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MIMICS OF TRAMADOL ON HYPOTHALAMUS AND LIVER – A PROBIOTIC DRUG THERAPY

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ABSTRACT

The present paper reveals to assess the mimics of induced toxicity profiles of Tramadol (capsule) and its effects on hypothalamus and liver by treatment of probiotic drug therapy and focus the therapeutic use of probiotics in the modern world. Tramadol, a widely used opioid in recent years, is an effective analgesic agent for the treatment of moderately severe acute or chronic pain. Its analgesic effect is seen in Hypothalamus as a result of its dual mechanism of action, that is, as a re-uptake inhibitor of norepinephrine and serotonin and agonist of the μ-opioid receptor. It is converted in the liver to O-desmethyl-tramadol, which itself is an active substance and 2 to 4 times more potent than tramadol and remaining is excreted by the kidneys. By using probiotic microorganisms drug therapy, the toxicity of tramadol to be controlled or to be reduced.

KEY WORDS: **Oral Tramadol, effects on Hypothalamus and Liver, Serotonin Syndrome (SS), Irritable Bowel Syndrome (IBS), Probiotic therapy.**

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INTRODUCTION

Tramadol was first synthesized in Germany (1962) by "Grunenthal gmbh''. He was introduced the tramadol by coupling of the corresponding Cyclohexanon with 3-methoxy- phenylmanesium bromide in a Grignard reaction[1] .Tramadol was used to treat moderately severe pains and also shivering of the body. The tramadol was first entered on West Germany in 1977, then Poland on 1992, US on 1995 and also in UK on 1997[2-3] .The Tramadol works immediately releases an onset of pain relief usually occurs within an hour of intake into the body[4]. By two different mechanisms, firstly, binds to the μ-opioid receptor and secondly, it inhibits the re up take of Serotonin and Norepinephrine[5]. The Tramadol may induces serious side effects like seizures increases risk of suicide, serotonin syndrome and drug addiction[6] and common side effects like constipation and nausea and other may lead to kidney and liver problems[7].Tramadol is also not recommended in breast feeding[8]. Tramadol is marketed as a racemic mixture of both R- and S-stereoisomer[9]. This is because the two isomers complement each other's analgesic activity. Tramadol is metabolized to O-desmethyl tramadol. It is more potent opioid. Tramadol has another mode of action, which is a local anesthetic effect, that is comparable to the effects of ondanserton in alleviating pain caused by propofol injections[10] .Tramadol is an opioid analgesic used for therapy of mild to moderate pain, but its overdose can cause acute liver failure and leads to seizures risks to the users. The Tramadol hydrochloride extended release is indicated for the management of moderate to severely chronic pain in adults who requires around the clock treatment of pain for an extended period of time. Tramadol is effective on two forms that is 20 % of its pain killing effects come from opioids, rather than 80% from ingredients that reuptake of serotonin and norepinephrine, these two chemicals are associated in the brain for mood and responsiveness to pain[11] . The international product name of Tramadol hydrochloride, and its chemical name is dertermaine as cis-(2-dimethylaminomethyl)-1-(3-methoxyphenyl)-cyclohexanol. The tramadol is biologically discretionary norepinephrine and serotonin reuptake inhibitor and also weak μ-opioid receptor agonist. The general common trade names of tramadol and also including the combinational medicinal products like Ultram, Ultramex, Urgendol, Adamon, Altadol, Actidol, Biotram, Boldol, Calmador, Cambidol, Tram cap, Tramada ,Tramacure etc., [12] .The Tramadol hydrochloride salt is a white crystalline powder, and it has bitter taste. The chemical structure of tramadol is cis-configuration and (1S,2S),(1R,2R). Molecular formula of Tramadol is $C_{16}H_{25}NO_2$ and general molecular weight is 263.4 (base), and its common melting point is determined by 180-181ºc. The Stereo isomeric form of Tramadol has two chiral centres in the Cyclohexanon ring. Consequently, four different stereo isomers exist (1R, 2R), (1S, 2S),(1R,2S), and (1S,2R)[13]. The Tramadol hydrochloride is readily soluble in water and methanol. It has a pka value of 9.41. The normal pH is 7. The tramadol may be identified by Infrared spectroscopy, Mass spectroscopy and also in Nuclear magnetic resonances[14] .

