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Changes in mood, depression and suicidal ideation after commencing pregabalin for neuropathic pain

Background

Pregabalin is a treatment option for patients with persistent neuropathic pain. Its use has been associated with changes in mood and the development of depression and/or suicidal ideation.

Objective

Case presentations were reviewed of five patients reporting changes in mood, depression and suicidal ideation from the first 50 (approximately) patients commenced on pregabalin at the clinic.

Discussion

Although these patients had a history of depression, their mood had been stable before commencing pregabalin. Soon after commencement they reported changes in mood, and development of depression and/or suicidal ideation, which improved with dose reduction or cessation of pregabalin. Ultimately, all five patients ceased pregabalin treatment. Suicidal ideation is a recognised adverse effect of pregabalin. Patients should be warned of and monitored for deterioration in mood.

Keywords

chronic pain; drug therapy; adverse drug reaction; quality improvement

from the first 50 (approximately) patients commencing pregabalin at the Gold Coast Interdisciplinary Persistent Pain Centre (GCIPPC) after it was listed on the Pharmaceutical Benefits Scheme (PBS)³ on 1 March 2013 for the management of persistent neuropathic pain.

Patient 1

Patient 1 was a woman, 48 years of age, who had painful diabetic peripheral neuropathy and lower back pain. She first presented to a clinic in April 2013. She had a diagnosis of bipolar affective disorder and had regular follow-up with a private psychiatrist. She reported taking duloxetine 60 mg daily, quetiapine 200 mg nocte, diazepam 5 mg as required, nitrazepam 5–15 mg at night, atenolol 50 mg daily and corticosteroids (pulse courses as required). Her medication regimen had been stable for several months. At the initial multidisciplinary team assessment, the psychologist noted a relatively stable mental state. The patient was frustrated by her pain but had no suicidal ideas, marked features of depression or mania. She enjoyed time with friends and had goals in her life. She was commenced on an increasing regimen of pregabalin, initially at 25 mg at night. One week later she was reviewed by the psychologist. Some minor anxiety symptoms were noted. After this appointment she was taking pregabalin 75 mg nocte and then experienced 4 days of intense 'black thoughts', depression and suicidal ideation. She stopped her pregabalin and saw her psychiatrist, who increased her dose of quetiapine. When reviewed by the

The product information for pregabalin (Lyrica) states that 'patients treated with any AED [anti-epileptic drug] for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behaviour, and/or any unusual changes in mood or behaviour'.¹ It also states that when compared with placebo the increased incidence of suicidal behaviour or ideation for patients treated with anti-epileptic drugs was approximately one case per 530 patients.² Here we report five cases of suicidal thoughts or increased depression

team in early May she reported her mental state had stabilised and she had no further depression or suicidal ideation.

Patient 2

Patient 2 was a man aged 42 years who had been a patient at the Centre for 2 years. He had longstanding cervical spine pain and psychosocial stressors, including a lack of stable employment. He developed significant depressive symptoms that persisted for about 1 month. He was started on citalopram 20 mg once daily and his depression eventually resolved in late May 2013. In July 2013 he had a stable mental state and was controlling his pain with small doses of paracetamol with codeine and gabapentin 200 mg three times daily. His gabapentin was changed to pregabalin 25 mg nocte and when seen 1 week later by the team's psychiatrist, he reported a sudden onset of depressive symptoms, with no suicidal ideas, associated with commencing pregabalin. On follow-up 1 month later, he noted that there was no further deterioration in his mood and he slowly returned to a euthymic state over 1 week. Subsequently he ceased pregabalin.

Patient 3

Patient 3 was a woman of 53 years who had painful diabetic peripheral neuropathy and lower back pain. She first presented to a clinic in early June 2013. She had previously received pain relief from a L4 nerve root injection performed by a private practitioner. She had a dysthymic disorder of moderate severity and had been taking dothiepin 100 mg twice daily, clonazepam 1 mg twice daily and oxazepam 30 mg twice daily for several years. She had no suicidal ideas. After the initial assessment, she was started on pregabalin, 25 mg nocte, with a planned increase to 25 mg twice daily after 1 week. When she was reviewed by the team's pharmacist in late June she reported she had stopped the pregabalin because of deterioration in mood and emerging suicidal ideas. When seen in late July by the team's psychologist she reported a slow improvement in her mood over the preceding month and was starting to engage in more pleasurable activities.

Patient 4

Patient 4 was a man aged 54 years who had persistent lumbosacral pain following a motor vehicle accident in 2008. He had been treated at a chronic pain clinic in another city and had an L5/S1 lumbosacral fusion. He reported taking gabapentin 300 mg three times daily and oxycodone/naloxone 20/10 mg three times daily. He had been taking amitriptyline, 50–70 mg per day, but had ceased this because he had vivid dreams that disturbed his sleep. He was assessed at our clinic in early April 2013. He denied having poor mood but reported mild symptoms of anxiety, irritability and hypervigilance, which were suggestive of partially remitted post-traumatic stress disorder. He was started on pregabalin 75 mg twice daily, equivalent to his previous dose of gabapentin, and soon reported feeling depressed and apathetic. Over 3 months, he reported that pregabalin had been beneficial for his pain, but he still had ongoing depressive symptoms despite gradual dose reductions to 25 mg twice daily by early August 2013. He has since opted to return to gabapentin rather than continue the pregabalin.

