Tricyclic antidepressants (TCAs), like the early antipsychotics, were developed from antihistamines with the aim to sedate disturbed psychiatric patients. They were first synthesized in the 1950s and derive their name from the three-amine ring structure that is common to this class of drugs. They have a variety of pharmacological actions, including serotonin and norepinephrine-reuptake inhibition as well as muscarinic, histaminic, and $\alpha_1$ adrenergic blockade. TCAs have been shown to improve depressive symptoms in randomized controlled trials (RCTs), but the precise mechanisms by which they achieve this are unclear, which perhaps is not surprising given the diverse pharmacological actions of these drugs.

Depressed patients often have chronic pain syndromes, and it was noted that pain symptoms were also improved by TCAs. This observation was confirmed by several RCTs. A Cochrane systematic review identified 17 RCTs involving 724 patients that evaluated the efficacy of TCAs in neuropathic pain and found these drugs were effective with a number needed to treat (NNT) of 4 (95% confidence interval [CI] 3 to 5) to produce at least a moderate improvement in pain compared to placebo.

The Evidence for TCAs in IBS

The cardinal symptom of irritable bowel syndrome (IBS) is abdominal pain so it is plausible that TCAs will also be beneficial for this disorder. Initial RCTs were not promising, and an early Cochrane systematic review suggested there was no clear evidence that TCAs were beneficial in IBS. Since then, however, there have been a number of RCTs and a further systematic review, and it has become clear that TCAs do have