ACTION OF TRAMADOL AND ITS MECHANISM ON THE PAIN

Orally administered Tramadol (100 mg tablet) is rapidly absorbed; the maximal serum concentration of the drug is achieved with an approximately 2 hours [15]. Tramadol is much higher than the bioavailability of Morphine [16]. Tramadol bioavailability is increases to approximately 90-100% during the multiple oral administrations. That is due to the saturation of the liver by pass effect mode of analgesic action of tramadol and then it influences on the pain descending inhibitory system[17].

Tramadol consists mainly of two pathways

1)Firstly it is originated from periaqueductal grey matter –PAG, in the midbrain, with synapses in the nucleus raphe magnus-(RM), from which fibers project to spinal cord. Then the neurotransmitter released in this pathway is serotonin (5-HT).

2) Secondly, the main pathway originates from the locus coeruleus in the Pons. That has projections to the spinal cord. The neurotransmitter released in this pathway is noradrenaline, which inhibit its pain responses in the spinal cord through an adrenergic mechanism[18].Periaqueductal grey matter –PAG, and rap-he magnus-RM in medulla oblongata and dorsal horns in the spinal cord possess an significant amount of endogenous opioid receptors. Activation of the descending pain inhibitory system is connected with the stimulation of inter neurons. That inhibits transmission of painful stimulations in synapses in the dorsal horn of the spinal cord by the action of endogenous opioids. The mechanism of analgesic action of tramadol involves the activation of both the descending sertonergic and noradrenergic pathway. Normally tramadol shows two racemic mixtures namely (-) and (+) enantiomers, the research regarding tramadol enantiomers as revealed that (-) tramadol is approximately 10 times more potent than (+) tramadol for inhibiting noradrenaline uptake[19] and the (+) tramadol is approximately 4 times stronger than (-) tramadol *et al* for inhibiting 5-HT uptake [20] .These both synergically enantiomers act towards improving analgesia and controls pain in body.

MEDICAL USES OF TRAMADOL

The tramadol is used for humans and also animals like dogs and cats etc, for often as pain reliever for post surgery pains and chronic conditions such a cancer or arthritis[6]. The tramadol is used primarily to treat for mild severe pains, acute and chronic[21-22] .Tramadol is a narcotic like pain reliever. In experimental studies tramadol has little immune suppressive effect[23]. It possesses antidepressant activity and also it's an effective as pethidine in the prophylaxis of ost-anesthetic shivering [24]. The Tramadol is combined with non opioids, namely like the paracetamol, to improvement in analgesia, but no increasing toxicity to users[25] .The important advantage of Tramadol is less constipation to codeine, DHC, morphine and Oxycodone[26] .The tramadol may be recommends for the patients with moderates as in some cases severe nociceptive and neuropathic pains[27] .In clinical practice, the tramadol is usually made up of older patients with GI tumors, and is considered as an alternative to DHC and

small doses of strong opioids like morphine, oxycodone, hydro-morphine, buprenorphine etc[28].,.

