

# Simple Acid Test Can Diagnose 'Sensitive Skin'

BY JANE SALODOF MACNEIL

Southwest Bureau

PHOENIX, ARIZ. Sensitive skin complaints in the absence of a recognizable skin disease or irritation in female patients should not be dismissed, Albert M. Kligman, M.D., said at a clinical dermatology conference sponsored by Medicis.

Sensitive skin is a real subclinical condition that can be verified with a simple skin test and treated with a daily application of

Nivea cream, said Dr. Kligman, professor emeritus of dermatology at the University of Pennsylvania, Philadelphia.

Between 30% and 50% of women in the United States, Europe, and Japan complain of itching, burning, stinging, dryness, tightening, or pain in reaction to topical skin care products, Dr. Kligman said. He blamed the problem on erosion of the stratum corneum by heavy use of skin care products in developed countries.

"Anything able to get through a leaky

stratum corneum [is] going to pick up afferent responses," he said. "There's no question that nerves are involved in this."

To identify credible complaints in a patient whose skin appears normal, Dr. Kligman recommended a "lactic acid stinging test" he developed with colleagues. He said to apply a 10% solution of lactic acid to the patient's medial cheek and ask about the sensation without offering any cues.

If the patient has sensitive skin, the acid should induce a stinging sensation in 1 or

2 minutes. This will reach a peak in 5 minutes, only to become insignificant in 15 minutes. Some highly sensitive women may find the sensation unbearable and ask to have the acid washed away in 3 minutes, Dr. Kligman said. If, however, a patient has an instant reaction, he would conclude she does not have sensitive skin. Most sensitive skin reactions are moderate, and take time to develop.

Women who react to lactic acid are usually hypersensitive to other substances, he added, listing cause-and-effect relationships between capsaicin and pain, histamine and itching, harsh soaps or cleansers and tightness, and balsam of Peru and burning.

Although sensitive skin may take decades to develop, the remedy can be as quick as 7-8 weeks with daily applications of Nivea cream or a comparable product. "Stingers become nonstingers if you improve their barrier—make their skins less permeable," he said. "It is possible to convert a stinging to a nonstinger just by putting on a bland moisturizer."

## Onychomycosis: Stretched Out Pulse Dosing

FLORENCE, ITALY — Terbinafine can cure onychomycosis in patients who take it for only 1 week every 2-3 months for up to a year, Martin N. Zaia, M.D., reported at 13th Congress of the European Academy of Dermatology and Venereology.

"From an economic point of view, our concern was that if a patient is taking a daily dose for 3 months, the cost is obviously going to be greater than taking a daily dose just 1 week of every 2 or 3 months," said Dr. Zaia, in private practice in Miami.

He noted that earlier studies by his group confirmed that terbinafine (Lamisil) remains in the nail bed for at least a month after being taken for 7 consecutive days at a 250-mg/day dosage.

Pulse dosing using a 1-week-per-month schedule became an accepted way to treat *Trichophyton rubrum* onychomycosis.

The current study was aimed at seeing how far that limit could be stretched.

"If 1 week out of the month worked, why not 1 week out of every 2 months ... or 3 months ... or 4?" he asked.

Nine of 10 patients recruited from Dr. Zaia's practice were cured within a year after taking the medication for 1 week every 2 months at the standard dosage of 250 mg/day. Twelve of 12 patients were cured taking terbinafine for 1 week every 3 months.

When the 1-week pulse was extended to every 4 months, however, the cure rate dropped to 10 of 17 patients tested.

The researchers monitored patients' progress by measuring the extent of involvement on the nail bed from a scalpel nick placed at the onset of the trial.

—Betsy Bates

### BRIEF SUMMARY of Prescribing Information—Before prescribing, please consult complete Prescribing Information.

**INDICATIONS AND USAGE: Bipolar Mania:** SEROQUEL is indicated for the treatment of acute manic episodes associated with bipolar I disorder, as either monotherapy or adjunct therapy to lithium or divalproex. The efficacy of SEROQUEL in acute bipolar mania was established in 12-week monotherapy trials and one 3-week adjunct trial of bipolar I patients initially hospitalized for up to 7 days for acute mania. Effectiveness has not been systematically evaluated in clinical trials for more than 12 weeks in monotherapy and 3 weeks in adjunct therapy. Therefore, the physician who elects to use SEROQUEL for extended periods should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient. **Schizophrenia:** SEROQUEL is indicated for the treatment of schizophrenia. The efficacy of SEROQUEL in schizophrenia was established in short-term (6-week) controlled trials of outpatients. The effectiveness of SEROQUEL in long-term use, that is, for more than 6 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use SEROQUEL for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

**CONTRAINDICATIONS:** SEROQUEL is contraindicated in individuals with a known hypersensitivity to this medication or any of its ingredients.

