Unravelling the efficacy of antidepressants as analgesics

Raguraman Janakiraman, Laura Hamilton, Aston Wan

Background

Chronic pain is a large and growing public health concern in Australia. Chronic pain is generally associated with physical, psychological, social and cultural risk factors.

Objective

Several antidepressants have been efficacious in the management of chronic pain. This article illustrates the use of antidepressants in major chronic neuropathic pain conditions.

Discussion

Knowledge of psychopharmacology is important in the management of chronic pain. The majority of patients with chronic pain have comorbid psychiatric conditions ranging from mild anxiety, depression and adjustment problems, to severe delusional and psychotic disorders. Depression and anxiety are known to enhance the perception of pain. Not all antidepressants have independent analgesic properties. There is now a convincing body of controlled data, as well as extensive longstanding clinical experience, supporting tricyclic antidepressants (TCAs) as analgesics independently of their antidepressant actions.

Chronic pain is reported in 17.1% of males and 20.0% of females in Australia. Having chronic pain is significantly associated with older age, female gender, lower levels of completed education and not having private health insurance. It is also strongly associated with receiving a disability or unemployment benefit.[1]

Case

Mrs K, aged 48 years, presented with chronic lower back pain of 10 months' duration. She was referred to the persistent pain management services of a teaching hospital.

History of the presenting illness

Mrs K presented with lower back and right lower limb pain. Her pain intensity fluctuated from 6/10 to 8/10 on visual analogue scale (VAS). She described her pain as being of a sharp, burning quality with occasional tingling, and pins and needles in the back of her right thigh and foot. Aggravating factors included forward bending, standing/walking at length, lifting weight, and cold weather. Bed rest, medications and heat packs generally relieved her pain.

Her symptoms began after a fall at work. During the assessment, she was found enmeshed in a complex web of circumstances that sustained her condition. Her diminished level of activity and persistent fear of losing control over her life had threatened her sense of self-integrity and self-confidence.

Mrs K was recently promoted, which increased her anxiety around independence and control. This probably resulted in Mrs K leaving her job to escape an untenable situation. Her pain behaviour was also maintained by the solicitous caretaking of her by her husband (secondary gain).

On physical examination Mrs K was tender at the L5 and S1 spinous process. She had hyperalgesia, dysaesthesia and hyperpathia on the medial aspect of her right foot and dorsum of her right big toe, highly suggestive of neuropathic pain.

Management options considered

Mrs K had extensive investigations through her family physician, including magnetic resonance imaging (MRI) of the lumbosacral spine. This showed multilevel degeneration and L4–5 disc herniation with minimal L5 nerve impingement on the right side. She used non-steroidal anti-inflammatory drugs (NSAIDs), a heat pack, and physical and psychological therapies. Having not shown improvement over a period of 10 weeks, she commenced on low-dose opioids and gabapentinoid, which gradually reduced her pain intensity. This helped her to participate in a few more physical therapy sessions. However, this improvement was short-lived and within three months she required escalation of her opioid dose.

© The Royal Australian College of General Practitioners 2016

Chronic pain and the use of antidepressants

Patients with neuropathic pain do not always respond to standard analgesics such as NSAIDs, and to some extent neuropathic pain is resistant to opioids. The pharmacological agents best studied and in longest use for the treatment of neuropathic pain are antidepressants and anticonvulsants.[2] Major depression and dysthymia are common in chronic pain, occurring in up to 50% and 75%, respectively, of patients.

Anxiety, depression and cognitive states such as catastrophisation are also associated with a heightened experience of pain through inhibition of modulatory pathways.[3,4]

Case continued

Mrs K commenced on amitriptyline 25 mg nocte, which was then gradually increased to 75 mg nocte. She continued to attend pain management services for physiotherapy and psychology sessions. Over a six-week period, she showed gradual progress. The increase in amitriptyline reduced her neuropathic pain, anxiety and associated distress. She successfully engaged in the multimodal treatment, which eventually reduced her pain intensity by about 60% on VAS and modified brief pain inventory (BPI). The opportunity was taken to reduce her opioid dose gradually.

