Depression is a major psychiatric disorder. It affects millions of people worldwide and inflicts tremendous economic burden on societies. The advent of selective serotonin re-uptake inhibitors as antidepressants has been a revolutionary advance in the treatment of depression and related disorders. However, selective serotonin re-uptake inhibitors are also associated with several undesirable properties, such as delayed onset of action, low response rate and side effects. The present search for a newer generation of antidepressants is focused on overcoming these issues. The patent literature covered in this review, during 2004 - 2006, illustrates several strategies employed by the pharmaceutical industry in the development of enhanced serotonin re-uptake inhibitors. Encouraged by the success of venlafaxine and duloxetine, several companies have pursued dual-acting serotonin and noradrenaline re-uptake inhibitors as drug candidates for depression treatment. Molecules with combined serotonin re-uptake inhibitor and 5-HT autoreceptor (5-HT(1A) and/or 5-HT(1B)) antagonist properties are being developed. In particular, recent research suggests that serotonin 5-HT(1B) antagonists alone or combined with selective serotonin re-uptake inhibitors might hold unique promise as efficacious antidepressants. Finally, efforts are underway to formulate new drug candidates with both serotonin re-uptake inhibitor and neurokinin 1 (NK(1)) antagonist activities. Despite mixed results from clinical trials with several NK(1) antagonists, effective therapeutic agents for depression may still emerge from compounds with combined serotonin reuptake inhibitor/NK(1) antagonist properties.