



BY PETER J. ZIEMKOWSKI, M.D.

## THE OFFICE

# Putting the Web to Use in Practice

I am a strong believer in using the resources we have so readily at hand to inform ourselves of the latest medical information and guidelines and to inform our patients. Every exam room in our

practice is wired with access to the Web and I refer to it during nearly every patient visit. Here's a quick look at sites that I'm currently using:

► **Social Bookmarking:** With the explosion of social networking sites in the past year, there has been a corresponding increase in sites, such as delicious.com, that allow you to explore and evaluate online resources in a collective way. These

bookmarking sites can run inside your browser. When you see a site you like, with one key stroke it can be added to your bookmarked list, which is then automatically organized by the frequency and prominence of keywords. The list that's compiled when you create bookmarks can then be easily shared with colleagues and you have access to their lists. If I've got a question relating to alterna-

tive medicine, for example, I'll turn to the bookmarks of a colleague who is a specialist in that area because I know he has already vetted them for me. All of us are smarter than any one of us.

► **Patient Education:** If a patient needs information, I turn to sites vetted by government agencies or medical organizations such as the American Academy of Family Physicians. The AAFP's site, [www.familydoctor.org](http://www.familydoctor.org), has handouts and short video clips on a variety of topics.

The National Library of Medicine (<http://medlineplus.gov>) provides patient-oriented, one-page overviews with links to more detailed information at other reviewed sites, providing "one-stop" shopping for patient information.

The Mayo Clinic's site ([www.mayoclinic.com](http://www.mayoclinic.com)) is frequently referenced by the NLM and provides reliable, well-written patient handouts.

Despite the fact that 54% of our residency program clinic patients are on Medicaid, a large number have access to a computer to look at these sites.

► **Physician Education:** When I'm searching for information for my own purposes, I use the same rule of thumb: Well-worn paths are best. When I'm looking for a high-level overview or when I can't remember a specific fact, I'll go to [www.fpnotebook.com](http://www.fpnotebook.com), which offers a lot of information for free. Another site that offers information for free is [www.emedicine.com](http://www.emedicine.com).

Through our hospital and residency program affiliate, I have access to [www.uptodate.com](http://www.uptodate.com), which is a fee-based resource with reliable information.

The 600-pound gorilla for drug information, of course, is [www.epocrates.com](http://www.epocrates.com).

The Agency for Healthcare Research and Quality's electronic Preventive Services Selector ([www.epss.ahrq.gov](http://www.epss.ahrq.gov)) offers downloadable applications that are useful for remembering preventive services that an individual may need. So if you have a new 48-year-old male patient who smokes, the application suggests a list of evidence-based screening services.

For guidelines on any topic, go to [www.guidelines.gov](http://www.guidelines.gov). Guidelines from [www.nhlbi.gov](http://www.nhlbi.gov) probably cover about 80% of my day.

To some degree I worry about physicians who aren't checking Web resources. As Dr. Larry Weed, the pioneer visionary of the information age in health care, once suggested: If you want to go on a trip, you don't go to a travel agent who has memorized all of the flight boarding times, you go to someone who knows how to utilize resources to pick the best trip for you.

Our memory of what we learned in medical school is imperfect. And what was true back then, has probably changed. ■

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**Table 2. Treatment-Emergent Adverse Reaction Incidence in Placebo-Controlled Trials in Fibromyalgia Patients (Events Occurring in at Least 2% of All Savella-Treated Patients and Occurring More Frequently in Either Savella Treatment Group Than in the Placebo Treatment Group)(continued)**

System Organ Class-Preferred Term	Savella 100 mg/day (n = 623) %	Savella 200 mg/day (n = 934) %	All Savella (n = 1557) %	Placebo (n = 652) %
<b>Vascular Disorders</b>				
Hot flush	11	12	12	2
Hypertension	7	4	5	2
Flushing	2	3	3	1