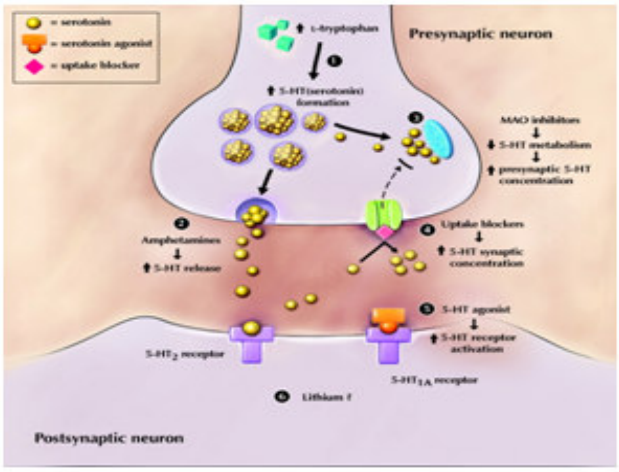
EPIDEMIOLOGY OF TRAMADOL

In many countries the Tramadol is used to treat moderate to severe pain or and it has a wide range of application in both acute like in postoperative, surgeries, trauma etc,. and chronic conditions like cancer and non cancer treatments, and also body pains like orthorites, hip and joints pains etc [29-31] .Tramadol is listed in many medical guidelines for pain treatment in now a days and it is mentioned as step two analgesic in the WHO guidelines for cancer pain reliefs[32] . On other hand , a meta analysis carried out on 2006 showed the efficacy of tramadol in the treatment of neuropathic pain treatments [33] .The tramadol manufacturer's records calculated the total amounted tramadol used on worldwide in the period from 1990 up to 2009 were calculated to be 11,758 million peoples were used [34-35] but, the tramadol is not listed in the WHO model as essential medicines.[36] However the tramadol is listed in several national essential medicines they are India , China, Egypt, USA, Philippines, Thailand, Myanmar, Sri lank, Bhutan ect.,. [37]

TRAMADOL METABOLISM ON BRAIN

Tramadol is a centrally acting analgesic agent with activity at μ-opioid, adrenergic and 5-hydroxy tryptamine (5-HT) receptors. Tramadol shows an analgesic effect as a result of dual mechanism of action, that is one as reuptake inhibitor of norepinephrine and serotonin and another as agonist of the μ-opioid receptor. Tramadol is marketed mixture of the (1R, 2R) and (1S,2S) enantiomers with a weak affinity for the μ-opioid receptor[38]. The ($1R^+$, $2R^+$) enantiomers are approximately four times more potent than the (1S, 2S) (-) enantiomers in terms of μ-opioid receptor affinity and 5-HT reuptake, where as the (1S, 2S) (-) enantiomers in responsible for noradrenalin reuptake effects. This type of action appears to produced a synergistic effect with (1R, 2R) (+) tramadol exhibiting tenfold higher analgesic activity than (1S, 2S) (-) tramadol[39].

Figure I
Schematic representation of tramadol metabolism in brain-hypothalamus [68]