Pharmacology of antidepressants

The current knowledge of the pharmacological actions of antidepressants has gradually evolved over many years. Tricyclic antidepressants inhibit the presynaptic reuptake of the monoamines serotonin and noradrenaline, have antagonistic effects on postsynaptic α-adrenoceptors, Histamine H1 receptors and muscarinic receptors.

A large number of neurotransmitters are involved in the descending neuromodulation system, which includes serotonin and noradrenaline, opioid peptides, gamma-aminobutyric acid (GABA) and glycine. TCAs increase the availability of serotonin and noradrenaline through dual reuptake inhibition that provides an analgesic effect.[5] Table 1 shows an evidence-based comparison of efficacy among various antidepressants.

Management in other pain conditions

Current drug treatments are focused mainly on dampening the neuronal input by suppressing axonal function (eg sodium channel blockade) or interfering with neurotransmission (blockade of excitatory and inhibitory neurotransmitters and modulators; see Table 2).

Other peripheral neuropathic pain

TCAs were shown to be effective in diabetic neuropathy and post-herpetic neuralgia. There is a close relationship between the duration of neuralgia and therapeutic efficacy. Prompt treatment shortens the progressive course of the disease and also decreases its severity. The benefits and harms of duloxetine for treating painful neuropathy and different types of chronic pain were assessed. An adequate amount of moderate-quality evidence has been found.[6]

Current evidence-based recommended treatments for neuropathic pain conditions are outlined in Table 3, and their suggested treatment doses are outlined in Table 4.

Central neuropathic pain

Lesions of the central nervous system (eg arising from stroke, spinal cord injury, multiple sclerosis, syringomyelia, radiation myelopathy and human immunodeficiency virus myelopathy) result in central neuropathic pain. There is level B evidence for the use of TCAs in central neuropathic pain.[7] A systematic review of randomised controlled trials on the analgesic effects of antidepressants in adult patients found TCAs to be effective for various types of neuropathic pain, including central neuropathic pain. Both TCAs and venlafaxine had a number needed to treat (NNT) of approximately 3.[8] There are insufficient data to assess the evidence for effectiveness for other antidepressants such as St John's wort and L-tryptophan.

Fibromyalgia

Meta-analysis shows significant clinical responses (improvement in self-rating of pain, stiffness, fatigue, global assessment of improvement and tenderness at the tender points) in about 30% of patients treated with TCAs.[9] Patients treated

Table 1. Comparison of antidepressants for the treatment of neuropathic pain[17]

Antidepressants	Efficacy	Evidence-based support	Side effects
Tertiary amine tricyclic antidepressants (amitriptyline, doxepin, imipramine)	Yes	+++	+++
Venlafaxine	Yes	++	+
Duloxetine	Yes	++	+
Bupropion	Yes	+	+
Secondary amine tricyclic antidepressants (desipramine, nortriptyline)	Yes	++	+++
Paroxetine, citalopram	Yes (modest)	+	+
Fluoxetine	No	–	+

High, +++; Moderate, ++; Low, +
Reproduced from Sansone RA, Sansone LA. Pain, pain, go away: Antidepressants and pain management. Psychiatry (Edgmont) 2008;5:16–19, with permission from Matrix Medical Communications

© The Royal Australian College of General Practitioners 2016

with antidepressants showed significant improvement when compared with those on placebo, and the overall NNT was 4 (95% CI: 2.9–6.3).[10]

Duloxetine is the only antidepressant approved by the US Food and Drug Administration for the treatment of neuropathic pain. It is purportedly a dual-action drug. Duloxetine has been confirmed in several studies as an effective agent in the treatment of neuropathic pain.[11] Duloxetine is well tolerated and has fewer withdrawals due to adverse events with 60 mg than with 120 mg. Most adverse events are reported to be mild or moderate, with nausea, somnolence, constipation, decreased appetite and dry mouth frequently mentioned. Duloxetine is equally effective for the treatment of painful diabetic neuropathy and fibromyalgia, judged by the outcome of at least 50% pain relief over 12 weeks, and is well tolerated. The NNT of 6 for 50% pain relief suggests that this is likely to be a useful drug in difficult-to-treat conditions such as fibromyalgia and comorbid depression, where typically only a minority of patients responded. Doses higher than 60 mg do not provide additional pain relief, but do cause slightly more withdrawals due to adverse events.[12]

