6 DISCUSSION

The World Health Organization recently categorized depression as one of the world’s most disabling diseases, affecting nearly 340 million people worldwide and 18 million people in the United States at any given time. Few lay people realize that major depression and related mood disorders are potentially deadly afflictions; unrecognized major depressive disorder (MDD) is associated with a suicidal risk of approximately 15%. Beyond the risk of suicide, depressed patients also show a higher risk of mortality from all causes. The Global Burden of Disease Study was initiated in order to objectively evaluate the burden of over 100 common medical conditions by utilizing the metric of disability-adjusted life years (DALYs). The report stated that psychiatric conditions, though responsible for little over 1% of deaths, accounted for almost 11% of the disease burden worldwide. Furthermore, MDD was found to be the fourth largest source of DALYs in 1990, and has been projected to rise to second place by 2020. In addition, independent studies have ranked MDD as the third most costly and disabling illness in the United States. Earlier Indian studies have reported prevalence rates of depression that vary from 21–83% in primary care practices. Given the scope of the public health need, significant improvement in the therapies available to treat major depression has potentially far-reaching beneficial consequences. The research efforts involved in developing the current generation of antidepressant agents have helped to increase awareness of the diagnosis and treatment of major depression. However, the antidepressant medications currently employed to treat MDD possess a number of limitations, including tolerability drawbacks or lack of efficacy and rather low probabilities of remission typically in the range of 35% to 45%.\[1\]

From many years, tricyclic antidepressants (TCAs) are used as the backbone of the treatment of MDD. Apart from the inhibition of 5-HT and NE reuptake, TCAs also act through adrenergic, muscarinic and histaminergic receptor sites. Because of the non-specific binding of the TCAs leads to adverse events and interactions. Because of these reasons, the use of TCAs becomes limited today.\[43\]

Another class of antidepressants is the serotonin selective reuptake inhibitors (SSRIs). SSRIs selectively block the 5-HT reuptake. In addition, SSRIs are the more tolerable and effective
drug than TCAs. Despite of presence of these antidepressants, the response rate was usually 60% to 70% and remission rate is around less than 50%. There was a still requirement of a more efficacious and tolerable antidepressant drug which can be used in the patients with severe depression and increase the patient compliance.\textsuperscript{[43]}

In general, antidepressants achieve a response (≥50% reduction in baseline depression score) in less than 70% of patients and remission (a complete absence of depressive symptoms) in less than 50%. Increasing evidence of the importance of NE in the etiology of depression\textsuperscript{[44]} and the idea that “two actions are better than one” have led to the development of a new class of compounds that block the reuptake of both 5-HT and NE without the nonspecific, side effect-inducing receptor interactions of TCAs. This class, the serotonin and norepinephrine reuptake inhibitors (SNRIs) comprising of duloxetine, venlafaxine, mirtazapine and milnacipran.\textsuperscript{[43]}

Milnacipran is not approved in the US and UK for the treatment of depression till date. Hence, detailed and extensive literature reports are not available for milnacipran. Out of the few available studies for milnacipran, most of them employed a placebo as a comparator, while others had tricyclic antidepressants (TCAs) or selective serotonin reuptake inhibitors (SSRIs) as a comparator. Previous clinical trials have provided inconsistent results with regard to milnacipran’s antidepressant effectiveness. Some clinical trials have shown that milnacipran has similar antidepressant efficacy in comparison with other antidepressants, such as imipramine,\textsuperscript{[48-50]} clomipramine,\textsuperscript{[51]} fluoxetine,\textsuperscript{[52]} fluvoxamine\textsuperscript{[53]} and paroxetine.\textsuperscript{[54]} However, Ansseau et al.\textsuperscript{[56]} reported a superiority of fluoxetine over milnacipran based therapy on continuous outcomes. On the other hand, although milnacipran is approved in India, none of the reported studies describe the trend of milnacipran in depression in Indian population. Moreover, there is paucity of reports on the comparison of milnacipran with other treatments including the serotonin–norepinephrine reuptake inhibitors (SNRIs), such as duloxetine, venlafaxine and mirtazapine.

The objective of this randomized, comparative, multi-centric study was to evaluate the efficacy and safety of milnacipran in Indian patients with major depressive disorder and its
simultaneous comparison with other SNRIs [duloxetine, venlafaxine and mirtazapine]. The present study, carried out in 240 adults suffering from MDD revealed a similar efficacy profile of SNRIs such as duloxetine, venlafaxine and mirtazapine to that of milnacipran. The rates of responders and remissions showed no relevant differences between the groups. Besides, no differences were found in achieving clinical improvement, remission or overall tolerability while comparing milnacipran with other antidepressants.

The primary efficacy endpoint was to assess the reduction in the HDRS score from baseline and to assess the reduction in the MADRS score from baseline. The secondary efficacy endpoint was the proportion of patient responding to the treatment. [Responder was defined as the patient showing reduction in HDRS ≥ 50% as compared to the baseline] The secondary efficacy endpoint was proportion of patient attaining remission on treatment [Remission was defined as the patient showing HDRS ≤ 7] and the reduction in the Clinical Global Impression (CGI) scale.

The findings implicated a significant difference in HDRS score from baseline till the end of treatment in the milnacipran group. Similar results were observed with the other SNRIs such as duloxetine, venlafaxine and mirtazapine. However, no significant difference was observed between the milnacipran and other SNRIs groups [duloxetine, venlafaxine and mirtazapine]. A research conducted by Leinonen et al., concluded that milancipran’s effects on HDRS scores were significantly greater in patients diagnosed of major depression disorder.\textsuperscript{[51]} This study affirm that milnacipran significantly decrease HDRS score in patients suffering of major depression disorder.

Furthermore, there was a significant difference in the MADRS score from baseline to the end of treatment in the milnacipran group and the same was observed with other SNRIs such as duloxetine, venlafaxine and mirtazapine. Nonetheless, no significant difference was observed between the milnacipran group and other SNRIs such as duloxetine, venlafaxine and mirtazapine. This study results were similar to the findings of a research conducted by Clerc et al., concluded that milancipran’s were significantly reduced MADRS scores in patients of major depression disorder.\textsuperscript{[53]}
This study affirm that milnacipran significantly decrease MADRS score in patients suffering of major depression disorder.

Comparable results were obtained for the secondary efficacy endpoints as well. In concordance with previous studies, Milnacipran showed comparable rate of responder, rate of remitter and reduction in CGI as other SNRIs such as duloxetine, venlafaxine and mirtazapine.\textsuperscript{[49,150]}

In course of the clinical study, all reported adverse events were expected and tolerable and they recovered completely during the study. Overall, all the treatment groups were found to be safe and well tolerated. Lopez-Ibor \textit{et al.}, reported that milancipran was advantageous as it showed lower incidence of anti-cholinergic, anti-adrenergic or anti-histaminic properties over the commonly observed side effects of tricyclic antidepressants.\textsuperscript{[50]} This study confirms that the dual action antidepressants are successful and show an improved safety profile. Thus, the study found out that use of milancipran in patients suffering from depression should be lesser side effects and it further facilitates prescription in clinical practice.

Thus, it was evident that milnacipran is effective in the Indian population for the treatment of major depressive disorder and was comparable to other SNRIs such as duloxetine, venlafaxine and mirtazapine.