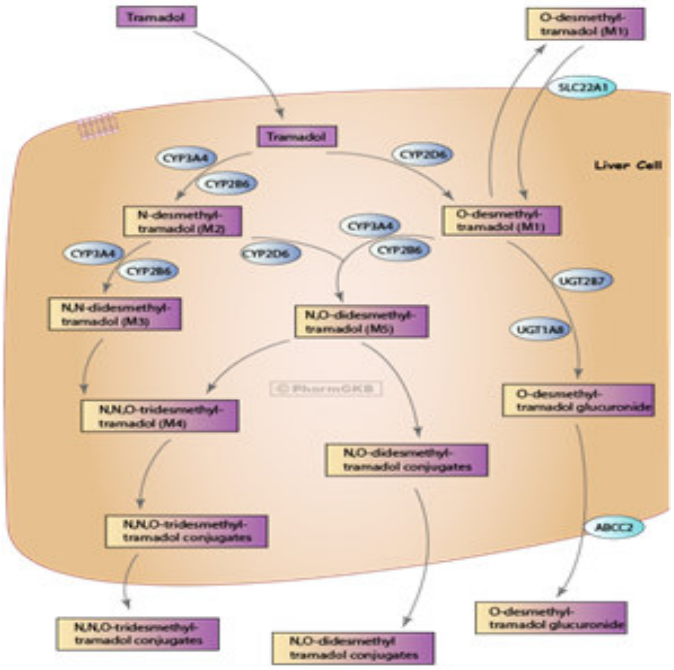
TRAMADOL METABOLISM ON LIVER AND KIDNEY

The central role of liver and kidney in drug metabolism predisposes them to toxic injury. Every drug has been associated with hepatotoxicity (toxic to the liver) almost certainly due to the role pivotal of the liver in drug metabolism. Hepatic metabolism is first and foremost, a mechanism that converts drugs and other compounds into products that are more easily and that usually have a lower pharmacologic activity than the portent compound. Thus metabolites may have higher activity and also greater toxicity than the original drugs, these type of metabolites are excreted from kidneys may also causes cellular damage and also leads to kidney dysfunction. In liver, the tramadol is converted to the o-desmethyl tramadol is itself convert as an active substance and 2 to 4 times more potent than normal tramadol, and then the biotransformation results of inactivated metabolites are excreted by kidneys[40] .The major metabolic pathway is appears to be N and O-demethylation and glucuronidation or sulfating in liver. One metabolite namely O- demethylation is denoted as M1, it is pharmacologically active in body. The formation of M1 is dependent on CYP2D6 and as such is subjected to inhibition. *In vitro* drug interaction studies in human liver microsomes indicated that inhibitors of CYP2D6 such as fluoxetiden and its metabolites norfluxetine inhibits the metabolism of tramadol to various degrees, that concomitation administration of these compounds could result in increases in tramadol concentration and decreased the M1 concentration. The concomitant use of serotonin reuptake inhibitors and MAO inhibitors may enhances the risk of adverse events like seizers and serotonin syndrome. Tramadol is eliminated primarily through metabolism by the liver and the metabolites are eliminated primarily by the kidneys. The metabolism of tramadol and M1 is reduced in patients with advance cirrhosis of liver [41] .The substrate of CYP3A4 and CYP2D6 enzymes are ability to inhibit or interact with tramadol. The Tramadol is metabolized via the CYP2D6 isoenzymes of cytochromes P450 to an active metabolite that will bind with μ-receptors. The

patients who metabolize drugs poorly via CYP2D6 may get less benefit from tramadol due to reduced formation of the active metabolite. Tramadol is metabolized by CYP3A4 so, its activities reduced by drugs which induce CYP3A4[42] .

Figure II

Schematic representation of tramadol metabolism in liver and kidney [69]

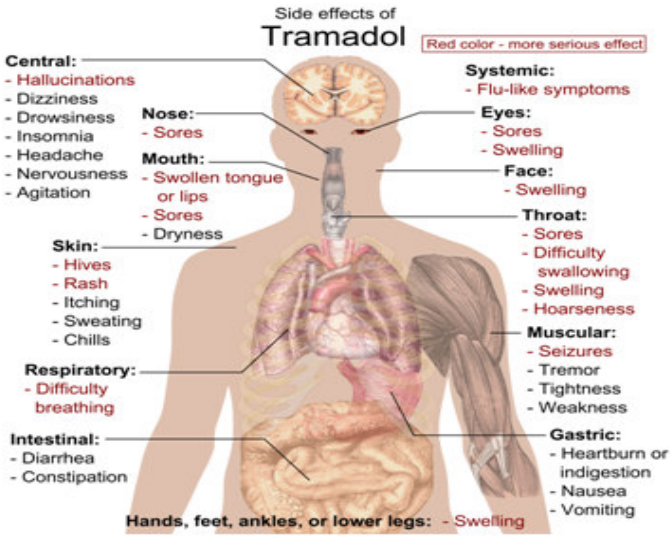


SIDE EFFECTS OF TRAMADOL

The most common adverse effects of tramadol include nausea, dizziness, dry mouth, indigestion, abdominal pain, vertigo, vomiting, constipation, drowsiness and headache.[43] .These large doses can causes overdose and that leads to increases the risk of adverse side effects, such as seizures. Other serious side effects of snorting tramadol include coma and breathing problems. Some symptomes of an overdose can include convulsions, trouble breathing, irregular breathing, pale skin and lips. Some patients may have decreased awareness or responsiveness to the point of loss of consciousness[6]. The Opioid pain reliever tramadol appears to be associated with an increased risk of hospitalization for Hypoglycemia, potentially fatal condition caused by low blood sugar. Its use is not advised for people deficient in CYP2D6 enzymes because it has crucial to the therapeutic effects of tamadol, by means of enabling tramadol metabolism to O- demethyltramadol[44] .Tramadol main adverse reaction are nausea, dizziness, sedation, dry mouth and sweating, respiratory depressions has been observed in small percentage of patients after intravenous and oral of tramadol administration[2-3] .Main side effects of tramadol: Red color denotes more serious effects, requiring immediate contact with health provider and rest of them are general side effects of tramadol.