Table 2. Efficacy of analgesics in pain[21,22]

Medications	Pain	NNT	NNH
Group 1 (non-addictive)	**Acute pain 'nociceptive'** **Inflammatory pain**		
• Paracetamol (4 g/day)	Arthritis pain Post-surgical pain	4–5 1.7	12 (GI SEs)
• NSAIDs – Ibuprofen – Meloxicam – Celecoxib – Diclofenac – Ketoprofen – Piroxicam	Acute pain Topical Migraine	1.6–4.2 4.5 6–9	• (GI SEs) • Low in small dose • Less than oral NSAIDs • Short-term use
Group 2 (addictive)	**Acute pain 'nociceptive'** **Inflammatory pain** **Neuropathic pain**		
• Tramadol (100 mg, 150 mg)	Post-surgical	2.4–4.8	8.3
• Paracetamol 500 mg + codeine 60 mg • Aspirin 650 mg + codeine 60 mg • Paracetamol 650 mg + propoxyphene 100 mg	Post-surgical Post-surgical Post-surgical	2.2 3.6 4	
Group 3 (non-addictive)	**Neuropathic pain**		
• Amitriptyline	Neuropathic pain	3.6	6
• Pregabalin • Gabapentin	Diabetic neuropathy Post-herpetic neuralgia Central neuropathic pain Fibromyalgia	2.9 3.9 5 13–22	3.7
• Venlafaxine	Neuropathic pain	3.1	16.2
• Duloxetine	Neuropathic pain	6–8	9.6
Group 4 (addictive)	**Acute pain 'nociceptive'** **Inflammatory pain** **Neuropathic pain**		
• Opioids (morphine, oxycontin, buprenorphine, fentanyl)	Acute pain Neuropathic pain	2.5–4.3	4.2 (nausea, constipation) 7.1 (dizziness, vomiting)

GI SEs, gastrointestinal side effects; NNH, number needed to harm; NNT, number needed to treat; NSAIDs, non-steroidal anti-inflammatory drugs

© The Royal Australian College of General Practitioners 2016

Table 3. Recommended treatment for neuropathic pain conditions[23]

Drug therapy	Diabetic polyneuropathy	Postherpetic neuralgia	Trigeminal neuralgia	Chronic regional pain syndrome
First-line	• Duloxetine • Gabapentin • Pregabalin • TCAs • Venlafaxine	• TCAs • Gabapentin • Pregabalin • 5% lignocaine patch • EMLA patch	Carbamazepine	• Gabapentin • Pregabalin • TCAs • Duloxetine
Second-line or third-line	Tramadol Tapentadol SR	Tramadol Tapentadol SR	Baclofen Lamotrigine	• NSAIDs • Oral prednisone • Bisphosphonates
Others (because of the associated risk of dependence in long-term therapy)	Opioids	Opioids		Topical capsaicin IV lignocaine Opioids

EMLA, eutectic mixture of local anaesthetics; IV, intravenous; NSAIDs, non-steroidal anti-inflammatory drugs; TCAs, tricyclic antidepressants
Adapted from Votrubec M, Thong I. Neuropathic pain: A management update. Aust Fam Physician 2013;42:92–97. Available at www.racgp.org.au/afp/2013/march/neuropathic-pain-update [Accessed 16 December 2015].