**Weight Changes-**In placebo-controlled fibromyalgia clinical trials, patients treated with Savella for up to 3 months experienced a mean weight loss of approximately 0.8 kg in both the Savella 100 mg/day and the Savella 200 mg/day treatment groups, compared with a mean weight loss of approximately 0.2 kg in placebo-treated patients. **Genitourinary Adverse Reactions in Males-**In the placebo-controlled fibromyalgia studies, the following treatment-emergent adverse reactions related to the genitourinary system were observed in at least 2% of male patients treated with Savella, and occurred at a rate greater than in placebo-treated male patients: dysuria, ejaculation disorder, erectile dysfunction, ejaculation failure, libido decreased, prostatitis, scrotal pain, testicular pain, testicular swelling, urinary hesitancy, urinary retention, urethral pain, and urine flow decreased. **Other Adverse Reactions Observed During Clinical Trials of Savella in Fibromyalgia-**Following is a list of frequent (those occurring on one or more occasions in at least 1/100 patients) treatment-emergent adverse reactions reported from 1824 fibromyalgia patients treated with Savella for periods up to 68 weeks. The listing does not include those events already listed in Table 2, those events for which a drug cause was remote, those events which were so general as to be uninformative, and those events reported only once which did not have a substantial probability of being acutely life threatening. Adverse reactions are categorized by body system and listed in order of decreasing frequency. Adverse reactions of major clinical importance are described in the *Warnings and Precautions* section. **Gastrointestinal Disorders** – diarrhea, dyspepsia, gastroesophageal reflux disease, flatulence, abdominal distension; **General Disorders** – fatigue, peripheral edema, irritability, pyrexia; **Infections** – urinary tract infection, cystitis; **Injury, Poisoning, and Procedural Complications** – contusion, fall; **Investigations** – weight decreased or increased; **Metabolism and Nutrition Disorders** – hypercholesterolemia; **Nervous System Disorders** – somnolence, dysgeusia; **Psychiatric Disorders** – depression, stress; **Skin Disorders** – night sweats. **Postmarketing Spontaneous Reports-**The following additional adverse reactions have been identified from spontaneous reports of Savella received worldwide. These adverse reactions have been chosen for inclusion because of a combination of seriousness, frequency of reporting, or potential causal connection to Savella. However, because these adverse reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These events include: **Blood and Lymphatic System Disorders** – leukopenia, neutropenia, thrombocytopenia; **Cardiac Disorders** – supraventricular tachycardia; **Eye Disorders** – accommodation disorder; **Endocrine Disorders** – hyperprolactinemia; **Hepatobiliary Disorders** – hepatitis; **Metabolism and Nutrition Disorders** – anorexia, hyponatremia; **Musculoskeletal and Connective Tissue Disorders** – rhabdomyolysis; **Nervous System Disorders** – convulsions (including grand mal), loss of consciousness, Parkinsonism; **Psychiatric Disorders** – delirium, hallucination; **Renal and Urinary Disorders** – acute renal failure, urinary retention; **Reproductive System and Breast Disorders** – galactorrhea; **Skin Disorders** – erythema multiforme, Stevens Johnson syndrome; **Vascular Disorders** – hypertensive crisis.

**DRUG INTERACTIONS:** Milnacipran undergoes minimal CYP450 related metabolism, with the majority of the dose excreted unchanged in urine (55%), and has a low binding to plasma proteins (13%). In vitro and in vivo studies showed that Savella is unlikely to be involved in clinically significant pharmacokinetic drug interactions [see *Pharmacokinetics in Special Populations*]. **Clinically Important Interactions with Other Drugs-Lithium:** Serotonin syndrome may occur when lithium is co-administered with Savella and with other drugs that impair metabolism of serotonin [see *Warnings and Precautions* – *Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-Like Reactions*]. **Epinephrine and norepinephrine:** Savella inhibits the reuptake of norepinephrine. Therefore concomitant use of Savella with epinephrine and norepinephrine may be associated with paroxysmal hypertension and possible arrhythmia [see *Warnings and Precautions* – *Effects on Blood Pressure and Effects on Heart Rate*]. **Serotonergic Drugs:** Co-administration of Savella with other inhibitors of serotonin re-uptake may result in hypertension and coronary artery vasoconstriction, through additive serotonergic effects [see *Warnings and Precautions*]. **Digoxin:** Use of Savella concomitantly with digoxin may be associated with potentiation of adverse hemodynamic effects. Postural hypotension and tachycardia have been reported in combination therapy with intravenously administered digoxin (1 mg). Co-administration of Savella and intravenous digoxin should be avoided [see *Warnings and Precautions*]. **Clonidine:** Because Savella inhibits norepinephrine reuptake, co-administration with clonidine may inhibit clonidine's anti-hypertensive effect. **Clomipramine:** In a drug-drug interaction study, an increase in euphoria and postural hypotension was observed in patients who switched from clomipramine to Savella. **CNS-active drugs:** Given the primary CNS effects of Savella, caution should be used when it is taken in combination with other centrally acting drugs, including those with a similar mechanism of action. **Monoamine Oxidase Inhibitors (MAOIs):** [see *Contraindications*].