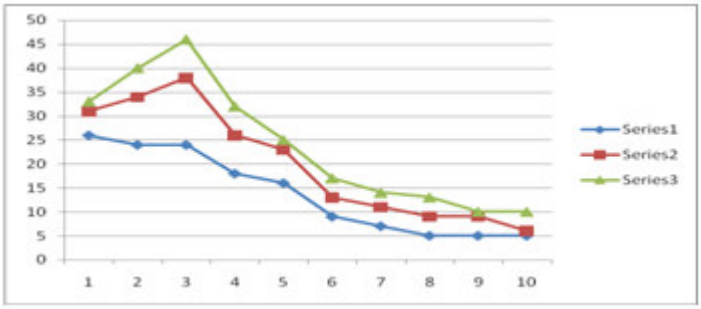
Figure III

Schematic representation of side effects of tramadol on humans[70]



The following graphical-I representation is cumulative incidence of adverse reactions for tramadol in Chronic trials of non-malignant pain percentage of patients with adverse reactions, the rows indicates that time periods of tramadol taken by the patients that is series 1 denotes for upto7days , series2 for up to 30 days and series 3 for up to 90days. the columns indicates that side effects of tramadol are listed as 1 dizziness, 2 nausea, 3 constipation, 4 headache,5 somnolence, 6 vomiting ,7 CNS stimulation- CNS Stimulation" is a composite of nervousness, anxiety, agitation, tremor, spasticity, euphoria, emotional liability and hallucinations, 8 dyspepsia,9 dry mouth,10 diarrhea[46].

Graph I



TRAMADOL EFFECT ON LIVER

After a single oral administration of 100mg dose, tramadol is rapidly absorbed the maximal serum concentration of the drug is archived within approximately 2 hours[15] .The mean bioavailability of tramadol after a single oral dose is 68% and is much higher than the bioavailability of morpine[16] .The tramadol bioavailability increases to approximately 90-100% during multiple oral administration, because due to the saturation of its effect first passes to the liver . The histopathology of liver after administration of opioids like tramadol, In liver microscopy of findings were revealed leucocytes sinusoidal permeation, congested blood vessels in the portal tract, degeneration of some hepatocytes and vacuolation of hepatocytes. Liver is responsible for the metabolism and extraction of tramadol[46-47]. Incubation of adult human hepatocytes with opioids, in therapeutic doses; for 24 hours is unlikely to produce irreversible damage to these cells in chemically defined culture conditions[48] .Experimental studies have also supported toxic effects of chronic use of opioids on liver and kidneys.

TRAMADOL EFFECT ON BRAIN

Tramadol a widely used opioid in recent years, is an effective analgesic agent for the treatment of moderately severe acute or chronic pain[40] .Its analgesic effects is seen in hypothalamus a result of its dual mechanism of action ,that is as reuptake inhibitor of norepinephrine and serotonin and agonist of mu- opioid receptor . Increasing serotonin and norepinephrine may also reduce inflammatory cytokines that are released by the brain in response to stress. The development of a potentially life threatening serotonin syndrome may occur with use of tramadol products, and also particularly with concomitant use of sertonergic drugs such as SSRIs, SNRIs ,TCAs ,MAOIs and with drugs that impair metabolism of serotonin and with drugs that impair metabolism of tramadol (CYP2D6 and CYP3A4 inhibitors).Tramadol products in excessive dose ,either alone or in combination with other CNS depressants, including alcohol ,are a major causes of drug related deaths[49] .Tramadol overdoses may induce seizures and ,increased Creatinine phosphokinase (CPK) and acute renal failure[50-51]. Seizures have been reported with tramadol at doses, ADRAC has received 66 reports involving convulsion and in 27 tramadol was the sole suspected drug. Tramadol should be avoid in patients with epilepsy and used cautiously in patients taking medicines which lower the threshold for seizures ,including tricycle antidepressants, selective serotonin reuptake inhibitor (SSRIs).The major tranquillizers, bupropion and opioids, Others serious adverse effects include hallucinations, hypertension and hypersensitivity reactions[42] .Many interactions with tramadol have been identified some involve changes in metabolism. Drug that inhibit CYP2D6 activity such as some SSRIs , Quinidine, phenothiaines and some proteases inhibitors will inhibit conversion to the active metabolite. Interactions may involve enhanced drug activity at receptor sites. A severs serotonin syndrome may occur when tramadol is combined with other drugs with also increase serotonin activity[52] .Such drugs include SSRIS, moclobemide and other monoamine oxidizes inhibitors, tricyclic antidepressants, sibutramine, . ADRAC has received 3 reports of serotonin syndrome in association with tramadol, usually in combination with other sertonergic drugs[53].

