactation. Dose varies from patient to patient. The initial dose is given for atleast 2–3 weeks. The maximum tolerated dose should be given for at–least 6 weeks for assessing efficacy. Treatment should be continued for a minimum of 6 – 9 months.[64]

Selecting antidepressant for pruritus

Selection of antidepressant for pruritus, which is unresponsive to conventional treatment, depends on cause of pruritus, age, and medical comorbidities. In review, paroxetine (20 to 30 mg/d) and mirtazapine (10 to 20 mg/d) have emerged as effective therapeutic options for pruritus due to malignancies. Sertraline

(50–150 mg/d) is an effective therapeutic option for pruritus due to chronic kidney disease or cholestasis. Amitriptyline (10 to 25 mg/d) and doxepin (10 to 20 mg/d) have also been useful in uremic pruritus. For unexplained pruritus, not responding to conventional treatment, most evidence is available for paroxetine. Dose titrations have been mentioned in the Table 8.

Miscellaneous agents

Anticonvulsants

PD indications of anti-epileptics include cutaneous neuropathic pain, itch, and complex cutaneous sensory syndromes, where CNS sensitization plays a role, repetitive excoriation behaviors such asprurigo nodularis, lichen simplex chronicus, skin picking, and TTM, psychophysiologic conditions such as urticaria, flushing, and social anxiety.[65]

Carbamazepine has been tried in neuropathic and chronic pain,[24] lamotrigine in pathologic skin picking,[66] and topiramate[67] in neurogenic pruritus, and skin picking. However, all these are not extensively used.

Present review focuses on commonly used drugs i.e., the Gamma aminobutyric acid (GABA) elevators.

Gamma aminobutyric acid elevators or neuroleptics

These are used for relief of neuropathic pain syndromes,[68] peripheral neuropathic and psychogenic itch, brachioradial pruritus, various allodynias, collectively known as cutaneous dysaesthesias. These include gabapentin and pregabalin, which inhibit neuropathic afferent pathway.

Gabapentin is a structural analogue of the neurotransmitter GABA. The starting dose is 300 mg at bedtime, increased by 300 mg every 2 to 3 days upto a maximum of 2400 mg/day. It has a lower potential for abuse. Side effects include somnolence, fatigue, ataxia, dizziness, gastrointestinal upset, dyspnea, peripheral edema, and weight gain.

A study involving 17 women with vulvodynia reported 82% response rate to gabapentin[69] a case series of 4 patients with glossodynia responded well to gabapentin[70] and another study on recalcitrant prurigo nodularis also reports good efficacy.[71]

Gabapentin has an off-label use for anxiety disorders. The onset of action is less rapid than benzodiazepines but faster than buspirone. The potential for abuse is lower, and it confers an added advantage of anti-pruritic effect.

Pregabalin is used at a dose of 150 mg per day, to a maximum of 600 mg per day. For neuropathic pruritus, starting dose is 75 mg bd, then slowly increased upto 300 mg per day. Side effects include dryness of mucosae, constipation, nausea, vomiting, flatulence, drowsiness, memory impairment, and rarely, serious cutaneous adverse reactions like SJS. Peripheral edema is encountered in 4–16% cases and weight gain in 4–12%.

Withdrawal of neuroleptics should be gradual, over a period of time, and should be used with caution in congestive cardiac failure (CCF) and renal impairment. Dosage adjustment is not required in hepatic disease and depends on the creatinine clearance rate in renal disease.

Naltrexone

This is an opioid antagonist chiefly used in the treatment of alcohol use disorder and opioid abuse but has an off-label indication for treating cholestatic pruritus and psychogenic pruritus as well as intractable pruritus contributing to psychological stress in inflammatory disorder.[72] A systematic review evaluating 22 RCTs, case series, and reports for the utility of naltrexone in dermatology found it to be effective in intractable pruritus associated with inflammatory diseases.[73] Low dose naltrexone (1.5–4.5 mg/day) was more effective as an anti-inflammatory agent in dermatology than high dose naltrexone (12.5–50 mg/day).[73] A meta-analysis of RCTs on naltrexone in the treatment of broadly defined behavioral addictions, which included TTM and skin picking showed a beneficial effect.[74] Dose adjustment is warranted in moderate to severe renal failure, and it is contraindicated in severe hepatic failure. Adverse effects include syncope, dizziness, headache, insomnia, nausea, vomiting, abdominal pain, anorexia, arthralgia, myalgia, pharyngitis, and increased levels of AST, ALT, CPK, and GGT.

N-acetyl cysteine

This thiol amino acid, a donor of cysteine, restores extracellular glutamate within the nucleus accumbens, the area of the brain associated with reward and motivation. It also alters dopamine level in neurons and has additional anti-inflammatory, potent antioxidant, vasodilator, and antiproliferative effects on fibroblasts and keratinocytes.[75]

Indications include TTM, trichoteiromania, onychotillomania, onychophagia, skin picking, and neurotic excoriations.[76] Usual dose is 1200 mg per day, given as 600 mg bd, increased upto a maximum of 3000 mg per day. Cochrane's systemic review demonstrates good evidence for its usefulness in TTM. There are studies substantiating[77] as well as refuting its effectiveness in TTM.[78]

At1, 200–2,400 mg per day, N-acetyl cysteine (NAC) significantly improved TTM showing a 56% improvement in TTM scale, as compared with placebo.[77] An RCT in skin picking (excoriation disorder) found it to be effective with very good improvement in 47% cases.[76] In onychophagia, an RCT showed statistically significant short-term improvement on 800 mg NAC per day, though

many relapsed.[79] Side effects include disagreeable taste, nausea, vomiting, abdominal pain, constipation, urticaria, skin rash, fever, and headache. It is contra-indicated in patients on nitroglycerine as it can cause vasodilatory hypotension and reverse the tolerance to nitroglycerates.[75]

Lactium

This is a milk protein hydrosylate, which contains a bioactive decapeptide, α-casozepine. It is a non-sedative, non-addictive anxiolytic which is claimed to be helpful in disease-associated anxiety by potentiating the effect of GABA by binding to GABA-A receptors causing an influx of chloride ions which hyperpolarizes the neurons and decreases the transmission of stress signals.[80] In spite claims, there are no studies regarding its efficacy.

Special populations

Children, adolescents, geriatric age group patients and patients with medical comorbidities constitute this group. General dictum for the usage of psychotropics in the geriatric population is "start low, go slow". For children and adolescents, lowest possible doses are suggested. The selection of psychotropic will depend on a person's medical comorbidity.

Conclusions

Patients with the suspected psychodermatologic disease should be assessed with a thorough psychiatric history. The appropriate psychotropics may be started according to the psychiatric diagnosis. It is better to be familiar with one or two drugs from each class. Usual doses required for treatment in dermatological conditions are much lesser than what are used in psychiatry. Adverse effects encountered with psychotropics are usually at higher doses, which are used for major psychiatric disorders, and at doses used in dermatology, chances of encountering adverse effects are minimal. However, the selection of a psychotropic depends on condition and comorbidities of patient and personalized therapy is the need of 3 h rather than one drug for one condition for all. Starting with a low dose and gradual escalation, being watchful for side effects and tapering before discontinuation is the key to effective management.

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Conflicts of interest

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