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TRIBUNE WATCHDOG DANGEROUS DOSES

# Prescription for harm

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BY KARISA KING AND SAM ROE | Chicago Tribune

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But the next signs were more puzzling. A sharp pain radiated through her chest. Her eyes turned red and itchy. It seemed like she

was fighting off some strange bug, or maybe it was just the normal exhaustion of keeping up with twin toddlers.

Then the scalding rash began.

Red spots popped up on Conway's face and neck. The next day, painful sores appeared in her mouth and then her throat.

Within hours Conway was in a hospital bed, watching with alarm as the rash spread across her torso, arms and face. The red dots turned into blisters that welted so quickly it looked like her skin was burning from the inside out.

No treatment could stop it. Within a day or two she wasn't recognizable. Eventually, the rash covered her eyelids with blisters and attacked the lining of her lungs. Her skin peeled off in sheets.

Only after it was too late to stop the rash did anyone figure out that Conway had taken a potentially dangerous mix of medications that can trigger the immune system to attack the body's own cells.

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Risks rising for drug interactions

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### Chicago Tribune

Sunday, February 14, 2016



PHOTO COURTESY OF BECKI CONWAY

What started as flu-like symptoms quickly escalated into a blistering rash so wildly out of control that it landed Becki Conway in an intensive care unit for burn victims. Only after it was too late to stop the rash did a health care worker realize that Conway had taken a potentially dangerous mix of medications that can trigger a deadly immune response.

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Drug interactions in which one drug alters the effect of another are a hidden epidemic in America, a decadeslong threat to public health that has been barely acknowledged, let alone addressed.

Many interactions involve relatively safe drugs that become dangerous only when taken at the same time. Hundreds of risky combinations involve common antibiotics, blood thinners, antidepressants, cholesterol drugs and medicine to treat migraines, heart problems and high blood pressure.

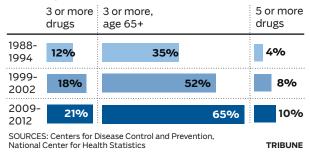
The tragedy is that much of the harm is preventable. The particular drug interaction that hospitalized Conway was identified years ago. But experts estimate that thousands of patients still become sick every year from drug interactions because of errors and neglect by front-line providers of medical care.

The result in such cases: Victims and their families are left with few answers, and the underlying safety failures go uncorrected.

The doctor who prescribed Conway's medications did not heed a black box warning about a fatal rash that could result from the drug pairing, according to medical and legal records and interviews. The pharmacy that dispensed the medicine did not call her attention to the danger. And as her symptoms rapidly worsened, a string of doctors and nurses missed the connection to the drug combination.

#### Risks rising for drug interactions

The percentage of U.S. residents who report taking multiple prescription drugs in the past 30 days has been increasing.



Most patients rely on their doctors to protect them, but studies show that prescribers often are unaware of harmful drug combinations or trust that pharmacists have more expertise. Pharmacists, in turn, tend to respect the discretion of doctors.

For pharmacists, warning patients about the risky mixing of drugs is one of the major responsibilities of the profession, according to the National Association of Boards of Pharmacy. Yet when injured patients sue, pharmacies often take the legal position that they have no duty to do so.

Pharmacies and hospitals use computer programs to screen for unsafe drug pairs. But those systems trigger so many alerts about potential drug interactions — including many that pose little risk to patients — that doctors and pharmacists frequently ignore them. Research has found that some pharmacists are more likely to approve dangerous mixes of prescriptions while working busy shifts.

When drug interactions hurt patients, the Food and Drug Administration along with most state medical and pharmacy boards do not require doctors and pharmacists to report cases. Pharmacists and doctors rarely face sanctions unless patients take the initiative to complain, according to the national pharmacy group.

"When you look at it from every conceivable aspect, the system is badly broken," said Philip Hansten, a professor of pharmacy at the University of Washington who has studied drug interactions for nearly 50 years. "It's really disheartening to see people are still dying from interactions we've known about for decades."

Dozens of legal complaints reviewed by the Tribune described how patients be-



E. JASON WAMBSGANS/CHICAGO TRIBUNE

Becki Conway, shown at a Florida eye clinic in 2014, is legally blind because of the trauma she suffered from Stevens-Johnson syndrome.

came sick or died from a toxic mix of drugs that was mishandled in nearly every health care setting, from family practice offices and corner pharmacies to specialty clinics, hospitals, emergency rooms and nursing homes.