EFFECTS OF SEROTONIN SYNDROME

Serotonin is a chemical produced by the body that enables brain cells and other nervous system cells to communicate with one another. Small amount of serotonin in the brain is through to play a role in depression. High amount of serotonin leads to excessive nerve cell activity, causing a potentially deadly collection of symptoms known as serotonin syndrome. Serotonin syndrome is a potentially life threatening condition associated with increased sertonergic activity the central nervous system. This is seen in therapeutic medication use, inadvertent interactions between drugs[54]. Serotonin syndrome has been reported due to tramadol overdose[50, 55]. Serotonin syndrome has been observed in all age groups, including newborns and the elders. Serotonin is also

found in platelets where it promotes platelet aggregation[56] .Babies who die of sudden infant death syndrome may have low levels of serotonin, a brain chemicals involving in regulating breathing and other vital functions, a new study suggests, that activation of the central 5- hydroxyl trypt -amine A receptors (5-HT1A) in the nervous system can explain the clinical features of serotonin syndrome[57] .

SEROTONIN SYNDROME CAUSING IBS

Serotonin plays a key role in the process of digestion and gut functions. When not have enough serotonin this causes to IBS or irritable blow syndrome. This leads to a person is experiencing excessive diarrhea, abdominal pain, and flatulence. This is very common condition affecting million of people[58] and having altered on serotonin receptors causes two symptoms of IBS that is increased pain and depression. Serotonin plays a role in both the perception of pain and depression. This well bee shows that altered serotonin receptors are more likely than causes the average person to suffer from depression[59.]Serotonin is known to regulate motility and sensory events in the gut, thus changes in its concentration may contribute to the sensory motor function in IBS[60].

PROBIOTIC INFLUENCE IN MODERN WORLD

Metchnikoff is regarded as the grand father of modern probiotics. He made a landmark observation that regular consumption of lactic acid bacteria in fermented dairy products, definition of probiotics was adopted as “live microorganisms which when administered in adequate amounts confer a health benefit on the host” The probiotic can maintain their health and well being and potentially reduced their long term risks of diseases of the gastrointestinal, urogential tracts, kidney, respiratory tract and cardiovascular tract. Probiotics uses in treating infectious diseases[61].

THE ROLE OF PROBIOTICS IN DISEASE TREATMENT

The probiotics could not only improve the health and it’s also control pathogenic infections and help in real diseases treatment and management. The most critical points are in understanding of the disease behavior and its causative agents. (I) supplying our bodies with the products of the missed gene products, (ii) supplying our bodies with suitable alternative products, (iii) supplying our bodies with the final products of a complete pathway which will be the best choice and in the case that none of the defective pathway metabolic intermediates will be accumulated in our cells in the case of a single or multiple gene deficiency which could block a certain pathway, (iv) Probiotics will be the best support for us when we become old. It will reduce the load on our biological system and will enable us to do extra activity, particularly those related to improving our ability to utilize food. Probiotics in their different forms highlight how much such wonderful microbes could do to promote our health, protect us and ensure treatment or management of diseases. Perhaps the most critical point of Probiotics, is that they come in natural forms and perform natural safe activities[61].