Table 4. Medications and suggested doses for treating neuropathic pain conditions[23]

Gabapentin	300–1200 mg three times a day
Pregabalin	50–300 mg twice a day
Carbamazepine	100–600 mg twice daily
Amitriptyline	10–75 mg at night
Duloxetine	30–90 mg a day
Venlafaxine	150–225 mg a day
Tramadol	50–400 mg a day
Tapentadol SR	50–250 mg twice a day
Morphine Oxycodone	Start 5 mg a day and titrate gradually (regular assessment is required due to risk of addiction and abuse potential)
5% lignocaine patch/EMLA patch	Apply to affected area for 12 hours per day (trigeminal neuralgia)

Adapted from Votrubec M, Thong I. Neuropathic pain: A management update. Aust Fam Physician 2013;42:92–97. Available at www.racgp.org.au/afp/2013/march/neuropathic-pain-update [Accessed 16 December 2015].

Headaches

In a meta-analysis, patients with migraine and tension headaches who were treated with antidepressants were twice as likely to improve, compared with those treated with placebo; overall NNT was 3.2 (95% CI: 2.5–4.3).[13] Amitriptyline is a level 1 recommended medication with a therapeutic dose range of 30–150 mg/day.[14] Similarly, in placebo-controlled trials with venlafaxine XR 75 or 150 mg/day, the higher dose was effective in reducing the frequency of migraine attacks while being well tolerated. When comparing venlafaxine with amitriptyline, both had similar effects in the prophylactic treatment of migraine.

Adverse effects of antidepressants

TCA use in patients with cardiac conduction disturbances, severe ischaemic heart disease or cardiac instability (eg after myocardial infarction) and epilepsy should be considered cautiously. Side effects, including dry mouth, sweating, dizziness, orthostatic hypotension, fatigue, constipation and problems with micturition, are often bothersome and may lead to discontinuation of TCAs in a number of patients.

The selective serotonin reuptake inhibitors (SSRIs) and serotonin–noradrenaline reuptake inhibitors (SNRIs) are generally better tolerated. SSRIs may induce nausea, vomiting and dyspepsia, and the same type of side effects are seen with the SNRIs. It was found that TCAs and SSRIs are associated with increased risk of hip fractures.[15]

A retrospective cohort study found that SSRIs and TCAs in doses less than 100 mg/day did not increase the risk of sudden cardiac death, whereas higher doses of TCAs were associated with two to three times increased relative risk.[16]

Conclusion

Several antidepressants are efficacious in the management of chronic pain.

© The Royal Australian College of General Practitioners 2016

It is notable that antidepressants are useful for many disorders other than depression, especially for anxiety disorders and neuropathic pain. There is evidence supporting TCA analgesia that is independent of their antidepressant actions.[17] Although not all antidepressants have independent analgesic properties, relieving depression and/or anxiety by any method is likely to decrease pain.[18] At present, there are no controlled data to support the use of SSRIs as adjuvants for pain.[19]

Recent evidence-based guidelines[20] recommend TCAs as the first choice of treatment along with gabapentin and pregabalin, and SNRIs such as duloxetine and venlafaxine should be second-choice treatment in painful neuropathy. In the elderly and in patients with cardiovascular adverse effects, SNRIs are preferable to TCAs. As is the case with any research, readers need to consider the presented results within the context of limitations.

Authors

Raguraman Janakiraman DIH, DPM, FIPS, FRANZCP, CertAdult Psych, Private Consultant Psychiatrist and Pain Medicine Fellow, Princess Alexandra Hospital, Metro South Service, Brisbane, QLD. psychiatrist4u@gmail.com

Laura Hamilton FRANZCP, CertCLPsych, Cert Child Psych, Consultant Psychiatrist, Pain Medicine, Mount Gravatt, Brisbane, QLD

Aston Wan FRACGP, FFPMANZCA, Director, Persistent Pain Management Service, Metro South Hospital Service, Mount Gravatt, QLD

Competing interests: None.

Provenance and peer review: Not commissioned, externally peer reviewed.