Patient 5

Patient 5 was a man aged 42 years with a history of lower back pain radiating down his right leg since the age of 20, and subsequent neck pain and headaches. He lived in another health district and had consulted that district's community mental health team for the treatment of depression. He was taking mirtazapine 15 mg twice daily and amitriptyline 50 mg nocte. He reported using marijuana regularly and amphetamines on an infrequent basis. He lived in a rural setting and was socially isolated. When initially seen at our clinic in early May 2013, he reported moderate depressive symptoms but denied any suicidal ideation and had no evidence of clinical depression on mental state examination. He was started on pregabalin 25 mg daily and his mental state was stable on review in early June 2013 when his dose increased to 50 mg twice daily. His pregabalin dose increased again to 75 mg twice daily and on telephone review he

reported sudden symptoms of depression, panic attacks and suicidal ideas. There had been no change to his circumstances or new psychosocial stressors. There had been no engagement with mental health services in his area during this time. He reduced his pregabalin to 50 mg twice daily and the symptoms resolved over 1–2 days. Since then he has ceased pregabalin.

Discussion

Shortly after commencing low doses of pregabalin for neuropathic pain symptoms, all five patients reported a significant decrease in mood and three reported suicidal ideation, which were previously absent. All five patients responded positively to stopping the medication. Two patients initially continued to take the medication at a reduced dose and with close monitoring but ultimately decided to cease taking it. Two patients had previously taken gabapentin, a medication similar to pregabalin in mode of action and physicochemical structure, without any ill effects; one of these patients recommenced gabapentin.

All patients had a long history of mental health issues, including moderate/severe depression, and were taking a number of medications. This is not unusual in a persistent-pain patient population. However, they were carefully assessed for depression on presentation and their mood had been stable prior to commencement of pregabalin. Similarly, use of all other psychoactive medication was stable at the point of initiation of pregabalin. The previous stability of depressive symptoms, the symptoms worsening with dose increases and improving with discontinuation or dose reduction, and a similar pattern in all five cases suggests that commencement of pregabalin caused the increase in depression and the suicidal ideation.

Associations between antiepileptic medications, including gabapentin and pregabalin, and varying levels of mood disturbance ranging from euphoria to suicidality have been reported. Anticonvulsant medications have been linked with suicidality and sudden unexplained deaths with anti-epileptics (SUDEP).⁴ Zaccara et al⁵ undertook

an analysis of central nervous system adverse effects with a range of anti-epileptic drugs and conducted a meta-analysis of placebo-controlled studies. Several of the studies reviewed indicated that depression and other psychological disturbances may be related to therapy with these drugs. Depression may be associated with symptoms of fatigue, commonly noted with anti-epileptic drugs, and may be caused by interference with serotonin function, although they noted that for pregabalin fatigue was not dose-related.⁵

Fuzier⁶ conducted a review of the French Pharmacovigilance Database in 2013 and confirmed a high rate of neuropsychiatric adverse effects (somnolence, confusion and dizziness) reported for both gabapentin (29.1%) and pregabalin (35.2%) but did not specifically mention reports of suicidal ideation. Pregabalin has been associated with depressed mood⁷ and suicidal ideation by other authors.^{8,9} The Therapeutic Goods Administration Database of Adverse Event Notifications (01/01/1971–19/09/2013) contains reports of depression (27), suicidal ideation (47), suicidal behaviour (4), attempted suicide (1) and completed suicide (2) associated with pregabalin but there are no similar reports associated with gabapentin.²

To complicate the issue, pregabalin has been associated with improvements in depression by management of pain^{10,11} and even the development of euphoria,^{12,13} particularly in high doses, and it has been assessed in the treatment of depression¹⁴ as an adjunct to antidepressant therapy.

GCI PPC has extensive experience with gabapentin in the management of neuropathic pain, which did not reveal a similar pattern of symptoms related to depression or suicidal ideation. This is in contrast to the cases described above where patients on even low doses of pregabalin have reported reduced mood or suicidal ideation. In our patients, the onset of depression symptoms occurred early in treatment, before analgesic effects might be expected to occur.

Our Persistent Pain Centre is a tertiary referral service and does not encounter patients with acute presentations of neuropathic pain. However, we believe the population studied would not be significantly different from

patients experiencing persistent pain with neuropathic symptoms in a primary care setting.

How best to titrate the dose of pregabalin to minimise side effects is unknown.¹⁵ Most adverse effects occur early in treatment and are often dose-related;¹⁶ an increasing daily dose is associated with increasing rates of discontinuation because of adverse drug effects.³ Studies suggest that discontinuation rates are lower when a flexible dosing regimen is used.^{15,17–20} The practice of this Centre is to start patients on pregabalin doses as low as 25 mg at night and then titrate these doses up as the patient becomes tolerant to side effects, particularly sedation.

Prescribers should monitor patients for depression following the initiation of pregabalin, and after any dose increases, particularly if the patient has a history of depression. Onset of analgesia is usually slow with this group of medications and slow dose titration might help patients develop tolerance to side effects. Patients commencing pregabalin should be made aware of potential adverse effects of mood disturbance and depression and advised to seek medical advice if they notice deterioration in mood.

Key points

- Depressed mood and suicidal ideation occurred in 5 of approximately 50 initial patients commencing pregabalin for the treatment of chronic neuropathic pain.
- Patients commencing pregabalin should be warned of and monitored for deterioration in mood.
- There is a risk that medication side effects are incorrectly attributed to an existing mood disorder or chronic pain and treated inappropriately.

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Competing interests: Tony Hall received payment from Mundipharma for talk on opioids in persistent pain. Michelle King has shares in the Commonwealth Serum Laboratories. Pfizer Australia paid for registration, flights and accommodation for Tony Hall, Bradley Ng and Heide Feberwee for attendance at conferences. Heide Feberwee attended GP practices with representatives from Pfizer Australia and received honoraria from Grunenthal Australia for discussing a volatile agent and giving feedback Australia, payment from Mundipharma for GP education talks, payment from Nevro for a pain specialist peer visit in Newcastle, and attended events sponsored by St Jude's Medical, Medtronic, Nevro, Pfizer, Mundipharma and Servier to discuss products.

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