Table II
This table is retrvied by the following of Amara[71]

Diseases name	Strains	References
Food allergies	Escherichia coli	*Loadinous zadniova et al.(2003)*
Immunity	*Bacillus circulans PB7 ,Lactobacilliusplantraum* 12028	*Bandyaopadhyay, Dasmohapatra(2009)and Cammarota etal.,(2009)*
Antibiotic effect removal	*Bifidobacterium strains, Lactobacillius casei, lactobacillius breis KB290*	*Botes etal., (2008), Fuao etal.,(2009)*
Gastro enteritis therapeutics	*Lacto bacillus casei*	*Yamada etal.,(2009)*
Intestinal hypermeability	*Lactobacilius plantarum 299(CP299)*	*Kennedy etal.,(2000)*
Urinary tract infection	*Lactobacillius rhamousus GR1, Lactobacillius reuteri RC-14*	*Anukam etal.,(2009)*
Intestinal dysbiosis	*Lactobacillius johnsonii La1*	*Hawrelak(2003), Silva etal.,(1987)*
Irritabble blowel syndrome	*Bifidobacterium infantis 35624,Escherichia coliDSM17252*	*Brenner and Chery (2009),Enck et al.,(2009), Whorwell etal.,(2006)*
Traveler s diarrhea	*Lactobacillius plantarum , Lactobacillius casei DN114001*	*Abernathy (2002),Giralt etal.,(2008)*
Crohns diseases	*Escherichia coli strain nissle1917*	*Boudeau etal., (2003)*
Prevention of Colon Cancer	*Entero coccus faecium M74, Lacto acid bacteria*	*Mego etal.,(2005)and Thiraubunzyanon et al.,(2009)*
Peptic ulcer disease	*Lactobacillius acid phulus*	*Larovenko etal.,(2005)*
Hyper cholestrolemia and Cardio vascular disease	*Enterococcus facecium M74, Lactobacillius plantarumPH04*	*Hilvak et al.,(2005)’ Nguyen et al,(2007)*

PROBIOTICS INFLUENCE ON TREATMENT FOR IBS

Probiotics microbes that provide benefit to their host and also they are given in adequate amounts support gut health by preventing harmful microbes from multiplying in the gut by reducing inflammation in the body. Because the traditional treatments have failed to provide consistent relief to IBS sufferers, some probiotics can benefit to many people with this condition. There are quality evidence for the empiric use of probiotics in IBS.

The randomized controlled trials that have been performed are typically small and are limited by publication bias, previous trails have typically included strains of *Lactobacillus* and *Bifidobacterium* species and along with different probiotic combinations such as VSL#3 and SCM-III etc.,

Table II

Physiological benefits of Probiotics on Irritable Bowel Syndrome as mentioned the following.

Name and combinations of Probiotics	Treatment on following weeks	Treatment and number of patients	Probiotics improvement and functions
VSL#3	8	48	VSL#3, the decrease in bloating was borderline significant, but there was no effect on gastrointestinal transit or other individual symptoms of IBS[78].
SCM-III	12	68	Improvement in overall efficacy in 80% of patients at 12 weeks (P<.01), as well as improvement in bloating, abdominal pain, and bowel habits at different time intervals throughout the 12-week period[74].
Lactobacillus and *Bifidobacterium* Species	2 & 4	70	Both treatment cohorts showed significant decreases in abdominal pain and severity scores at 2 and 4 weeks; however, the major limitation of this study[75].
Lactobacillus salivarius UCC4331, *B. infantis* 35624,	8	77	Assessed for the cardinal symptoms of IBS (abdominal pain/ discomfort, novceness, bloating/distension, and difficulty of bowel movement), quality of life, and blood sampling for interleukin-10 and -12[76].
Bifidobacterium B. infantis 35624	4	362	A significant decrease in abdominal pain/discomfort (the primary endpoint) at 4 weeks, along with improvement in the secondary endpoints of bloating/distension, sensation of incomplete evacuation, passage of gas, straining, bowel habit satisfaction, and a reduction in composite symptom score[77].
Bifidobacterium animalis (*regula ris*) DN-173 010	6	274	The health-related quality-of-life discomfort score improved, as well as bloating symptoms (both of which were primary end points), and there was an increase in stool frequency in patients with fewer than 3 stools per week[73].
Lactobacillus species		200	No significant benefit in alleviating IBS symptoms in 200 patients[79,80].