**WARNINGS: Neuroleptic Malignant Syndrome (NMS):** A potentially fatal symptom complex sometimes referred to as NMS has been reported in association with administration of antipsychotic drugs, including SEROQUEL. Rare cases of NMS have been reported with SEROQUEL. Clinical manifestations of NMS are hyperreflexia, muscle rigidity, altered mental status, and evidence of autonomic instability. See full Prescribing Information for more information on the manifestations, diagnosis and management of NMS. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored since recurrences of NMS have been reported. **Tardive Dyskinesia:** A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown. The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely. If antipsychotic treatment is withdrawn, antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown. Given these considerations, SEROQUEL should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who appear to suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically. If signs and symptoms of tardive dyskinesia appear in a patient on SEROQUEL, drug discontinuation should be considered. However, some patients may require treatment with SEROQUEL despite the presence of the syndrome. **Hypertension and Diabetes Mellitus:** Hypertension, in some cases extreme and associated with retinopathy or hypertensive encephalopathy, has been reported in patients treated with antipsychotics, including SEROQUEL. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hypertension-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hypertension-related adverse events in patients treated with atypical antipsychotics are not available. Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (eg, obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients require continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

**PRECAUTIONS: General: Orthostatic Hypotension:** SEROQUEL may induce orthostatic hypotension associated with dizziness, tachycardia and, in some patients, syncope, especially during the initial dose-escalation period, probably reflecting its  $\alpha_1$ -adrenergic antagonist properties. Syncope was reported in 1% (23/2367) of patients who received SEROQUEL. The risk of orthostatic hypotension and syncope may be minimized by limiting the initial dose to 25 mg bid. If hypotension occurs during titration to the target dose, a return to the previous dose in the titration schedule is appropriate. **Cataracts:** The development of cataracts was observed in association with quetiapine treatment in chronic dog studies. Lens changes have also been observed in patients during long-term SEROQUEL treatment, but a causal relationship to SEROQUEL use has not been established. Nevertheless, the possibility of lenticular changes cannot be excluded at this time. Therefore, examination of the lens by methods adequate to detect cataract formation, such as slit lamp exam or other appropriately sensitive methods, is recommended at initiation of treatment or shortly thereafter, and at 6-month intervals during chronic treatment. **Seizures:** During clinical trials, seizures occurred in 0.6% (18/2792) of patients treated with SEROQUEL compared to 0.2% (1/607) on placebo and 0.7% (4/527) on active control drugs. As with other antipsychotics SEROQUEL should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold, eg, Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older. **Hypothyroidism:** Clinical trials with SEROQUEL demonstrated a dose-related decrease in total and free thyroxine (T4) of approximately 20% at the higher end of the therapeutic dose range and was maximal in the first two to four weeks of treatment and maintained without adaptation or progression during more chronic therapy. In nearly all cases, cessation of SEROQUEL treatment was associated with a reversal of the effects on total and free T4, irrespective of the duration of treatment. About 0.4% (12/2791) of SEROQUEL patients did experience TSH increases in monotherapy studies. Six of the patients with TSH increases needed replacement thyroid treatment. In the mania adjunct studies, where SEROQUEL was added to lithium or divalproex, 12% (24/196) of SEROQUEL-treated patients compared to 7% (15/203) of placebo-treated patients had elevated TSH levels. Of the SEROQUEL-treated patients with elevated TSH levels, 3 had simultaneous low free T4 levels. **Cholesterol and Triglyceride Elevations:** In schizophrenia trials, SEROQUEL-treated patients had increases from baseline in cholesterol and triglyceride of 11% and 17%, respectively, compared to slight decreases for placebo patients. These changes were only weakly related to the increases in weight observed in SEROQUEL-treated patients. **Hyperprolactinemia:** Although an elevation of prolactin levels was not demonstrated in clinical trials with SEROQUEL, increased prolactin levels were observed in rat studies with this compound, and were associated with an increase in mammary gland neoplasia in rats (see **Carcinogenesis**). Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecostasia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time. **Transaminase Elevations:** Asymptomatic, transient and reversible elevations in serum transaminases (primarily ALT) have been reported. In schizophrenia trials, the proportions of patients with transaminase elevations of > 3 times the upper limits of the normal reference range in a pool of 3- to 6-week placebo-controlled trials were approximately 8% for seromolnol, compared to 1% for placebo in patients on SEROQUEL compared to 1% of placebo patients. In acute bipolar mania trials using SEROQUEL as monotherapy, seromolnol was reported in 16% of patients on SEROQUEL compared to 4% of placebo patients. In acute bipolar mania trials using SEROQUEL as adjunct therapy, seromolnol was reported in 34% of patients on SEROQUEL compared to 9% of placebo patients. Since SEROQUEL has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about performing activities requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating a piece of machinery until they are reasonably certain that SEROQUEL treatment does not affect their adversely. **Priapism:** One case of priapism in a patient receiving SEROQUEL has been reported prior to market introduction. While a causal relationship to use of SEROQUEL has not been established, other drugs with alpha-adrenergic blocking effects have been reported to induce priapism, and it is possible that SEROQUEL may share this capacity. Severe priapism may require surgical intervention. **Body Temperature Regulation:** Although not reported with SEROQUEL, disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing SEROQUEL for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, eg, exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration. **Dysphagia:** Esophageal dysmotility and aspiration have been associated with antipsychotic drug use.

