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A New Formulation Containing Sunscreen (SPF-15) And 1% Metronidazole (*ROSASOL* Cream) In The Treatment Of Rosacea

New Drug Spotlight

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ABSTRACT

ROSASOL *Cream is a novel topical formulation of 1% metronidazole in a vehicle containing sunscreens (SPF 15). This product has demonstrated efficacy in the treatment of inflammatory lesions, erythema, and telangiectasiae associated with rosacea.*

Key Words: *metronidazole, sunscreens, inflammatory lesions, erythema, telangiectasia, rosacea*

ROSASOL Cream (Stiefel Canada) was issued a Notice of Compliance by TPP – Canada in October 2000, for the treatment of inflammatory lesions (papules and pustules), erythema, and telangiectasia associated with rosacea. This new formulation combines 1% metronidazole in a cream vehicle containing the sunscreens *Parsol* 1789 and MCX, as well as cyclomethicone and phenyl trimethicone. The latter ingredients have been shown to reduce potential irritation associated with the use of sunscreens in rosacea patients.[1] The sunscreens were formulated to provide SPF 15.

Development was based on the importance of sun protection in the management of rosacea,[2,3] and the demonstrated efficacy of topical metronidazole (see Table 1).

Mechanism of Action

Current evidence suggests that the mechanism of action of metronidazole in rosacea is via inhibition of release of neutrophil-

Study	Investigational drug	Sample size	Duration	Efficacy*	No demonstrated efficacy
Tan et al (2001)[4]	1% cream with sunscreens	120	12 weeks**	↓inflammatory lesions ↓erythema ¯telangiectasiae	
Bitar et al (1990)[5]	1% cream	100	8 weeks	↓inflammatory lesions	Erythema Telangiectasiae
Bjerke et al (1989)[6]	1% cream	97	8 weeks	↓inflammatory lesions ↓erythema	Telangiectasiae
Gamborg Nielsen (1983)[8]	1% cream	81	8 weeks	↓inflammatory lesions ↓erythema	Telangiectasiae
Jorizzo et al (1998)	1% cream	277	10 weeks	↓inflammatory lesions ↓erythema	Telangiectasiae not assessed
Breneman et al (1998)	1% cream	156	10 weeks	↓inflammatory lesions ↓erythema	Telangiectasiae not assessed

Table 1: Randomized placebo-controlled trials of topical metronidazole in treatment of rosacea.
*Indicates statistical significance at 0.05 level
**A reduction in inflammatory lesions and a significant decrease in telangiectasiae were seen by week 4. There was a significant decrease in erythema by week 8.

Product	Cost	Cost/gm	Application frequency	Cost/day
ROSASOL Cream 1% (Stiefel Canada)	$14.81/30gm	$.49	BID	$ .98
Noritate 1% (Dermik)	$14.81/30gm	$.49	BID	$ .98
Metrocream 0.75% (Galderma)	$22.20/45gm	$.49	BID	$ .98
Metrogel 0.75% (Galderma)	$17.43/30gm	$.58	BID	$1.16
Sunscreen SPF 15	~$12.00/120ml	~$.10/ml	PRN	

Table 2: Dosage and Cost (CDN) of drugs used to treat rosacea, and of SPF 15 sunscreen. Formulary prices are from *La Regie de l'assurance maladie* (2001 Apr) and the *Ontario Drug Benefit Formulary* (2001 Mar).

induced inflammatory mediators such as reactive oxygen species.[9] *Parsol* 1789 and MCX are broad-spectrum sunscreens that are effective in both UVB and UVA wavelengths.

Pivotal Clinical Trial

A Canadian multi-center double-blind randomized trial of 120 patients against sunscreen vehicle demonstrated that *ROSASOL Cream* applied twice daily was significantly more effective in the treatment of rosacea.[4] At the end of 12 weeks of treatment, mean reductions for *ROSASOL Cream* (in comparison to placebo) were:

- inflammatory lesions by 70% (placebo: 23%, P = 0.005)
- erythema scores by 41% (placebo: 27%, P = 0.021)
- telangiectasia scores by 17% (placebo: 4%, P = 0.043).

ROSASOL Cream was well tolerated with the majority of patients noting a reduction in itching, dryness and stinging over the course of the 12-week study.