The trials involving by using *Bifidobacterium* were included in this meta analysis and showed a trend toward improving IBS symptoms in 379 patients, The efficiency of an encapsulate probiotic *Bifido bacterium infantis* 35624 in women with irritable bowel syndrome. The Brenner and coworkers conducts a Meta analysis in 2009 that included 6 randomized controlled trials evaluating the efficiency, safety and tolerability of probiotics in IBS patients. The *B. infantis* 35624 was the only probiotic that showed any significant beneficial effect in the symptom in relief of IBS either as a single agent or in combination with other probiotics[81].

DISCUSSION

The tramadol is an opioid to use as pain relief in recent days; it shows effective work on pain relieving within one hour by showing two mechanisms. Firstly it binds to the μ-opioid receptor and secondly it inhibits the reuptake of Serotonin and Nor-epinephrine. [5] There are controversies about the seizure inducing effect of tramadol. Some studies have documented that tramadol can only provoke seizures if used in overdoses in patients with existing seizure disorder or when co-administered with antidepressants, alcohol, etc.,.[62-63] .Because of this mechanism the excessive serotonin release in the body and that leads to the serotonin syndrome. Small amount of serotonin in the brain is thought to play a role in depression. High amount of serotonin leads to excessive nerve cell activity, causing a potentially deadly collection of symptoms known as serotonin syndrome[54] among the side effects of serotonin syndrome, sometimes lethal and causes irritable blows and diarrhea to humans and also animals. By using the probiotics, which containing live are attenuated bacteria, or bacterial products that ingested may have beneficial effects to the patients health by altering the gastrointestinal flora [64] .It is hypothesized that inflammation or disproportion of the gastrointestinal bacterial flora, may play a part in the good bacteria of gastrointestinal tract can improve the gut flora and that can promote the human health [65] .Data presented in the above table, there is the evidence to suggest that certain strains of probiotics may stimulated an anti inflammatory response or improve visceral hypersensitivity that can theoretically lead to an improvement in symptoms of IBS [66] .According to the National Digestive Diseases Information Clearinghouse (NDDIC) approximately one in five adults living in the U.S. experience symptoms of irritable bowel syndrome (IBS), which makes this condition one of the most commonly diagnosed as IBS disorders [67] .Some doctors have theorized that IBS is caused by a colon, or large intestine, that is particularly sensitive and reactive to certain foods and stress. The immune system, which fights infection, may also be involved. An increased presence of “good” bacteria can assist the body's immune system in fighting infection and illness. Because *Bifidobacterium infantis* is a beneficial bacterium, also known as a probiotic, it could be theorized that increasing the amount of *Bifidobacterium infantis* may help to build the body's natural defense mechanisms. In this way, an increase in the amount of *Bifidobacterium infantis* in the large intestine may help relieve the symptoms of IBS.

CONCLUSION

The Tramadol is a generally used as a pain killer but in some cases it causes many adverse effects on regular use and high doses. The changes in dosages of Tramadol causes nausea, dizziness, dry mouth, indigestion, abdominal pain, vertigo, vomiting, constipation, drowsiness and headache, recently Serotonin syndrome has also been reported due to Tramadol overdose. The long term or regular users like chronic patients with cancer and arthritis are facing the above problems. Now a day’s using probiotic micro organisms we can maintain their health and well being

by potentially reducing their long term risks of gastrointestinal, urogential tracts, kidney, respiratory tract and cardiovascular tract diseases. Many trials using *Bifidobacterium infantis* 35624 were included in this review and emphasized toward improving IBS symptoms which are caused by serotonin imbalance with Tramadol in 379 patients.

CONFLICT OF INTEREST

Conflict of interest declared none.

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