One physician prescribed the cholesterol drug simvastatin to a patient in north suburban Niles who was already taking ketoconazole and cyclosporine because of a kidney transplant years earlier. The potentially lethal mix led to a toxic buildup of the heart medication and left the man too sick to walk and requiring hospital care, according to a lawsuit that was later settled.

In North Carolina, the state pharmacy board found that a CVS pharmacist had ignored computer safety warnings about combining allopurinol for gout and the kidney transplant drug azathioprine. The 49-year-old woman who took the medications together for weeks grew increasingly ill as her bone marrow failed to produce enough blood cells, leaving her hospitalized, according to pharmacy board and medical records.

The interactions don't always set off a toxic reaction. In many cases, one drug makes the other drug ineffective, leaving patients vulnerable to the effects of HIV, cancer and other serious ailments.

When Becki Conway sought help, trusted health care providers failed her at nearly every turn, leaving her in a fight for her life.

#### A case of anxiety

At 37, Conway was a high-energy mother of five children ranging in age from 2-year-old twin boys to a 17-year-old son.

The summer of 2009 was one of the most hectic periods in her life. She and her husband were working full time, installing a new roof on their two-story brick home in central Michigan and preparing to open a pizzeria in a month. Their twins were not yet potty-trained.

Making matters worse, Conway was battling an ex-boyfriend in a child custody dispute and had been feeling extremely anxious. She found herself lashing out at her husband and shouting at the kids.

Conway worked at Sparrow Urgent Care in the town of Mason, registering pa-

tients as they arrived at the clinic. She decided to seek help from a doctor she was friendly with, Thomas Bellinger. The two met for 15 minutes in a break room where employees often chatted, drank coffee and ate lunch, according to interviews and documents in a later court case.

Conway mostly talked about her family history, childhood abuse and previous medications. She told Bellinger she had taken medicine for depression years earlier but hadn't taken anything since. He told her he empathized with her and promised to bring her a book on bipolar disorder.

Bellinger had practiced family and emergency medicine since receiving his medical degree in 1985 from Michigan State University. He worked at several hospitals and urgent care clinics in Michigan before taking a job at the Sparrow clinic.

Minutes after their consultation, Bellinger approached Conway at her desk and handed her two prescriptions: one for Lamictal, the other for Depakote, according to medical records and her legal deposition. Both drugs are used to treat epilepsy and bipolar disorder. Lamictal carries the FDA's strongest label, a "black box" warning, which highlights the potential danger of combining Lamictal and Depakote.

Research on the ability of doctors to identify harmful drug pairs shows that although many physicians consider the issue when they write prescriptions, their specific knowledge about drug interactions is generally poor.

In one 2008 study, researchers asked 950 prescribers to classify various drug combinations by severity of risk. More than a third of the prescribers answered "not sure" for half of those pairs. For three of the four highest-risk combinations, less than 25 percent of the prescribers correctly recognized that the drugs should not be taken together.

Training on specific drug interactions in medical schools is lacking because of time constraints and the vast number of hazardous combinations, said Dr. Alfred George, chair of the pharmacology department at Northwestern University's Feinberg School of Medicine. Doctors also are not required to demonstrate knowledge of drug interactions to state licensing boards or when seeking hospital credentials, he said.

"New drugs are hitting the market every day, and clinicians rarely have time to read all the literature on the drugs they prescribe," George said.

Adding to the problem, no list of medications automatically follows patients from one medical provider to another. One physician may not know what another doctor has prescribed.

The label for Lamictal warns that the drug's concentration level in the body more than doubles when taken with Depakote. To lower the risk of a deadly reaction, the label advises doctors to decrease the normal starting dose of Lamictal by half when it is combined with Depakote.

Physicians may read such warnings but make prescribing decisions at their own discretion. Bellinger gave Conway a prescription for the full initial dose of Lamictal.

In depositions, Bellinger said his diagnosis of bipolar disorder was based on multiple conversations with Conway over a period of months and that his prescriptions were in line with successful treatment plans for other patients. He said he was familiar with the black box warning but assessing the combined risk of the two drugs was difficult because Lamictal also can cause a dangerous skin rash when taken alone.

Citing language on the drug label, Bellinger said the extent to which Depakote potentially increases the risk is unclear. He believed the possible risk posed by giving Conway the full dose of Lamictal was outweighed by the danger of giving her a dose that was too low to relieve her symptoms.

In her deposition, Conway said Bellinger made a prediction as he handed over the prescriptions: She would feel better by the next day.



