Objective – We assessed safety and efficacy of the serotonin and norepinephrine reuptake inhibitor (SNRI) milnacipran in depressed adolescents, which is approved for the treatment of depression from age 15 in Austria. Methods – We conducted an open and naturalistic 12-week trial with the SNRI milnacipran in 15 adolescents aged 15 to 18 years suffering from major depression (DSM-IV: 296.2) or dysthymia (DSM-IV: 300.4), who received milnacipran in a mean dose of 133 mg daily. Clinical symptoms and side-effects were rated according to Clinical Global Impressions Scale (CGI), Montgomery-Asberg (MADRAS) and Hamilton Depression (HAM-D) Scale. Results – HAM-D scores at baseline were 22.9 (SD=0.5) and 3.8 (SD=5.3) at endpoint. MADRAS scores declined from 30.9 (SD=5.6) at baseline to 5.3 (SD=3.0) after 12 weeks. Patients showed a reduction in CGI severity scores from 4.5 at baseline to 1.7 after 12 weeks which was statistically significant (p< .001) HAM-D scores as well as MADRAS scores declined significantly (p< .001). Approximately 92% of the 12 patients who finished 12 weeks of treatment showed a CGI-R score of 2 (much improved). Mild and transient side-effects were observed, the most frequent were headache in 21% and nausea in 14% within the first 2 weeks. Conclusions – Data from this 12-week open trial with the SNRI milnacipran suggest a favorable safety profile, comparable to that seen in SSRI treated patients, and good clinical efficacy in depressed adolescents.