INTRODUCTION

Chronic pain can result in impairments in quality of life, mood, sleep and cognition\(^1\)\(^-\)\(^5\). A high degree of comorbidity often exists between chronic pain and psychiatric disorders, including depression and anxiety, and the co-existence of depression and chronic pain may result in increased difficulties in treating both conditions\(^5\)\(^-\)\(^9\). In the relationship between depression and pain, it appears that one can influence the development of the other, i.e., major depression can be a strong predictor of subsequently developing pain and vice versa\(^8\). There is still considerable uncertainty about the reasons for the co-occurrence of pain and depression, although this is an active area of research\(^5\)\(^-\)\(^12\).

Patients experiencing chronic pain are often treated with antidepressants\(^13\)\(^-\)\(^18\). Most of the antidepressants produce increased functional availability of the biogenic amines noradrenaline (NA) and/or 5-hydroxytryptamine (5-HT, serotonin)\(^19\)\(^,\)\(^20\), and there is now considerable evidence also implicating GABAergic and glutamatergic mechanisms in the antidepressant effects of these drugs\(^21\)\(^-\)\(^23\). Interestingly, these four neurotransmitter systems also appear to be involved in the development and/or modulation of pain\(^24\)\(^-\)\(^30\), suggesting common mechanisms for the development of depression and chronic pain. However, while selective serotonin reuptake inhibitor antidepressants (SSRIs) are used frequently in treatment of depression, they are not as effective as tricyclic antidepressants (TCAs) or serotonin-noradrenaline reuptake inhibitor antidepressants (SNRIs) for most chronic pain conditions\(^9\)\(^,\)\(^14\)\(^,\)\(^15\)\(^,\)\(^31\).

Since monoaminergic systems are involved in both depression and chronic pain, it is not surprising that antidepressants have been used frequently for treating chronic pain. However, it should also be noted that many antidepressants have a true analgesic effect in that they are effective at reducing pain in people without depression\(^5\)\(^,\)\(^10\)\(^,\)\(^13\)\(^,\)\(^14\). Pain conditions in which antidepressants are used for treatment include irritable bowel syndrome, central pain syndrome, arthritis, fibromyalgia, low back pain, migraine, diabetic neuropathy, chemoinduced neuropathies and postherpetic neuralgia (shingles-associated pain)\(^5\)\(^,\)\(^10\)\(^,\)\(^14\)\(^,\)\(^16\)\(^,\)\(^17\). Often these pain conditions are treated with TCAs, which are inhibitors of the reuptake of NA and 5-HT. The relative lack of responsiveness to SSRIs and relative success of TCAs in many chronic pain patients suggest that noradrenergic pathways may be more important in chronic pain than in major depressive disorder. The SNRIs are also reported to be more effective than SSRIs in the management of chronic pain\(^17\)\(^,\)\(^31\)\(^,\)\(^32\), further supporting the importance of NA in pain. Interestingly, it has been reported that TCAs with a more balanced inhibition of reuptake of NA and 5-HT tend to be more effective in treating neuropathic pain than those that are much more potent at inhibiting reuptake of NA than that of 5-HT\(^13\). TCAs can also affect other systems directly or indirectly (5-HT binding to its receptors; NA’s interaction with α2-adrenoreceptors; opioid receptor density in the brain; binding to NMDA...
and/or AMPA glutamate receptors; blockade of voltage-gated sodium channels; adenosine uptake in the periphery; and indirect dopaminergic actions)\textsuperscript{10,13}, and some of these additional effects may be contributing to their analgesic actions. However, it should also be remembered that TCAs may be poorly tolerated by the elderly and that cardiotoxicity is a potential risk with TCAs\textsuperscript{13,17,32}.

The main focus of research on the involvement of biogenic amines in pain and depression has been on NA and 5-HT, but there is increasing evidence for a role of dopamine in the perception and regulation of pain\textsuperscript{33-36}. Although the TCAs have very little effect on dopamine reuptake, their adrenergic effect may produce indirect dopaminergic effects via desensitization of dopamine D2 receptors\textsuperscript{33}. In addition, the atypical antidepressant bupropion (inhibits reuptake of NA and dopamine) has been reported to be effective in treating neuropathic pain\textsuperscript{37}.

According to some authors, monoamine oxidase inhibitors (MAOIs) should not be used in treating pain disorders\textsuperscript{10,38}, but phenelzine (PLZ), an MAOI which also elevates brain GABA levels and has anxiolytic properties, has been reported to be effective in treating neuropathic pain associated with depression\textsuperscript{39,40}. This drug produces a marked elevation in brain and spinal cord levels of 5-HT and NA\textsuperscript{41,42} and also appears to attenuate pain in the EAE animal model of multiple sclerosis (Benson, Mifflin, Baker and Kerr, unpublished), a neurological disorder in which pain is a frequent symptom.

The differing analgesic effects of antidepressants based on their ability to inhibit reuptake of NA and 5-HT and the reported success with bupropion in treating neuropathic pain, along with the proposed indirect actions of TCAs on the dopaminergic system, suggest that treatment of chronic pain using triple reuptake inhibitor antidepressants (which inhibit NA, 5-HT and dopamine reuptake) may be an interesting avenue to pursue. Such drugs are currently being investigated for possible use in pain and depression\textsuperscript{43-45}.

There has been a great deal of interest in the NMDA receptor antagonist ketamine and its rapid acting antidepressant action when infused\textsuperscript{46,47}, and it is interesting that this drug has also been used in treatment of therapy-resistant chronic pain\textsuperscript{48}. Several neuroactive steroids (NASs), which are rapid acting allosteric modulators at receptors such as the GABA-A receptor and the NDMA glutamate receptor, have been reported to have antidepressant and analgesic properties\textsuperscript{49-54}. These NASs or perhaps analogues of them or drugs that have specific actions on these NASs should be of increased interest in future studies on the treatment of pain.

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