E. JASON WAMBSGANS/CHICAGO TRIBUNE

Conway and her family now live in Florida, where the humid climate provides some relief for her eyes. Her bout with Stevens-Johnson syndrome destroyed her tear ducts.

#### No warnings

Conway faxed the prescriptions to her usual pharmacy at Sparrow Hospital in nearby Lansing, part of the same health system as the urgent care clinic. Her husband, Tim Conway, worked there transporting patients and picked up her prescriptions the next day.

No one at the pharmacy called his attention to the potentially lethal drug pair, he said in an interview. No one mentioned that the dose of Lamictal exceeded the guidelines for taking it with Depakote. And no one talked to him about a rash.

"There were no special warnings — nothing," he said.

Pharmacists serve as the last line of defense against bad drug combinations. Those who see a potentially unsafe pairing can ask questions of the patient, consult with the physician and ultimately withhold the medications.

"If a patient has a significant drug interaction that the pharmacist should've been aware of and didn't catch, then their license could be affected," said Carmen Catizone, executive director of the pharmacy group.

Yet pharmacists who are busy, distracted or inundated with alerts may fail to intercept potential drug interactions.

Sophisticated software systems automatically screen prescriptions for risky drug combinations and alert pharmacists about the danger. But more than a decade of research shows those systems fail to fully protect patients.

The safety checks produce a flood of alerts about a range of potential dangers, including drug interactions that cause only minor side effects. Pharmacists must contend with so many alerts that they can become desensitized to even the most serious warnings and dismiss them. One study found that pharmacists overrode more than 90 percent of alerts, including warnings about some risky drug interactions.

Heavy workloads for pharmacists also pose a threat. A 2007 study by University of Arizona researchers found that the risk of dispensing two drugs that could interact rose about 3 percent for each additional prescription filled by a pharmacist in an average hour.

The pharmacist who filled Conway's prescriptions, Ryan Hamelin, later testified

in a deposition that he handled as many as 80 orders on a busy shift. He signed off on her medications at 6:51 a.m., nine minutes before his overnight shift ended.

When a technician entered the two prescriptions into a pharmacy computer, a red screen appeared with a warning that required a pharmacist's review, Hamelin said. The alert noted a potential overlap between the medications, which are both used to treat the same illnesses, but it did not call attention to the drug interaction, he said.

Hamelin, who had received his doctor of pharmacy degree a year earlier, said he had seen such drugs paired together previously. He also said he was aware of the drug interaction and the black box warning on Lamictal.

But it seemed to him that the doctor had used some discretion when writing the prescriptions, as Bellinger had prescribed initial doses that increased over time. Hamelin trusted the prescriber's judgment, he said.

Hamelin said he did not see a need to warn Conway personally about the drug pair. Package inserts that advise patients about drug risks typically satisfy a pharmacist's obligation to warn about such dangers, he said.

Hamelin approved the scripts and left work.

#### 'This is not right'

That day, Conway began taking the two drugs. She felt better almost immediately.

But two weeks later, she felt a tickle in her throat and pain inside her ears. She had a cough and bloodshot eyes. Then she woke up with her eyes matted shut with thick gunk. Conway went to work early to get medication for what she assumed was pinkeye.

At the urgent care clinic, Conway told the medical staff about taking Lamictal and Depakote, according to her deposition. She described her symptoms, including chest pains she suffered for a day or so before the episodes stopped.

No one realized that the seemingly unconnected symptoms foretold an agonizing condition called Stevens-Johnson syndrome in which the immune system attacks the patient's skin and mucous membranes.

The cells in the lining of Conway's eyes, mouth and lungs were self-destructing. It was as if some switch in her body had been flipped and nothing could shut it off.

Exactly how the disease develops is not fully understood, but it is most often triggered by medications. Numerous drugs including Lamictal have been linked to the condition when taken on their own. There is no cure; the best treatment is to stop taking the drugs that caused it.

Had Conway's condition been diagnosed, she would ideally have been sent to a hospital burn unit, which is best suited to treat the massive loss of skin as the disease progresses, said Jean McCawley, director of the Stevens Johnson Syndrome Foundation, a patient advocacy group.

Instead, Conway's chest pains became the main concern. A doctor at the clinic ordered X-rays and an electrocardiogram to test for possible heart problems. Both showed normal results. To be cautious, Conway was sent by ambulance to nearby Sparrow Hospital for more comprehensive heart tests, medical records show.

Conway told the hospital intake nurse that she was taking Lamictal and Depakote. Because Conway's eyes were too inflamed for her to see, the nurse pulled the pill bottles from Conway's purse and noted the medications in a hospital record.

