Therapeutic Effect of Amitriptyline in Patients Suffering from Irritable Bowel Syndrome

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ABSTRACT

Irritable bowel syndrome (IBS) belongs among the most common disorders diagnosed by GPs and gastroenterologists. Antidepressant amitriptyline is safe, well tolerated and effective treatment for patients suffering from IBS with diarrhea. It has been shown in adults with IBS to be significantly more effective than placebo in producing global improvement, increasing feelings of well-being and the same good news concern adolescents and children too.

Keywords: Irritable Bowel Syndrome (IBS); Amitriptyline; Therapy

Introduction

Patients suffering from irritable bowel syndrome (IBS) form a part of the most frequent visitors in GP and gastroenterologist. Pathophysiology of irritable bowel syndrome consists of abnormal bowel motility including the pathological gastro-colic reflex with an abnormal character of stool consistency (IBS-C with constipation, IBS-D with diarrhea and IBS-A - mixed type of both), visceral hypersensitivity and hyperalgesia with increased perception of physiological stimuli, bloating, postinfective consequences in the bottom-up type with gut dysmicrobia and abnormal intestinal secretion. Some patients exhibit different kind of food intolerance without allergy. There is also frequent (~ 40%) psychiatric comorbidity of major depressive disorder and anxiety spectrum disorders. The quality of life in IBS patients is lowered and patients show evidence of various social fears. As far as the emotions concerned there is a hypothesis that negative emotions even in subclinical intensity may play an important role in pathogenesis, clinical severity and illness experience too. It is especially anxiety, depression and hostility existing together under the umbrella of „neuroticism“, one of the features of Big Five.

These emotions may influence physical health. They are probably entangled with neurobiological and immunological factors and they are in relation with higher plasma concentrations of some proinflammatory cytokines (IL-1β, IL-6, TNF, CRP) [1]. The prevalence of IBS is between 10 – 20 % and the course is varied from spontaneous remission through intermittent episodes to lifelong severe chronic problem. There are a lot of therapeutic recommendations: adjustment of diet, probiotics, spasmyotics, opioids and opioid receptor agonists, sertrons, antibiotics, sulphonamides, anxiolytics, antidepressants, acupuncture, cognitive behavioral psychotherapy and placebo because there are many placebo-responders among IBS patients [2], and not only children. Amitriptyline is an antidepressant from the RUI family (Re-Uptake Inhibitors) known also as tricyclics. It blocks reuptake of two main neurotransmitters: norepinephrine (NE) and serotonin (5-HT), acts as an inhibitor of norepinephrine and dopamine transporters, and operates also as antagonist of H1, M and α1 receptors. Its analgesic potency (agonist of substance P) is ensured by opioid receptors.

The first extra-psychiatric indication of tricyclics was pain treatment. Antidepressant became part of the WHO analgesic ladder in oncology: nonsteroidal analgesic + mild opioid + antidepressant. Tricyclics are much more effective than SSRI (selective serotonin reuptake inhibitors). Psychiatrists are the first specialists who started to treat IBS-D patients with amitriptyline after their recognition of unwanted side effects of this antidepressant – constipation [3]. Alike as in pain treatment the low dose of amitriptyline (10 – 50 mg) is sufficient in IBS patient therapy. In comorbid psy-
chiatric disorder the dose must be higher. Whereas as pure antide-
pressant is amitriptyline almost obsolete, in psychosomatic sphere
as medication for IBS patients is obviously effective. Even in animal
studies is amitriptyline used as therapeutic standard in the con-
trol group [4]. Its effect on visceral hypersensitivity is proven [5,6],
and low doses are sufficient because concentrations of tricyclics in
tissues are ordinarily higher than their plasmatic concentrations
[7]. Our psychosomatic group published in 1978 results of clinical
trial with 30 patients [8].

We achieved improvement in 27 participants (full remission
12, very good 10, good 5). We assessed also the motility of GIT by
X-ray with contrast and we found mainl a slowdown, only in one
case we found mild acceleration of bowel movements; but this pa-
tient achieved full remission. To gastroenterology amitriptyline
came into use with delay but with the same success [9]. Vahedi et
al. [10]. in 2008 have assessed the therapeutic role of antidepres-
sant drugs, because they believed that there was insufficient evi-
dence to support their use and prepared a double-blind trial with
54 patients. Participants were randomly selected, and half took 10
mg amitriptyline per day and half took placebo. After 2 months, the
amitriptyline group showed greater (P < 0.05) reduction in the in-
cidence of loose stool and feeling of incomplete defecation. Patients
receiving amitriptyline showed greater complete response, defined
as loss of all symptoms, compared with those receiving placebo
(68% vs. 28%, P = 0.01). Adverse effects were similar between the
two groups. Chassany and Duracinsky [11] displayed some meth-
odological doubts in connections with small number of participants
in this trial, but authors in replay defended their results.

And Trinkley and Nahata in their metaanalysis [12] put this trial
to methodological category 1A. Some reviews bring attention
to therapeutic value of amitriptyline in this indication [13,14], and
there are also many studies dealing with the application in children
and adolescents. Bahar et al. conducted a trial [15] with thirty-
three adolescents (12-18 years) with newly diagnosed IBS. They
were for 13 weeks on placebo arm (n=17) or amitriptyline (n=16).
Their conclusions: Patients receiving amitriptyline were more
likely to experience improvement from baseline in overall QOL at
6, 10, and 13 weeks (P = .019,.004, and .013). They also experience
improvement of diarrhoea. Mohammad et al. [16]. performed a subana-
lysis of the database of a multicenter randomized placebo-
controlled trial designed to assess the efficacy of amitriptyline
in children with abdominal pain-associated FGID (Functional
Gastro-Intestinal Disorders; Rome II criteria). This included 50.7%
children with IBS, 42.4% with functional abdominal pain, and 6.9%
diagnosed as having functional dyspepsia. Treatment satisfaction
(good or excellent) 60.2%. Symptom relief (better) 48.2%.

The longitudinal study [17] confirmed safety of amitriptyline in
children also in long time duration (up to 30 months). Interesting
are results of Saps’ team [18]. They found the same good or excellent
results (~60% improvement) after placebo (40 children) as after
amitriptyline (43 children). Trinkley and Nahata (cit.12) in their
extentive review from literature found amitriptyline as effective
but put it to the second group. The first and the most recommended
is the group which include lubiprostone, linaclotide, rifaximin, fiber
supplementation, and peppermint oil. There are two meta analyses
dealing with the efficacy of TCAs in the management of IBS. In
the first Rahimi et al. [19] in 2009 collected seven double blind
placebo-controlled trials investigating the efficacy of TCAs in the
management of IBS. published from 1966 until September 2008.
The pooled relative risk for clinical improvement with TCA therapy
was 1.93 (95% CI: 1.44 to 2.6, P < 0.0001), and their conclusion of
metaanalysis is that low dose TCAs exhibit clinically and statistically
significant control of IBS symptoms.

The second is focused to amitriptyline only; Chao and Zang
[20] found four randomized, placebo-controlled clinical trials that
met their criteria and were included in the meta-analysis. The
pooled relative risk for clinical improvement with amitriptyline
therapy was 4.18 (95% CI: 2.00 to 8.77, p=0.0001). Conclusion:
It was thus concluded that amitriptyline exhibits a clinically and
statistically significant control of IBS symptoms. The last published
case report [21] presented a man suffering from IBS in stressful
situations. Brief psychotherapy and 50 mg of amitriptyline daily led
to normalization of GIT functions within three months.

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