Adverse Effects

The 37 adverse events attributed to *ROSASOL Cream* in the Canadian double-blind study occurred at the site of application and consisted of stinging (13 cases), erythema (8 cases), itching (5 cases) and dryness (4 cases). All patients recovered completely without sequelae.[4]

Conclusion

ROSASOL Cream, a topical product containing 1% metronidazole with sunscreens, is efficacious and well-tolerated in treatment of rosacea. In addition to improving the inflammatory and vascular clinical manifestations of this condition, it also provides the additional benefit of photoprotection in this combined product.

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Importance of Skin Cancer Screenings for Middle-Aged and Older Men Reinforced by New Study

A review of the American Academy of Dermatology's (AAD) National Skin Cancer Screening Program indicates that middle-aged and older men are not detecting melanoma in its early stages when it is most curable because they are the least likely to perform monthly skin self-examinations or visit a dermatologist regularly.

Melanomas are characterized by the uncontrolled growth of pigment-producing cells. They may suddenly appear without warning, but can also develop from or near a mole. They can occur anywhere on the body, but are found most frequently on the upper backs of men and women, or on the calves of women.

The study included 242,374 screenings conducted between 1992 and 1994, as part of the AAD's National Skin Cancer Screening Program*. Overall, 3,476 individuals were given a presumptive diagnosis of melanoma or possible melanoma. However, melanoma was more than three times as common among middle-aged and older men than among all those screened. This group of men comprised more than 44% of patients

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Antidepressant Drugs in Dermatology

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ABSTRACT

Antidepressant drugs can be an important component of the dermatologists' therapeutic armamentarium. When considering the use of psychotropic agents in dermatology two major factors should be considered: (1) the accurate diagnosis of the comorbid psychiatric disorder, and (2) the presence of proper indications for the use of antidepressant agents. Antidepressant drugs are used in the management of the psychiatric syndromes,[13] which are most frequently comorbid with dermatolgic disorders, i.e., Major Depressive Disorder, Obsessive-Compulsive Disorder, Body Dysmorphic Disorder, Post-traumatic Stress Disorder and Social Phobia. The antihistaminic and analgesic properties of some antidepressants such as doxepin and amitriptyline, are also be of benefit in the treatment of some pruritic and neuralgic states. The specific guidelines, side effect profile, drug-drug interactions, and the most current indications should always be obtained for any particular antidepressant agent before it is prescribed.

KEY WORDS: *antidepressant, serotonin reuptake inhibitors, tricyclic antidepressants*

Antidepressants (Table 1)[1–5], can be classified as tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRI) and the atypical group. TCAs increase the synaptic concentration of norepinephrin (NE) and/or serotonin (5HT) in the central nervous system (CNS) by (1) inhibiting their reuptake in the presynaptic neuronal membrane, and (2) changing post-synaptic β-adrenergic receptor sensitivity. TCAs produce prominent peripheral and CNS anticholinergic effects, as well as sedative effects due to strong binding affinity for histamine H1 receptors, and orthostatic hypotension due to alpha adrenergic receptor blockade. The TCAs have a quinidine-like effect on the heart and, like quinidine, can moderately slow ventricular conduction in therapeutic doses. An overdose can cause severe conduction block and ventricular arrhythmias.

The SSRIs inhibit serotonin reuptake, thereby enhancing serotoninergic function. Their relatively selective effect on 5HT is believed to be the basis for their antiobsessional activity. In contrast to TCAs, the SSRIs have very minimal histamine H1, cholinergic and β1-adrenergic blocking effects.