The second round of heart tests showed no abnormalities, and Conway was released from the hospital with a suspected strained chest muscle, records show. Her husband came to the emergency room to take her home.

After receiving her discharge papers, Conway went to a bathroom to change out

of her hospital gown. She glanced at herself in the mirror before getting dressed. On her way out, she caught another glimpse and stopped to stare. Bright red spots had popped up on her face and neck. It looked like someone had thrown red pepper on her.

Conway flagged down a nurse and pointed to her face. "This is not right," Conway said, according to her deposition.

"Wow," the nurse said.

The nurse retrieved a doctor, who examined Conway. But no one connected the outbreak to the two new medications she had reported to nurses and doctors twice that day.

The nurse gave Conway a shot of Benadryl and sent her home.

#### **Deadly diagnosis**

Spotting the signs of a dangerous mix of medications can be critical to saving a patient's life. But because the interactions often cause common symptoms, such as low blood pressure or confusion, health care providers can easily miss the clues.

"Drug interactions hurt and kill like nobody has any idea," said David Juurlink, head of clinical pharmacology and toxicology at Sunnybrook Health Sciences Centre in Toronto.

Juurlink has treated patients who arrived at the emergency room after taking an antibiotic with certain types of blood pressure medication, which can cause a deadly spike in the level of potassium in the blood. Such a death likely would be attributed to heart disease and old age instead of a drug interaction, he said.

After Conway got the Benadryl shot she went home and went to sleep. She woke up at 4 a.m. with painful blisters in her mouth. Her skin rash was turning into red welts. Conway drove herself to the clinic where she worked and was examined by Dr. Kellie Donahue.

The doctor asked Conway about her symptoms and any medication she had been taking. When Conway told her about the Lamictal and Depakote, Donahue stopped taking notes and looked up at her.

"I think you have Stevens-Johnson syn-

### Avoiding risky drug interactions

Experts say there are important steps patients can take to help protect themselves from a harmful mix of medications.

- With every new prescription, ask your doctor and pharmacist about what other medications you should avoid, including over-the-counter drugs, foods and dietary supplements.
- Carry a list of all current medications and bring it to any medical appointments. The list should include drugs taken only occasionally, overthe-counter medications, patches, tablets, inhalers, drops, liquids, ointments and injections, as well as herbal, vitamin and dietary supplements.
- Read the complete package insert for all medications you're taking.
- Use one pharmacy for all your prescriptions.
- Educate yourself about potential drug interactions for any medications you are taking.
- If a doctor provides you with a new drug sample, ask if it interacts with the medications you're currently taking. Routine computer safety checks may have been skipped.
- Take as few medications as possible.
- Do not take medications prescribed to someone else.
- Karisa King



CAROLYN VAN HOUTEN/FOR THE CHICAGO TRIBUNE
Nurse Kathy Sandoval cared for Conway at Sparrow Hospital in Lansing, Mich., and knew how lethal Stevens-Johnson
can be. Conway was transferred to a burn unit in Ann Arbor at Sandoval's insistence.

drome," she said, according to Conway's deposition.

Donahue, the first medical professional to notice the dangerous drug mix, explained to Conway that she was suffering from a serious skin rash caused by medications.

But even Donahue didn't realize how severe the rash would become.

After telling Conway to stop taking the drugs, which Conway had done when the chest pains began, Donahue gave her a steroid shot and sent her home.

Conway took a short nap and woke up with blisters spreading into her throat. She called Donahue, who instructed her to go to the hospital immediately.

Her first night in the hospital, Conway sat up in bed until dawn researching Stevens-Johnson syndrome on her laptop computer. She'd never heard of the disease. The more she learned, the more alarmed she became. She discovered that, in its most extreme form, many victims die. The biggest risks stem from infections.

In the next days, Conway's blisters spread and erupted. Swallowing food was too painful. She couldn't stop coughing and complained that she was struggling to breathe.

Her skin began to peel off in sheets, leaving angry patches of exposed flesh that turned black and bloody.

Worried about infection, her husband laid down a trail of towels so she didn't have to walk to the bathroom on the hospital floor. He spent the nights at her bedside in a chair. He didn't know what to tell the kids, especially the three youngest. He didn't want them to visit their mother — her wounds looked too gruesome. He did not disclose his biggest fear, that she might not come home.

Conway sporadically roused herself from a stupor of morphine, but mostly she was in too much pain to speak or open her eyes.