References

1. Blyth FM, March LM, Brnabic AJ, Jorm LR, Williamson M, Cousins MJ. Chronic pain in Australia: A prevalence study. Pain 2001;89:127–34.
2. Woolf CJ, Mannion RJ. Neuropathic pain: Aetiology, symptoms, mechanisms, and management. Lancet 1999;353:1959–64.
3. Ossipov MH, Dussor GO, Porreca F. Central modulation of pain. J Clin Invest 2010;120: 3779–87.
4. Ren K, Dubner R. Descending modulation in persistent pain: An update. Pain. 2002;100:1–6.
5. Dworkin RH, O'Connor AB, Backonja M. et al. Pharmacologic management of neuropathic pain: Evidence-based recommendations, Pain 2007;132:237–51.
6. Lunn MPT, Hughes RAC, Wiffen PJ. Duloxetine for treating painful neuropathy, chronic pain or fibromyalgia. Cochrane Database Syst Rev 2014;1:CD007115.
7. Verdu B, Decosterd I, Buclin T, Stiefel F, Berney A. Antidepressants for the treatment of chronic pain. Drugs 2008;68:2611–32.
8. Saarto T, Wiffen PJ. Antidepressants for neuropathic pain: A Cochrane review. J Neurol Neurosurg Psychiatry 2010;81:1372–73.
9. Arnold LM, Keck Jr PE, Welge JA. Antidepressant treatment of fibromyalgia. A meta-analysis and review. Psychosomatics 2000;41:104–13.
10. O'Malley PG, Balden E, Tomkins G, et al. Treatment of fibromyalgia with antidepressants: A meta-analysis. J Gen Intern Med 2000;15:659–66.
11. Jann MW, Slade JH. Antidepressant agents for the treatment of chronic pain and depression. Pharmacotherapy 2007;27:1571–87.
12. Sultan A, Gaskell H, Derry S, Moore RA. Duloxetine for painful diabetic neuropathy and fibromyalgia pain: Systematic review of randomised trials, BMC Neurol 2008;8:29.
13. Tomkins GE, Jackson JL, O'Malley PG, et al. Treatment of chronic headaches with antidepressants: A meta-analysis. Am J Med 2001;111:54–63.
14. Tort S, Urrútia G, NishishinyaMB, Walitt B. Monoamine oxidase inhibitors (MAOIs) for fibromyalgia syndrome. Cochrane Database Syst Rev 2012;4:CD009807.
15. Hubbard R, Farrington P, Smith C, Smeeth L, Tattersfield A. Exposure to tricyclic and selective serotonin reuptake inhibitor antidepressants and the risk of hip fracture. Am J Epidemiol 2003;158:77–84.
16. Ray WA, Meredith S, Thapa PB, Hall K, Murray KT: Cyclic antidepressants and the risk of sudden cardiac death. Clin Pharmacol Ther 2004:75:234–41.
17. Sansone RA, Sansone LA. Pain, pain, go away: Antidepressants and pain management. Psychiatry (Edgmont) 2008;5:16–19.
18. Harvard Health Publications, Harvard Medical School. Depression and pain. Boston: Harvard University, 2015. Available at www.health.harvard.edu/mind-and-mood/depression_and_pain [Accessed 11 December 2015].
19. Warfield CA, Bajwa ZH. Principles & practice of pain medicine. 2nd edn. New York: McGraw-Hill, 2004.
20. Gilron I. Treatment of neuropathic pain: Antiepileptic and antidepressant drugs. In: Raja SN, Sommer CL, editors. Pain: A refresher course. 15th World Congress on Pain. Washington DC: IASP Press, 2014. Available at http://iasp.files.cms-plus.com/AM/Images/GYAP/Neuropathic/treatment_of_neuropathic_pain_antiepileptic_and_antidepressant_drugs.pdf [Accessed 16 December 2015].
21. Government of Western Australia, Department of Health. Pain health: Musculoskeletal pain. Perth: Government of Western Australia, Department of Health, 2015. Available at http://painhealth.csse.uwa.edu.au/resources/painHealth-NNT-and-NNH-for-pain-medications.pdf [Accessed 16 December 2015].
22. Saarto T, Wiffen PJ. Antidepressants for neuropathic pain. Cochrane Database Sys Rev 2007;4:CD005454.
23. Votrubec M, Thong I. Neuropathic pain: A management update. Aust Fam Physician 2013;42:92–97.

correspondence **afp@racgp.org.au**

© The Royal Australian College of General Practitioners 2016