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The purpose of this feature is to heighten awareness of specific adverse drug reactions (ADRs), discuss methods of prevention, and promote reporting of ADRs to the US Food and Drug Administration's (FDA) MedWatch program (800-FDA-1088). If you have reported an interesting, preventable ADR to MedWatch, please consider sharing the account with our readers. E-mail Dr. Mancano at michael.mancano@temple.edu. Your report will be published anonymously unless otherwise requested. This feature is provided by the Institute for Safe Medication Practices (ISMP) in cooperation with the FDA's MedWatch program and Temple University School of Pharmacy. ISMP is an FDA MedWatch partner.

Longitudinal Thumbnail Fissures Due to Erlotinib

A 58-year-old Caucasian male displayed bilateral thumbnail lesions associated with tenderness in his nail beds presented to his physician. At the time of symptom presentation, he had a 12-month history of stage IV adenocarcinoma of the right lung, metastatic to bones. Family history and environmental factors were unremarkable.

The patient had been receiving erlotinib (Tarceva) 150 mg by mouth daily for 12 months with a good partial response and monthly infusions of zoledronic acid (Reclast) for treatment of bone pain. He developed a self-limiting acneiform rash 3 weeks into erlotinib therapy and noticed dry skin and nail thinning 24 weeks after erlotinib initiation. Twelve months after beginning erlotinib therapy, he noticed longitudinal fissures affecting the central parts of his thumbnails. No other fingernails or toenails were affected. Over the next 16 weeks, the fissures became more prominent. Physical exam confirmed these fissures and was also remarkable for a grade 1 acneiform rash involving the face, neck, and chest, and xerosis of both hands.

The oncologist decided to continue erlotinib therapy and monitor the nail lesions because of the patient's good partial response to therapy. A dermatology consult was not deemed necessary and no biopsy or culture was pursued. The patient was instructed to apply colloidal oatmeal lotion to the lesions 3 times a day. Several weeks later, the patient reported stabilization of the lesions and decreased anxiety over their

appearance. The average duration of clinical response to erlotinib is approximately 11 months; however, this patient developed central longitudinal thumbnail fissures at 12 months of therapy with erlotinib, and his disease remains in a good partial response 18 months after initiating erlotinib.

Erlotinib is an epidermal growth factor receptor–tyrosine kinase (EGFR-TK) antagonist currently used in the treatment of lung cancer. This agent is associated with several dermatological side effects: acneiform rash involving the face, neck, chest, and/or back; dermatologic toxicities including xerosis (abnormal dryness of the skin); paronychia (inflammation of the tissues adjacent to the nail of a finger or toe); fingertip fissures; and some reports of trichomegaly (increase in length, curling, pigmentation, or thickness of eyelashes). These side effects are thought to be due to its complex effects on keratinocyte growth and differentiation, but the exact mechanism is unknown.

The authors¹ believe that erlotinib is the agent responsible for the nail lesions because the patient also experienced other adverse effects related to the drug, acneiform rash, xerosis, and nail thinning, earlier in therapy. Zoledronate, the other agent the patient was receiving, is not associated

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with nail lesions. A relationship between erlotinib and the patient's nail fissures is at least probable because of a score of 5 on the Naranjo Adverse Drug Reaction Probability Scale (a scale created to assess the casualty for adverse drug reactions). More studies are needed to uncover the relationship between nail changes due to EGFR-TK inhibitors and clinical outcomes.

Priapism Associated With the Use of ExtenZe

A 40-year-old African American male presents to the emergency department with the chief complaint of a continuous erection for the past 3 days. His medical history includes diabetes mellitus, schizoaffective disorder, and a seizure disorder. His medications include aripiprazole 20 mg daily, olanzapine 20 mg daily, valproate acid 500 mg twice daily, and topiramate 100 mg twice daily. He stated he had recently ingested a dosage of ExtenZe greater than the recommended dose of one tablet daily to relieve his sexual dysfunction. ExtenZe is an over-the-counter (OTC) herbal supplement marketed as a sexual enhancer. ExtenZe contains yohimbe, which is an α 2-adrenergic agonist with pro-erectile potential.

The patient's vital signs were within normal limits with the only significant finding on physical examination was a nontender, fully erect penis. His liver function tests, basic metabolic profile, kidney function tests, and thyroid function tests were within normal limits. White blood cell count elevation of 23.3×10^9 cells/L (normal range, 4.5 – 11×10^9 /L) with elevated mature neutrophils of 70.1% (normal range, 40%–60%) of unclear etiology was noted. His sickle cell test was negative. A chest radiograph was found to be unremarkable and urine toxicology screen was negative for illicit drugs.