**USE IN SPECIFIC POPULATIONS: Pregnancy-**Pregnancy Category C. Milnacipran increased the incidence of dead fetuses in utero in rats at doses of 5 mg/kg/day (0.25 times the MRHD on a mg/m<sup>2</sup> basis). Administration of milnacipran to mice and rabbits during the period of organogenesis did not result in embryotoxicity or teratogenicity at doses up to 125 mg/kg/day in mice (3 times the maximum recommended human dose [MRHD] of 200 mg/day on a mg/m<sup>2</sup> basis) and up to 60 mg/kg/day in rabbits (6 times the MRHD of 200 mg/day on a mg/m<sup>2</sup> basis). In rabbits, the incidence of the skeletal variation, extra single rib, was increased following administration of milnacipran at 15 mg/kg/day during the period of organogenesis. There are no adequate and well-controlled studies in pregnant women. Savella should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nonteratogenic Effects:** Neonates exposed to dual reuptake inhibitors of serotonin and norepinephrine, or selective

serotonin reuptake inhibitors late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of these classes of drugs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome [see *Warnings and Precautions*]. In rats, a decrease in pup body weight and viability on postpartum day 4 were observed when milnacipran, at a dose of 5 mg/kg/day (approximately 0.2 times the MRHD on a mg/m<sup>2</sup> basis), was administered orally to rats during late gestation. The no-effect dose for maternal and offspring toxicity was 2.5 mg/kg/day (approximately 0.1 times the MRHD on a mg/m<sup>2</sup> basis). **Labor and Delivery-**The effect of milnacipran on labor and delivery is unknown. The use of Savella during labor and delivery is not recommended. **Nursing Mothers-**There are no adequate and well-controlled studies in nursing mothers. It is not known if milnacipran is excreted in human milk. Studies in animals have shown that milnacipran or its metabolites are excreted in breast milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from milnacipran, a decision should be made whether to discontinue the drug, taking into account the importance of the drug to the mother. Because the safety of Savella in infants is not known, nursing while on Savella is not recommended. **Pediatric Use-**Safety and effectiveness of Savella in a fibromyalgia pediatric population below the age of 17 have not been established [see *Box Warning and Warnings and Precautions*]. The use of Savella is not recommended in pediatric patients. **Geriatric Use-**In controlled clinical studies of Savella, 402 patients were 60 years or older, and no overall differences in safety and efficacy were observed between these patients and younger patients. In view of the predominant excretion of unchanged milnacipran via kidneys and the expected decrease in renal function with age renal function should be considered prior to use of Savella in the elderly [see *Dosage and Administration*]. SNRIs, SSRIs, and Savella, have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event [see *Warnings and Precautions*].

**DRUG ABUSE AND DEPENDENCE: Controlled Substance -** Milnacipran is not a controlled substance. **Abuse-**Milnacipran did not produce behavioral signs indicative of abuse potential in animal or human studies. **Dependence-**Milnacipran produces physical dependence, as evidenced by the emergence of withdrawal symptoms following drug discontinuation, similar to other SNRIs and SSRIs. These withdrawal symptoms can be severe. Thus, Savella should be tapered and not abruptly discontinued after extended use [see *Discontinuation of Treatment with Savella*].

**OVERDOSAGE:** There is limited clinical experience with Savella overdose in humans. In clinical trials, cases of acute ingestions up to 1000 mg, alone or in combination with other drugs, were reported with none being fatal. In postmarketing experience, fatal outcomes have been reported for acute overdoses primarily involving multiple drugs but also with Savella only. The most common signs and symptoms included increased blood pressure, cardio-respiratory arrest, changes in the level of consciousness (ranging from somnolence to coma), confusional state, dizziness, and increased hepatic enzymes. **Management of Overdose-**There is no specific antidote to Savella, but if serotonin syndrome ensues, specific treatment (such as with cyproheptadine and/or temperature control) may be considered. In case of acute overdose, treatment should consist of those general measures employed in the management of overdose with any drug. An adequate airway, oxygenation, and ventilation should be assured and cardiac rhythm and vital signs should be monitored. Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in symptomatic patients. Because there is no specific antidote for Savella, symptomatic care and treatment with gastric lavage and activated charcoal should be considered as soon as possible for patients who experience a Savella overdose. Due to the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be beneficial. In managing overdose, the possibility of multiple drug involvement should be considered. The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians' Desk Reference* (PDR).

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