### SEROQUEL® (quetiapine fumarate) Tablets

Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. SEROQUEL and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia. **Suicide:** The possibility of a suicide attempt is inherent in bipolar disorder and schizophrenia; close supervision of high risk patients should accompany drug therapy. Prescriptions for SEROQUEL should be written for the smallest quantity of tablets consistent with good patient management, and should be issued to avoid the possibility of abuse. **Use in Patients with Concomitant Illness:** Clinical experience with SEROQUEL in patients with certain concomitant systemic illnesses is limited. SEROQUEL has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies. Because of the risk of orthostatic hypotension with SEROQUEL, caution should be observed in cardiac patients (see **Orthostatic Hypotension**). **Information for Patients:** Patients should be advised to consult the physician who prescribes SEROQUEL for details of the following issues to discuss with patients for whom they prescribe SEROQUEL: Orthostatic Hypotension, Interference with Cognitive and Motor Performance, Pregnancy, Nursing, Concomitant Medication, Alcohol, and Heat Exposure and Dehydration. **Laboratory Tests:** No specific laboratory tests are recommended. **Drug Interactions:** The risks of using SEROQUEL in combination with other drugs have not been extensively evaluated in systematic studies. Given the primary CNS effects of SEROQUEL, caution should be used when it is taken in combination with other centrally acting drugs. SEROQUEL potentiated the cognitive and motor effects of alcohol in a clinical trial in subjects with selected psychiatric disorders, and alcoholic beverages should be avoided while taking SEROQUEL. Because of its potential for inducing hypotension, SEROQUEL may enhance the effects of certain antihypertensive agents. SEROQUEL may antagonize the effects of levodopa and dopamine agonists. **The Effect of Other Drugs on Quetiapine:** Phenytoin: Coadministration of quetiapine (250 mg bid) and phenytoin (100 mg bid) increased the mean oral clearance of quetiapine by 5-fold. Increased doses of SEROQUEL may be required to maintain control of symptoms of schizophrenia in patients receiving quetiapine and phenytoin, or other hepatic enzyme inducers (eg, carbamazepine, barbiturates, rifampin, glucocorticoids). Caution should be taken if phenytoin is withdrawn and replaced with a non-inducer (eg, valproate). **Divalproex:** Coadministration of quetiapine (150 mg bid) and divalproex (500 mg bid) increased the mean maximum plasma concentration of quetiapine at steady state by 17% without affecting the extent of absorption or mean oral clearance. **Thioridazine:** Thioridazine (200 mg bid) increased the mean oral clearance of quetiapine (200 mg bid) by 65%. **Cimetidine:** Administration of oral cimetidine (400 mg bid for 4 days) resulted in a 20% decrease in the mean oral clearance of quetiapine (150 mg bid). Dosage adjustment for quetiapine is not required when it is given with cimetidine. **P450 3A Inhibitors:** Coadministration of ketoneconazole (200 mg once daily for 4 days), a potent inhibitor of cytochrome P450 3A, reduced oral clearance of quetiapine by 84%, resulting in a 355% increase in maximum plasma concentration of quetiapine. Caution is indicated when SEROQUEL is administered with ketoneconazole and other inhibitors of cytochrome P450 3A (eg, itraconazole, voriconazole, fluconazole, fluvoxamine, imipramine, haloperidol, and risperidone). Coadministration of fluoxetine (60 mg once daily); imipramine (75 mg bid), haloperidol (7.5 mg bid), or risperidone (3 mg bid) with quetiapine (300 mg bid) did not alter the steady-state pharmacokinetics of quetiapine. **Effect of Quetiapine on Other Drugs:** **Lorazepam:** The mean oral clearance of lorazepam (2 mg, single dose) was