Treatment was initiated, and the patient received intracavernosal phenylephrine, which was unsuccessful. A Winter's shunt procedure was successfully performed and completely resolved the priapism. A Winter's shunt is the insertion of a large biopsy needle through the glans penis lateral to the meatus into the underlying distal end of one or both of the rigid corpora cavernosa. The patient was discharged 3 days later on ciprofloxacin 500 mg twice a day for 7 days and oxycodone 5 mg/acetaminophen 325 mg for pain. He was instructed to continue his home medications.

The authors² point out that the patient's medication history included aripiprazole, olanzapine, valproate acid, and topiramate and it should be noted that psychotropic medications may cause sexual side effects that impact penile erection, libido, lubrication, retrograde ejaculation, sexual arousal, and overall sexual satisfaction. Some strategies for managing psychotropic-related sexual dysfunction include decreasing the dosage, switching antipsychotics, or adding a phosphodiesterase-5 inhibitor. Sexual dysfunction may be uncomfortable for patients to discuss with their physician. The ease of being able to pick up an OTC product, such as ExtenZe, without a prescription makes it

an attractive alternative to patients. However, these medications are dangerous because they lack FDA regulation and studies demonstrating pharmacological interactions with other medications. In addition, in November 2013 the FDA issued an alert that counterfeit ExtenZe also contains sildenafil. The combination of excessive use of yohimbine with or without sildenafil may exaggerate its vasodilatory effects and cause priapism.

The authors argue that mental health practitioners should do more to educate patients on psychotropic-associated sexual dysfunction and the potential dangers of OTC sexual enhancement supplements. The patient in this case had psychotropic medications and diabetes mellitus as risk factors for sexual dysfunction, but the authors seem to believe that his psychotropic medications were most likely the culprit. More studies are necessary to address sexual dysfunction associated with antipsychotics such as dose reduction, drug holidays, and switching to other agents.

Blindness From a Nevirapine-Based HAART Regimen

A 3 year 5 month old child presented to a health care facility with a 5 week history of low-grade fever, dry cough, watery rhinorrhea, and progressive anorexia. Despite multiple treatments with acetaminophen, quinine, cotrimoxazole, and antiparasitics, the symptoms persisted. The patient's physical examination showed nontender submandibular lymph nodes and splenomegaly which led to the diagnosis of HIV infection (WHO stage III) with a CD4+ cell count of 311 c/ μ L (normal range, 500–1500 c/ μ L). According to the Cameroon National AIDS Control Committee (NACC) guidelines (first line at the time; March 2013), the patient was initiated on a highly active antiretroviral therapy (HAART) regimen consisting of zidovudine 60 mg, lamivudine 30 mg, and nevirapine 100 mg once daily. Nevirapine was started at a dose of 100 mg once daily with planned titration to twice daily over the following 2 weeks. The patient was also initiated on cotrimoxazole 480 mg daily for prophylaxis against opportunistic infections. Eight days after initiating HAART, the patient presented with systemic symptoms including a 3-day history of fever, restlessness, oral ulceration, sticky eyes, and widespread painful pruritic skin eruptions.

Patient's heart rate was 111 beats/min (normal range, 80–100 beats/min), axillary temperature was 98.9°F (normal range, 96.6°F–98°F), and respiratory rate was 37 breaths/min (normal range, 20–30 breaths/min). Physical examination revealed massive facial and truncal epidermal loss with raw oozing dermis, hemorrhagic crusting of the lips, and involvement of the skin in the genital area. Epidermis featured irregular erythematous maculopapular zones, widespread confluent bullae and targetoid lesions over the limbs. Patient had a positive Asboe-Hansen sign (extension of blister when pressure is put on top of bulla to adjacent nonblistered skin) and Nikolsky sign (entire skin covering stripped

and peeled off with minor manipulation). The patient presented with bilateral blindness. Ophthalmic examination revealed extensive bullae in left eye, sloughing of the skin, erythematous macules, and patches on the right eye. On anterior segment examination, there was conjunctival hyperemia, palpebral synechiae, and symblepharon formation (adhesion of the eyelids). Patient's lesion had extended to involve about 90% of total body surface area (TBSA). Other lab results were white blood cell 8.5×10^9 cells/L (normal range, $4.5\text{--}11 \times 10^9$ /L), hemoglobin 11.8 g/dL (13.5–17.5 g/dL), and glucose 104 g/dL (70–100 g/dL). Diagnosis of toxic epidermal necrolysis (TEN) was made based on TBSA >30%, temporal relationship, positive drug history, and a positive Nikolsky sign.

