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## Milnacipran: recent findings in depression

Milnacipran is a serotonin and norepinephrine reuptake inhibitor (SNRI) which was first approved for the treatment of major depressive episodes in France in December 1996. It is currently marketed for this indication (as Ixel<sup>®</sup>, Toledomin<sup>®</sup>, Tivanyl<sup>®</sup> or Dalcipran<sup>®</sup>) in over 45 countries worldwide including Japan. It was approved for the management of fibromyalgia in the US in 2009.

This supplement, which is based on a symposium at the International Forum on Mood and Anxiety (IFMAD) held in Monaco in November 2009, highlights several recent clinical studies with milnacipran in depression.

The World Health Organization (WHO) classes suicide as one of the ten leading causes of death for all ages with more than 1.5 million deaths per year estimated for 2020.<sup>1</sup> Reports of higher rates of suicide-related adverse events during treatment with selective serotonin reuptake inhibitors (SSRIs) and other antidepressants<sup>2</sup> prompted regulatory bodies in the US and Europe to issue suicide risk warnings during the first weeks of antidepressant treatment. More recent evidence, however, suggests a favorable benefit – risk ratio for treating depressed patients with antidepressants with the possible exception of those less than 25 years of age.<sup>3</sup>

In the first paper in this supplement, Philippe Courtet presents recent research on suicidal behavior and specifically a study of the effects of milnacipran on suicidal behavior in depression patients. This study showed that suicidality decreased progressively in parallel with other depressive symptoms and was essentially absent at the end of the study. At no time during treatment was there any increase of suicidal risk.

Depression is common in patients with diabetes and the co-morbidity has a serious negative impact on self-care, adherence to treatment and the general prognostic of diabetes. In particular co-morbid depression is associated with decreased metabolic control, a higher incidence of angiopathic complications and decreased quality of life for diabetes sufferers.<sup>4</sup>

In the second paper, Peter Hofmann discusses the treatment of co-morbid depression in diabetes patients and in particular the question as to whether antidepressant treatment can improve diabetes symptoms. SSRIs appear to treat the depression effectively but there is no evidence of any major effect on metabolic control. A recent study of milnacipran in diabetes patients with co-morbid depression showed, however, that a wide range of diabetes parameters were all significantly improved in patients with an antidepressant response but not in patients whose depressive symptoms had not responded to milnacipran.

Milnacipran and venlafaxine are both SNRIs but with differing selectivities for the two monoamines. Milnacipran has a balanced ratio of potency (1:1.16) for the inhibition of reuptake of the two neurotransmitters.<sup>5</sup> One study has shown it to inhibit norepinephrine uptake with greater potency than serotonin (2.22:1).<sup>6</sup> In contrast, venlafaxine has a 30-fold greater potency for the serotonin transporter than for the norepinephrine transporter.<sup>5</sup> At low doses venlafaxine acts essentially as a SSRI, with significant noradrenergic activity occurring only at higher doses. Thus the choice of dose is critical for any meaningful comparison with venlafaxine.

In the third paper, Lucilla Mansuy discusses the various indirect comparisons that have been made between the two SNRIs. She then presents the first direct head-to-head comparison between venlafaxine and milnacipran with both drugs flexibly titrated to 150 to 200 mg/day and which shows the two SNRIs to have similar efficacy and tolerability.

In the fourth and final paper, Siegfried Kasper presents an updated overview of milnacipran in depression. He concludes that its distinct combination of favorable characteristics,

namely its wide efficacy, good tolerability, low risk of pharmacokinetic drug – drug interactions, minimal, if any, sexual dysfunction or withdrawal effects, and safety in overdose, qualifies milnacipran as a first-line antidepressant treatment for any depressed patient. It may be particularly well-suited for low-energy, slowed-down patients.

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