In drug-drug interactions involving the use of psychotropic agents in dermatology, the cytochrome P450(CYP)2D6 and CYP3A3/4 are the most important. Some SSRIs such as fluoxetine and fluvoxamine are moderate inhibitors of cytochrome P450 3A3/4 (CYP 3A3/4) isoenzymes, and can slow down the metabolism of medications that are metabolized by CYP3A3/4 isoenzymes. Concurrent use of the antipsychotic agent pimozide, a CYP3A3/4 substrate, and fluoxetine has been associated with bradycardia.[1] In vitro studies have shown that fluvoxamine blocks the metabolism of the antihistamines astemizole and terfenadine, which are CYP3A3/4 substrates. This can result in potentially fatal QT prolongation and torsades des pointes. The co-administration of fluvoxamine with astemizole and terfenadine is contraindicated.[1,2] Co-administration of fluoxetine with single doses of terfenadine (a CYP3A3/4 substrate), showed no increases in terfenadine levels.[2] In vitro studies have shown that ketoconazole, a potent CYP3A3/4 inhibitor, is at least 100 times more potent than fluoxetine as an inhibitor of the metabolism of several substrates of this enzyme.[2] Alternately, the SSRI paroxetine is a very weak inhibitor of CYP3A3/4 and interactions with medications that are metabolized by CYP3A3/4 are unlikely.[1,2] The SSRIs paroxetine, fluoxetine and sertraline are also inhibitors of CYP2D6 isoenzyme, and can increase the blood levels of drugs that are metabolized by the CYP2D6 isoenzyme such as the tricyclic antidepressants, antipsychotics, codeine, and cardiac antiarrhythmics.[1,2]

Possible Uses Of Antidepressants For Conditions That Are Not Psychiatric Disorders

The TCA, oral doxepin, 10mg taken three times daily for 2 weeks, has been shown to be effective in the treatment of chronic idiopathic, and cold urticaria.[6,7,8] Topical 5% doxepin cream is also used for the treatment of pruritus.[9] The efficacy of doxepin in urticaria is not directly related to its antidepressant effect. The H1 and H2 antihistaminic and anticholinergic properties of the TCAs are important reasons for their efficacy. Doxepin, amitriptyline and trimipramine are potent H1-receptor (e.g., doxepin is 800 times more potent than diphenhydramine) and H2 receptor antagonists. The strongly antihistaminic TCA, trimipramine (50mg/day) has been used to treat the pruritus of atopic dermatitis.[10] Amitriptyline has been shown to be effective for postherpetic neuralgia[11], and amitriptyline or desipramine for the pain of diabetic neuropathy.[12]

Possible Uses of Antidepressants For Conditions That Represent Psychiatric Pathology

Major Depressive Disorder[13]

This disorder is characterized by one or more major depressive episodes (i.e., depressed mood or loss of interest or pleasure), and is accompanied by ≥4 vegetative symptoms such as change in sleep, appetite, fatigue, psychomotor agitation or retardation, and a reduced ability to concentrate. A wide range of dermatologic disorders[4,5] such as atopic dermatitis, psoriasis, chronic idiopathic

Generic (trade) name	Usual daily starting dose* (mg)	Usual daily dose range*(mg)	Relative histamine H_1-receptor blocking potency	Relative anticholinergic potency	Relative β1-adrenergic receptor blocking potency
Selective serotonin reuptake inhibitors (SSRI)					
• Fluoxetine(*Prozac*)	10–20	10–60	low/absent	low/absent	low/absent
• Sertraline (*Zoloft*)	50	50–200	low/absent	low/absent	low/absent
• Paroxetine(*Paxil*)	10–20	20–50	low/absent	very mild	low/absent
• Fluvoxamine(*Luvox*)	50	100–200	low/absent	low/absent	low/absent
Tricyclic compounds					
• Clomipramine	25–50	100–200	moderate	high	moderate
• Amitriptyline (*Elavil* and others)	50–75	100–150	high	high	moderate/high
• Doxepin (*Sinequan*, *Adapin*)	25–75	100–150	high	high	high
• Trimipramine (*Surmontil*)	25–75	75–100	high	high	moderate
• Imipramine (*Tofranil*)	25–75	100–150	moderate	moderate	high
Atypical antidepressants					
• Bupropion (*Wellbutrin*)	100	200–300	absent	mild/absent	absent
• Nefazadone (*Serzone*)	100–150	200–400	high	mild/absent	mild/absent
• Venlafaxine (*Effexor*)	37.5–75	75–150	mild	hild	mild

Table 1: Antidepressants: dosage and post-synaptic receptor affinities of some agents[1–5]

* Doses above 150 mg of imipramine or equivalent should be used with close monitoring for adverse reactions. All antidepressants are contraindicated in combination with monoamine oxidase inhibitors.

urticaria, alopecia areata, and acne are comorbid with depressive illness. Depression severity has been directly correlated with pruritic severity in psoriasis, atopic dermatitis and chronic idiopathic urticaria.[14] Patients with clinically mild acne who blame their vocational problems on their acne may be clinically depressed. Antidepressants have been used to treat neurotic excoriations and 'depressive equivalents' such as a burning sensation in the scalp and glossodynia.[1,2] Clomipramine has been used to treat trichotillomania.[15] When prescribing psychotropic agents, the clinician should always determine whether the patient poses a significant suicide risk, in which case the total amount of medication in the prescription should be a non-lethal dose.