Patient's HAART regimen and clotrimazole was discontinued and was provided immediate care. Patient was started on intravenous (IV) lactate ringer's and normal saline for rehydration. IV acetaminophen 500 mg every 8 hours with meticulous wound care with petroleum stained dressing for pain relief. Combination eye drops of tobramycin 0.3%/dexamethasone 0.1% were given for ophthalmic therapy. Patient's condition improved over the next 5 days with resolution of skin lesions and reepithelialization 9 days after hospitalization. Supportive therapies were continued until day 24 of hospitalization. Patient was initiated on HAART regimen but instead of nevirapine, efavirenz was started on day 17. Cotrimoxazole was rechallenged on day 21. There was no development of any skin lesions. Ophthalmoscopy was done prior to discharge and during first follow-up visit 1 month later. There was no ocular complaint or reoccurrence of rash during the follow-up visits over the next 5 months. Patient was lost to follow-up and returned 3 years later with total loss of vision.

The authors³ point out that sulfonamide antibiotics and nevirapine are reported to be the most common drugs causing TEN. This patient had previously taken cotrimoxazole prior to initiation of HAART and was rechallenged later without any developments of any lesions which made nevirapine the most likely culprit. The authors also point out that blinding ocular sequelae are the most devastating long-term consequences for survivors of an acute TEN; however, this is not common. This patient had no eye complaints during the initial follow-up visits but presented with complete blindness 3 years later. The authors conclude that there may be a link between HIV infection and nevirapine-induced TEN and emphasizes the need for strict monitoring for patients on HAART especially during the early days of therapy. Furthermore, ocular complications following TEN can occur months to years after initial presentation so regular ophthalmologic checkups and long-term lubricants are warranted.

Hyperprolactinemia and Galactorrhea Due to Aripiprazole

A 16-year-old adolescent girl was diagnosed with disruptive mood dysregulation disorder and was prescribed aripiprazole 5 mg/day at night. One month later, the patient seemed to be

improving in her disruptive mood disorder symptoms but developed breast tenderness and milky discharge from her nipples. The patient's serum prolactin level was 42 ng/mL (normal range, 4–20 ng/mL). Other metabolic parameters, blood tests, and a brain magnetic resonance imaging were unremarkable. The increased serum prolactin level and galactorrhea was thought to be caused by aripiprazole and the medication was discontinued. Two weeks after stopping aripiprazole, the patient's galactorrhea symptoms had resolved, and her prolactin level was 8.25 ng/mL. Upon follow-up 1 month later, the patient's disruptive mood dysregulation symptoms returned, and the patient was restarted on aripiprazole. Within 3 weeks, the patient's galactorrhea symptoms recurred and her prolactin level was again elevated at 38.7 ng/mL. Aripiprazole was changed to quetiapine 100 mg/day and resulted in eventual resolution of symptoms of galactorrhea and a normal prolactin level of 7.9 ng/mL.

The author⁴ point out that there have been case reports of aripiprazole-associated prolactinemia and galactorrhea in patients all over the age of 18. In those case reports, the patients were on aripiprazole 15 mg/day. This patient is the first reported case of aripiprazole-related hyperprolactinemic galactorrhea in an adolescent girl as well as with a low dose of only 5 mg/day. Aripiprazole is a dopamine partial agonist working at D2 receptors. It is possible that in presence of dopamine, aripiprazole may function as an antagonist elevating prolactin levels. There is a linear relationship between aripiprazole dose and D2 receptor occupancy. With higher doses, aripiprazole may act as a full antagonist making a patient more likely to experience hyperprolactinemia. This patient had hyperprolactinemia at a lower dose which makes this case stand out. The author concludes that this side effect of aripiprazole should be kept in mind especially in children and adolescents even at a lower dose.

Trypophobia Associated With Gabapentin

A 67-year-old woman with situational anxiety and depression presented with chronic burning and itching paresthesias in a cape like distribution over her arms and shoulders. The patient was prescribed gabapentin 1800 mg/d to treat her paresthesia. Her other medical history included type II diabetes mellitus, hypertension, hyperlipidemia, and cataracts with no record of psychiatric symptoms before the onset of the paresthesia. Her other medications included aspirin, glimepiride, lisinopril, metformin, simvastatin, and alprazolam. When she started taking the gabapentin, she noticed an onset of trypophobia.

Trypophobia is an aversion to the sight of irregular patterns or clusters of small holes, or bumps. It is not officially recognized as a mental disorder but may fall under the broad category of specific phobia if fear is involved and the fear is excessive and distressing. The patient's trypophobia presented as a fear more than repulsion. Things she found

frightening included light emitting diode arrays in traffic lights (to the point where she was unable to drive), certain stimuli on the television (images of insect eyes), shower heads, pictures of lotus flowers, and holes in pitted olives. When she presented to the clinic, she refused to participate in tryphophobic stimuli to quantify her stress because it was too upsetting for her. The patient was started on duloxetine 20 mg per day to help with the paresthesia and reduce her dependence on gabapentin. On days when she was able to avoid gabapentin, she noticed her tryphobia was significantly reduced. Duloxetine did not completely remove her paresthesia, so she began taking the gabapentin again only to see her tryphobia return. Her duloxetine was then titrated up to a dose of 40 mg 3 times a day. She no longer needed the gabapentin and the tryphobia was no longer present. Six months later, she had to stop taking the duloxetine due to insurance coverage problems and restarted the gabapentin which caused her tryphobia to return. After discussing with the insurance company, they settled on covering a reduced dose of duloxetine, 30 mg twice daily, with supplemental gabapentin, 300 mg once daily. At this reduced dose of gabapentin, the tryphobia was very minimal and did not interfere with her quality of life.

