A 55-year-old woman was brought by police to our emergency department. Upon arrival she was in a state of agitation and confusion. She complained of physical abuse from her husband and that he had “superhuman speed” and was poisoning her. After examination, she was assessed as psychotic and was found to be experiencing severe paranoid delusions. At admission, the patient only knew her name and had impaired recent and remote memory. She was also found to be experiencing auditory and visual hallucinations and specific paranoid delusions regarding other family members.

Approximately 1 to 2 weeks before admission, her family noticed transient confusion and mild paranoia. Over the next several days, she became progressively more paranoid and confused. A few days before admission, the patient reported to the police that she was being physically abused and poisoned by her family members, which she later acknowledged was untrue.

Her relevant medical history includes stage IV endometrial cancer treated with maintenance therapy of an oral chemotherapy pill. She also experienced chronic, difficult-to-control pain from multiple places on the body. The pain was treated by a pain management team at an outside hospital. At admission, the patient was unable to recall what medication was being administered through her intrathecal pain pump. Other medical history included chronic obstructive pulmonary disease treated with an albuterol inhaler, and gastritis treated with Nexium (AstraZeneca, London, UK).

The patient’s psychiatric history included major depressive disorder treated with trazodone and anxiety treated with 0.5 mg of clonazepam twice a day. At admission it was presumed that she had no previous history of psychosis.

Laboratory investigations showed a negative blood alcohol level and a thyroid-stimulating hormone level within normal limits. A complete blood count and other routine chemistries were unremarkable. A urine drug screen was negative for all substances tested. A urinalysis showed blood and was positive for leukocyte esterase. Urine microscopy showed red blood cells and white blood cells, but no bacteria were present. The urine findings were determined to be due to the presence of a ureteral stent. A serum rapid plasma reagin was nonreactive. Hepatitis and human immuno deficiency virus studies were negative. A computed tomography scan of the head with and without contrast showed no abnormalities.

After admission to the inpatient psychiatric unit, she was started on 6 mg of Invega (Janssen, Titusville, NJ). On day 2, she was no longer
experiencing auditory or visual hallucinations. She continued to experience intermittent confusion, paranoia, and delusions, including accusing staff of poisoning her. Six days after admission, she received a 234-mg injection of Invega Sustenna (Janssen, Titusville, NJ). She continued to experience paranoid delusions and confusion, although they became less severe.

At this time, records were received from the pain management team at the outside hospital. The care team then discovered that the patient was receiving intrathecal ziconotide. The patient had been treated with ziconotide for approximately the past 7 months. In order to gain better control of her pain, the dose of ziconotide was increased 2 weeks before admission from 1.68 mcg/day to 2.53 mcg/day. The pain management team also reported a previous episode of hallucinations and confusion after a dose increase of her intrathecal ziconotide, both of which promptly resolved after lowering the dose.

Family members first noticed the transient confusion and mild paranoia a few days after the recent dose increase. Her psychiatric symptomatology progressively worsened until admission. The care team began coordinating with the outside hospital to reduce the concentration of ziconotide being administered. The care team consulted several departments at the home institution, but was unable to find anyone who could adjust an intrathecal pain pump. Throughout her 2-week admission, she continued to experience paranoia and waxing and waning confusion but was less agitated, and at times she recognized that her previous thinking was extreme.

**D I A G N O S I S**

**Ziconotide-Associated Psychosis**

**DISCUSSION**

We have written this case to describe the sequence of events as they unfolded for the psychiatric team. Given her age and cognitive deficits, the team initially presumed that there could be an organic cause of her symptomatology, although none were apparent. The diagnostic challenge was made substantially more difficult by a lack of integration and coordination of services.

Ziconotide is not a common option for the treatment of chronic pain. It is the first drug in a new class of analgesics that targets neuron-specific calcium channels. This prevents the conduction of pain signals in the spinal cord. Ziconotide is approved for use in patients with severe chronic pain that is refractory to other analgesic options.

Ziconotide has a package insert black box warning regarding severe psychiatric adverse events. The prescribing information from the drug manufacturer indicates that in clinical trials 33% of patients experienced confusion, 12% experienced hallucinations, 3% experienced paranoid reactions, and 1% experienced psychosis. The full black box warning is shown in Figure 1.

Although the warning regarding the relationship between ziconotide and psychiatric disturbances is present, psychiatric adverse effects are not well described in the literature. A PubMed search for “ziconotide and hallucinations” found five sources, which included two case series, two review articles, and one phase II trial. In each of these sources, the major psychiatric adverse effects were hallucinations and cognitive impairment. In the case series describing the use of ziconotide in complex regional pain syndrome, only one patient experienced psychotic delusions. A PubMed search using the terms “ziconotide and psychosis” found only one case report describing prolonged delirium with psychotic features in a patient who had no psychosis and that resolved after discontinuation of the intrathecal ziconotide. Another similar case report described a prolonged delir-

**WARNING:**

Severe psychiatric symptoms and neurological impairment may occur during treatment with PRIALT. Patients with a pre-existing history of psychosis should not be treated with PRIALT. All patients should be monitored frequently for evidence of cognitive impairment, hallucinations, or changes in mood or consciousness. PRIALT therapy can be interrupted or discontinued abruptly without evidence of withdrawal effects in the event of serious neurological or psychiatric signs or symptoms.

Figure 1. The package insert black box warning for ziconotide.
ium caused by ziconotide that was successfully treated with electroconvulsive therapy. PubMed searches for “ziconotide and paranoia” and “ziconotide and delusions” did not yield any results.

Our patient is different from the cases described in the literature because psychosis and paranoia were the predominant features in her presentation. Additionally, although cognitively impaired, our patient was not delirious, and, in particular, there was no autonomic instability. Our patient is also different because she was treated with an antipsychotic agent prior to and subsequent to the identification of the likely etiological agent.

The prescriber’s information from the manufacturer states that ziconotide is only indicated for patients with pain that is refractory to or who are intolerant of all other analgesic options, including intrathecal morphine. Additionally, the prescribing information from the manufacturer indicates that psychiatric adverse events should be managed by discontinuing ziconotide. Management of the psychiatric adverse events may also require treatment with psychotherapeutic agents and hospitalization. The manufacturer reports that the median time to reversal of cognitive adverse effects ranges from 3 to 15 days. They do not report a median time to reversal of psychiatric adverse effects. Other studies have found the time to reversal of psychiatric adverse effects to be highly variable, ranging from 48 hours to 9 days after dose reduction or temporary discontinuation.

These data are limited by our search strategies and by the study designs described as case reports or limited case series. Nevertheless, there would appear to be a clear association in these reports between the initiation of ziconotide and the onset of delirium and psychotic symptomatology and between the amelioration of these symptoms with discontinuation of ziconotide.

We do not know how often ziconotide is prescribed nor do we know the prevalence of psychiatric problems that arise related to its use. Together, these case reports suggest that ziconotide should be prescribed very cautiously, especially in individuals with psychiatric comorbidities. Moreover, when prescribed, pain specialists, psychiatrists, and oncologists should work closely together to monitor for and treat psychiatric symptoms should they arise. We need to collect more data on the psychiatric complications of ziconotide. In this case, as we have described, there was a lapse in the adequacy of monitoring for further psychiatric complications. Therefore, psychiatrists have an important role to play in the secondary prevention of psychiatric complications related to treatment with ziconotide.

REFERENCES