Obsessive Compulsive Disorder[13] (OCD)

Symptoms include repetitive behaviors such as hand washing, hair plucking, picking of the skin including skin lesions, and ritualistic grooming. It may be the underlying pathology in trichotillomania, and neurotic excoriations and acne excoriee. Agents that inhibit 5-HT reuptake such as clomipramine and the SSRIs are effective in OCD. SSRIs are generally effective for OCD in higher doses when compared with the antidepressant dosage,[1,2] e.g., OCD may require 60-80mg/day of fluoxetine while a depressive illness will typically respond to a lower dose.

Body Dysmorphic Disorder[13] (Dysmorphophobia)

Patients with this condition exhibit a preoccupation with an imagined defect or a minor anomaly involving the face or head, such as thinning hair, wrinkles, acne, scars, vascular markings, or excessive facial hair. SSRI antidepressants may be effective, but the onset of action usually takes longer (about 6 weeks).

Post-traumatic Stress Disorder[13] (PTSD)

This condition is often under-recognized in dermatology. Patients have a history of having experienced a traumatic event that involved the threat of death, injury or severe harm and their response involved intense fear, horror and helplessness. PTSD patients who experience trauma such as sexual abuse, severe emotional abuse or neglect, loss of a caregiver in early life, or a very chaotic childhood may self-inflict lesions, e.g., dermatitis artefacta and trichotillomania, or self-excoriate an existing skin lesion, e.g., acne excoriee. Since some patients experience dissociative episodes, they may not recall self-inflicting the lesions. SSRI antidepressants help attenuate some symptoms of hyperarousal in PTSD and decrease the frequency of self-injury.

Social Phobia[13]

Patients with social phobia experience fear being humiliated or embarrassed in public, and this may lead to the avoidance of certain social situations. A cosmetically disfiguring skin condition can theoretically contribute to the development of social phobia. SSRIs, nefazodone, and venlafaxine may be effective in the management of social phobia in some patients.

Some Guidelines For The Use Of Antidepressant Agents[1–5]

- Evaluate the patient to determine the presence of correct indications, assess suicide potential, and perform complete blood count, liver and renal function tests, as well as ECG, if indicated

by cardiac history or if there is potential for cardiotoxicity present.

- SSRIs have replaced the TCAs as the drug of first choice when treating depression because of their safety, their much lower cardiovascular side effects and better tolerability. Furthermore, treatment can be initiated with a dosage of SSRI that is in the therapeutic range, in contrast to the TCAs where the dosage often has to be gradually increased.
- An SSRI should be chosen if anti-obsessional effects are desired, or anxiety is a prominent symptom. Strong antihistaminic antidepressants such as doxepin, trimipramine or amitriptyline should be chosen if sedative or antihistaminic effects are desired. Dermatology patients may respond to a dosage of medication that is lower than the antidepressant dose when the TCA is being used for its antihistaminic/sedative properties.
- For a significant antidepressant effect to become established 4–6 weeks of treatment are usually necessary and the patient should be advised about this when therapy is first initiated, as this is likely to improve compliance. The antidepressant should be continued for 6–12 months after an acute episode of major depression.
- Adverse effects (refer to information on a specific agent prior to prescribing[1,2]):
  - Cardiovascular-orthostatic hypotension related to β1-adrenergic receptor blocking potency
  - ECG changes such as QT prolongation and T wave inversion, intraventricular conduction defects and arrhythmias
  - Increased risk of cardiotoxicity when used in conjunction with antihistamines, eg., diphenhydramine, hydroxyzine
  - Anticholinergic — blurred vision, precipitation of narrow angle glaucoma, urinary retention, decreased bowel motility, dry mouth
  - Hematologic-agranulocytosis (rare)
  - Neurologic — lowering of seizure threshold, sedation, with SSRIs may experience restlessness and anxiety
  - Some cutaneous reactions include photosensitivity, increased sweating, pruritus, maculopapular rashes, urticaria, cutaneous vasculitis, erythema multiforme and alopecia.