The author⁵ notes that in the medical literature, tryphobia is relatively new topic of discussion with only 7 articles published. There is a symptom scale used to quantify the severity of the disease, but in the patient's case it upset her too much to be administered. The author of this article reports that this is the first case of any specific phobia that is reversibly associated with a medication. The gabapentin was a highly probable cause of the tryphobia via the Naranjo Adverse Drug Reaction Probability Scale score of 8. The mechanism of this adverse drug reaction is unclear, but it is theorized that because gabapentin targets the $\alpha 2\delta$ subunit of voltage sensitive calcium channels, it reduces calcium flux through the channel and impairs the calcium-dependent release of monoamine neurotransmitters which are involved in arousal states. More research needs to be done on potential correlations between individual calcium channel complements and specific phobias to understand this unusual phenomenon.

Coadministered Linezolid and Methadone Cause Serotonin Syndrome

A 39-year-old man with a medical history of drug addiction and HIV presented to the emergency department with a fever of 39.5°C (normal level, 36.2°C-37.1°C), pain in the abdomen, dorsal and lumbar-sacral spine, and lower limbs for the past 2 months. He also reported fatigue, hypotension, and oliguria during the last 24 hours. His current medications included methadone 40 mg daily, lamivudine 300 mg daily, tenofovir 245 mg daily, and darunavir 800 mg/ritonavir 100 mg daily.

On admission he appeared dehydrated with a high fever, blood pressure of 90/50 mm Hg, heart rate 125 beats/min (normal range, 60-100 beats/min), respiratory rate of 35 breaths/min (normal range, 12-20 breaths/min), and multiple erythematous and tender swelling of the right elbow and arm, left side of the chest wall, and abdomen. The patient was oriented and responsive. His laboratory findings included hematocrit 37.6% (normal range for males, 45%-52%), white blood cell count $15.15 \times 10^9/L$ (normal range, $4.5-11.0 \times 10^9/L$), platelet count $95 \times 10^9/L$ (normal range, $150-450 \times 10^9/L$), C-reactive protein 340 mg/L (normal range, < 3 mg/L), and creatinine 1.2 mg/dL (normal range for males, 0.6-1.2 mg/dL). His computed tomography (CT) revealed multiple cavitated nodular infiltrates in both pulmonary fields, multiple muscle abscesses in the abdomen, and pyomyositis (pus-filled abscesses) of the left psoas muscle. He tested negative for endocarditis. He was treated with normal saline for rehydration and empiric antibiotics including ceftriaxone 2 g IV daily and amoxicillin/potassium clavulanate 1000 mg/200 mg IV every 8 hours. On the fifth day, his blood and pus cultures were confirmed positive for methicillin-resistant *Staphylococcus aureus*. Therefore, his current therapy was stopped, and he was switched to linezolid 600 mg IV twice daily plus clindamycin 600 mg IV 4 times daily. Three days after this change, the patient was febrile, sweating, increasingly confused, disoriented, agitated, had fluctuating pulse and blood pressure, was unable to carry on a conversation, and was scored a 10 out of 15 on the Glasgow Coma scale (range 3-15, 15 being the most severe). There was a suspicion of serotonin syndrome and his linezolid was suspended causing progressive improvement of his condition in the following 48 hours.

Serotonin syndrome is a life-threatening adverse drug reaction caused by excessive serotonergic agonism in the central and peripheral nervous system serotonergic receptors. Serotonin syndrome can be caused by a single agent or combinations of agents, most commonly selective serotonin reuptake inhibitors (SSRIs) and monoamine oxidase inhibitors (MAOIs). The effects of serotonin syndrome can range from mild to life threatening and include a variety of mental, autonomic, and neuromuscular changes. The authors⁶ state that the mechanism for this patient's serotonin syndrome is thought to be due to the interaction between linezolid and methadone which blocked serotonin reuptake and the serotonin presynaptic release which caused increased levels of serotonin in his central nervous system. The authors also state that this is the first report of linezolid and methadone causing serotonin syndrome without any other serotonergic agents being involved. It is important for health care workers to be vigilant of this drug interaction and be more cautious when prescribing antibiotic therapy to methadone maintained patients.

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