On Conway's 10th day at the hospital, nurse Kathy Sandoval was assigned to treat her. The nurse had treated one other Stevens-Johnson victim years earlier, but when she walked into the room, she had never seen anything that compared to how Conway looked that day, Sandoval recalled in an interview.

From head to toe, only patches of skin could be seen. "It was red, open, exposed,"

Sandoval said. "She wasn't gushing blood, but there was blood everywhere."

Sandoval was afraid to touch Conway.

"She looked like she'd been in a fire," Sandoval said.

She knew how lethal the condition could be and worried that the sloughing tissue in Conway's lungs and throat might block her airway. Sandoval hovered over Conway's bed watching for signs of distress.

That night, at Sandoval's insistence, Conway was transferred in unstable condition from Sparrow to an intensive care burn unit at the University of Michigan Medical Center, records show.

At that point, about 70 percent of Conway's skin had blistered or peeled off. She could barely communicate.

The next day, an ophthalmologist tried to examine the damage in her eyes, but Conway was in too much pain to cooperate. In the doctor's notes from that day, he wrote that Conway told him she didn't expect to survive.

#### Fighting to live

Medical records document the flurry of activity that surrounded Conway at the Ann Arbor hospital. Nurses checked her vital signs at regular intervals. Doctors inserted a feeding tube. The wound care was constant. Every hour, nurses pried open her eyelids to apply drops of medicine.

"They're just trying to keep the patient alive at that point," said McCawley of the Stevens-Johnson advocacy group. "Patients are usually monitored 24/7 with the most intensive care they can give them. ... The reaction has to run its course."

On Conway's third day at the hospital, her condition improved slightly. She was able to sit up on her own and was taken off contact isolation, which meant that staff no longer had to wear gowns and gloves to enter her room.

Over the next few days, the rash stopped spreading and parts of her skin began to grow back.

In an attempt to save her eyesight, doctors grafted amniotic membrane onto her eyes to help them heal. She continued to gain strength and looked better.

Medication was more effective in easing her extreme pain. The lesions on her face were clearing. Doctors removed her feeding tube and she was able to swallow soft food.

After nearly three weeks, Conway returned home with her eyes stitched shut so they could heal from surgery. Wounds were still red and visible on her face and neck. Her twins were too scared of her appearance to sit on her lap, so her husband turned off the lights in the living room and they sat with her on the couch.

She held their hands in the dark, tracing the outlines of their small fingers. Unable to see, she learned to distinguish the boys by the shape of their fingernails.

Conway spent the next two months unable to open her eyes and later received training on how to walk with the help of a long white cane. In the years since, she has slowly regained her strength, taking long walks and working on home repair projects with her husband.

But the trauma left Conway legally blind. In her left eye she can see only shadows and light. By holding a computer tablet close to her right eye and magnifying the text, she can read in limited amounts.

She can't drive a car or watch the kids at sports events or read a paperback book. She also suffers stabbing pains in her eyes from nerve damage, leaving her unable to get out of bed on her worst days. She must frequently apply medicated eyedrops because her tear ducts were destroyed. She fights a constant cough caused by her lung injuries. The family now lives in Florida where the high humidity provides some relief for her eyes.

Conway said her approach to taking medication has changed.

"The general public trusts that what their doctors give them is OK," she said. "They don't question it, but they should question it — every time."

In 2012, Conway filed a lawsuit against Bellinger and Sparrow Health System that was settled in 2014 under confidential terms. She and her husband talked about her ordeal in several interviews but declined to disclose the names of the defendants, whom the Tribune identified through court records.

Her attorney, Andrea Dalton, said she has handled more than a dozen lawsuits for other patients, many of them children, who suffered from Stevens-Johnson syndrome after taking the same drug combination as Conway. The cases fit a pattern of errors, Dalton said.

"It starts with a hospital or physician error, then there's a pharmacy error and diagnostic errors, and that becomes the perfect storm," she said. "At the end of this is someone who has to live with it for the rest of their life."

Citing a confidentiality agreement, Bellinger's attorney declined to comment on the case. An attorney for Sparrow Health System said Hamelin, the pharmacist, turned down requests for interviews. The health system released a brief statement saying: "Sparrow cannot discuss specifics of this case due to the nature of the settlement agreement. But the safety and security of patients is always our top priority."

Bellinger stopped prescribing the two drugs together after Conway became ill, he said in a deposition. It wasn't worth the risk, he decided.

The case did not appear to change anything for Hamelin, the pharmacist who handled the prescriptions. He testified he would not have a problem filling the same order again.