Conclusion

Antidepressant agents can play an important role in the management of a wide range of dermatologic disorders. The strongly antihistaminic properties of some tricyclic antidepressants are beneficial in conditions such as urticaria and pruritus. TCAs and SSRI antidepressants are used for the treatment of Major Depressive Disorder, a disease that can coexist with a wide range of skin disorders. TCAs that act on serotonin and the SSRIs are effective in the treatment of Obsessive-Compulsive Disorder, which may underlie many self-induced dermatoses. The SSRIs are also effective in some cases of Body Dysmorphic Disorder, often seen in patients who present with cutaneous body image problems, Posttraumatic Stress Disorder, which underlies some self-induced dermatoses, and Social Phobia, which may coexist with cosmetically disfiguring skin disorders.

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Update on Drugs

Class	Name/Company	Approval Dates and Comments
Antibacterial Agents	**Moxifloxacin HCl** *Avelox* Bayer	The US FDA approved an additional indication for this fluoroquinolone antibiotic in April 2001, as a once daily treatment for uncomplicated skin and skin structure infections due to *Staphylococcus aureus* and *Streptococcus pyogenes*. The US FDA originally approved *Avelox* in December 1999, for treatment of common adult community-acquired respiratory tract infections
Enzymes	**Recombinant Human Iduronidase (IDUA)** Novazyme Pharmaceuticals	The US FDA granted orphan drug status in April 2001, for this proprietary treatment for mucopolysaccharidosis I (MPS I). MPS I is a genetic disease that is characterized by the body's inability to break down mucopolysaccharides, due to the lack of necessary enzymes. The mucopolysaccharides then accumulate in the body's cells causing progressive damage to various organs. IDUA is nearly identical to the enzyme present in healthy persons.
Neurotoxins	**Botulinum Toxin Type A** *BOTOX* Allergan	TPP – Canada approved an additional indication in April 2001, for the treatment of glabellar lines associated with corrugator and/or procerus muscle activity. A supplemental Biologics License Application was made to the US FDA in January 2001.
Wound Care	**Graftskin** *Apligraf* Novartis	The European Medicines Evaluation Agency received a marketing application in April 2001, for Apligraf to treat diabetic foot ulcers and venous leg ulcers. The US FDA approved this skin substitute in June 2000, for the treatment of diabetic foot ulcers > 3 weeks duration.
Drug News		
Anti-inflammatory Agents	Phase III trials have begun for *Artisone* (dapsone, Atrix Laboratories) for the treatment of moderate to severe acne using Atrix's delivery system that allows the topical administration of water-insoluble drugs. There was approximately a 50% reduction in inflammatory and non-inflammatory lesions in Phase I and II trials. Furthermore, serum dapsone levels were about 1/600 of the level that causes safety concerns with oral dosing. This suggests that *Artisone* may combine the power of a systemic drug with the safety of a topical drug.	
Anti-inflammatory Agents	Positive data was reported from Phase I and II trials of HCT-1026 (Nicox SA), a topical formulation of a nitric oxide-releasing derivative of the nonsteriodal anti-inflammatory drug (NSAID) flurbiprofen. A 1% ointment formulation demonstrated significantly greater anti-inflammatory activity than its reference NSAID, flurbiprofen four hours after application.	
Photodynamic Therapy	Schering AG/Berlex is expected to launch its photodynamic therapy product, *Levulan Kerastick* (5-aminolevulinic acid) in the US soon for the treatment of actinic keratoses of the scalp and face. Levulan was approved by the US FDA in December 1999, and is awaiting approval from TPP – Canada.	
Antipsoriatic Agents	Phase II study results were recently reported for *AMEVIVE* (Alefacept, Biogen). When patients with moderate to severe chronic psoriasis, who had previously been treated with this drug, received another treatment course, approximately half of the patients achieved >50% reduction of their disease, using the Psoriasis Area and Severity Index. Patients maintained their clinical improvement between 5 and 17 months after their course of therapy. *AMEVIVE* is an immunomodulator that specifically targets a subset of lymphocytes which play a pivotal role in causing psoriasis.	

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