reduced by 20% in the presence of quetiapine administered as 250 mg bid. **Divalproex:** The mean maximum concentration and extent of absorption of total and free valproic acid at steady state were decreased by 10 to 12% when divalproex (500 mg bid) was administered with quetiapine (150 mg bid). The mean oral clearance of total valproic acid (administered as divalproex 500 mg bid) was increased by 11% in the presence of quetiapine (150 mg bid). The changes were not significant. **Lithium:** Concomitant administration of quetiapine (250 mg bid) with lithium had no effect on any of the steady-state pharmacokinetic parameters of lithium. **Antipyrene:** Administration of multiple daily doses up to 750 mg/day (on a bid schedule) of quetiapine to subjects with selected psychiatric disorders had no clinically relevant effect on the clearance of antipyrene or urinary excretion of quetiapine. **Fluorescein:** These results indicate that quetiapine does not significantly induce hepatic enzymes responsible for cytochrome P450 mediated metabolism of antipyrene. **Carcinogenesis, Mutagenesis, Impairment of Fertility, Carcinogenesis:** Carcinogenicity studies were conducted in C57BL/6 mice and Wistar rats. There were statistically significant increases in thyroid gland follicular adenomas in male mice at doses of 250 and 750 mg/kg or 1.5 and 4.5 times the maximum human dose on a mg/m<sup>2</sup> basis and in male rats at a dose of 250 mg/kg or 3.0 times the maximum human dose on a mg/m<sup>2</sup> basis. Mammary gland adenocarcinomas occurred significantly increased in female rats at all doses tested. There were no statistically significant increases in thyroid gland follicular adenomas in male mice at doses of 250 and 750 mg/kg or 1.5 and 4.5 times the maximum human dose on a mg/m<sup>2</sup> basis and in male rats at a dose of 250 mg/kg or 3.0 times the maximum human dose on a mg/m<sup>2</sup> basis. Mammary gland adenocarcinomas were not observed in female rats at all doses tested. There were no statistically significant increases in thyroid follicular cell adenomas may have resulted from chronic stimulation of the thyroid gland by thyroid stimulating hormone (TSH) resulting from enhanced metabolism and clearance of thyroxine by rodent liver. Changes in TSH, thyroxine, and thyroxine clearance consistent with this mechanism were observed in subchronic toxicity studies in rat and mouse and in a 1-year toxicology study in rat; however, these changes were not definitive. The relevance of these changes in thyroid follicular cell adenomas to human risk, through whatever mechanism, is unknown. Serum measurements in a 1-year toxicity study showed that quetiapine increased mean serum prolactin levels a maximum of 32- and 13-fold in male and female rats, respectively. Increases in mammary neoplasms have been found in rodents after chronic administration of other antipsychotic drugs and are considered to be prolactin-mediated. The relevance of this increased incidence of prolactin-mediated mammary gland tumors in rats to human risk is unknown (see **Hyperprolactinemia**). **PRECAUTIONS, General: Mutagenesis:** The mutagenic potential of quetiapine was tested in six *in vitro* bacterial gene mutation assays and in an *in vivo* mammalian gene mutation assay in Chinese Hamster Ovary cells. However, sufficiently high concentrations of quetiapine may not have been used for all tester strains. Quetiapine did produce a reproducible increase in mutations in one Salmonella typhimurium tester strain in the presence of metabolic activation. No evidence of clastogenic potential was obtained in an *in vivo* chromosomal aberration assay in cultured human lymphocytes or in an *in vivo* micronucleus assay in rats. **Impairment of Fertility:** Quetiapine decreased uterine and fetal body weights in rats. 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