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REVIEW ARTICLE

Narcotic bowel syndrome

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Abstract

Among opioid bowel dysfunction, narcotic bowel syndrome (NBS) is one of the most common abnormality. Opioid bowel syndrome can be distinguished from NBS by frequent or chronic stomach pain that is increased by using excessive dose of opioids. NBS is not much known but is increasing day by day due to excessive use of narcotics for the treatment of chronic painful disorders. It mostly occurs in those patients whose history is not related to GIT disorders. Recent studies propose three accepted mechanisms that lead to increase in pain. First is bimodal opioids regulation system, second one is counter regulated mechanism, third is glial cell activation. X-rays, CTs, MRIs, ultrasounds, colonoscopies, endoscopies, and multiple blood tests are common approaches used to diagnose NBS. Its treatment involves early diagnosis of this syndrome, doctor patient relationship, gradually discontinuing of narcotics according to specific schedule of withdrawal and taking the medications which lessen the effect of abandonment.

Keywords

Opioid bowel dysfunction
Narcotic bowel syndrome
Diagnosis
Symptoms
Treatment

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Narcotic bowel syndrome: Among opioid bowel dysfunction, narcotic bowel syndrome is one of the common condition (Locke et al., 2008). It is most commonly considered as constipation; but its other symptoms include bloating, reflux, nausea, stomach pain and ileus (Kurz and Sessler, 2003; Bell et al., 2009; Panchal et al., 2007; Furlan et al., 2006; Pappagallo, 2001; Rogers and Cerda, 1989; Mehendale and Yuan, 2006). Opoid bowel syndrome can be distinguished from NBS by frequent or chronic stomach pain that is increased by using excessive dose of opioids.

Introduction

Motility of gastrointestinal tract is affected by opiates (Pappagallo, 2001; Mehendale and Yuan, 2006). These effects are called opioids bowel dysfunction and describes as constipation, nausea, bloating and pain (Kurz and Sessler, 2003; Seiler et al., 2005). When major symptom is pain then this condition is called NBS. Its diagnostic features include increased abdominal pain so the dose of narcotics is increased in order to relief the pain (Grunkemeier et al., 2007). In United States, it was reported about 20 years ago and in china about 10 years ago (Chen et al., 1995).

Clinical presentation of narcotic bowel syndrome: Abdominal pain which is Chronic and frequently occurring is experienced by the patient who is treated with narcotics. Chronic abdominal pain becomes severe when effect of narcotic decreases (Grunkemeier et al., 2007). Narcotic is helpful in the start but with the passage of time when pain free period become shorter and tachyphylaxis occur this will lead to increased doses of narcotic. This increased dose further causes many adverse drug reactions on pain sensation and delay the motility of GIT resulting in development of narcotic bowel syndrome. This syndrome is not related to any medical condition. It is observed in many disorders. Narcotic bowel syndrome is also observed in

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patients when high dose of IV narcotic is used postoperatively. Narcotic bowel syndrome (NBS) can occur in GI (gastrointestinal) disorders. General approach to the treatment of NBS is slowly withdrawing of narcotics. But there is subsequent increase in the use of opioid drugs over time (Table 1). In this article, we will discuss about the clinical features epidemiology, diagnosis, treatment and other characteristics of narcotic bowel syndrome (NBS).

Table 1: percent change in the use of opioid drugs

	1997	2006	% change
Morphine	5,922,872	17,507,148	195.6
Hydrocodone	8,669,311	29,856,368	244.4
Oxycodone	4,449,562	37,033,986	732.3
Methadone	518,737	6,621,687	1176.5

Functional pain disorders particularly vulnerable to treatment with narcotics: Chronic abdominal pain is the key feature that is associated with narcotic bowel syndrome. Almost 43% of patients, who are admitted to hospital with this pain, are discharged without any description of this pain.

Epidemiology of narcotic bowel syndrome: This syndrome is under recognized and may be becoming more widespread. According to study of NIH 110 million Americans suffer from chronic abdominal pain. Cost of untreated or under treated pain is estimated to over 60 billion annually. Prevalence of NBS includes a survey of 2,913 patients out of which 117 were taking narcotics. Half had some form of abdominal pain while 5 met criteria for NBS (Locke et al., 2009; Tuteja et al., 2010). Newly the prevalence of NBS is determined. It's result includes the fact that only 1 person among 20 is at the risk of having NBS (Locke et al., 2009; Tuteja et al., 2010).

Causes: NBS is a chronic abdominal pain and it is usually caused when narcotics are used in moderate to high dose for more than two weeks. Adverse effects of morphine and opioids includes GIT symptoms such as biliary and GIT motility is decreased. It also causes constipation, nausea and vomiting (Crain and Shen, 1990). There are two types of opioid receptors one is G coupled receptors(GI/GO) and second one is SS-coupled receptors. GI/GO coupled receptors produce analgesia and GS coupled receptors cause anti analgesic effect. So, when tolerance against opioid analgesia start to produce with the increase in time then due to GS Coupled receptors anti analgesic effect start to produce that cause hyperalgesia. So, this hyperalgesia may be considered as the cause of NBS (Rogers and Cerda, 1989; Grunkemeier et al., 2007; Gintzler and Chakrabarti, 2000).

Physiological mechanism for pathological pain facilitation: Increase in pain is related to long term use of narcotics. Recent studies propose three accepted mechanisms that lead to increase in pain. First is bimodal opioids regulation system, second one is counter regulated mechanism and third is glial cell activation (Wood and Galligan, 2004).

Bimodal modulation system of opioids: When opioid receptors are activated, afferent signaling is reduced. Research conducted in mice showed that it not only produces analgesia but also hyperalgesia because of Gs protein activation. Therefore, the action potential is modulated in sensory neurons. Low concentration of opioids (1-10ηm) in dorsal horn prolongs the action potentials which leads to excitatory effects and enhances the release of neurotransmitters. But higher concentration such as ~1μm decreases action potential and cause the inhibition of release of neurotransmitter. These Opioids activate GI/GO protein, cause the inhibition of neurotransmission and produce analgesia. Activation of Gs protein, cause the activation of neurotransmission and produce excitation, anti-analgesia and Tolerance (Crain and Shen, 2000). The excitatory effects of opioids are masked by their inhibitory effects when they are used in excessive doses. Low dose opioids activates excitatory (Gs) mechanism and masks inhibitory (GI/GO) mechanism and produce hyperalgesia (Crain and Shen, 1992). High dose of opioids activates inhibitory mechanism and masks excitatory mechanism and produce analgesia. Excessive usage of opioids unmasks the excitatory effects and cause hyperalgesia (Crain and Shen, 2000; Crain and Shen, 1992).

Pain facilitation through CCK and dynorphin activation: Periaqueductal gray, Rostral Ventral Medulla (RVM) prefrontal cortex, and cingulate modulate the incoming signals of pain within the spinal cord. All these specific regions produce analgesia by causing inhibitory effect on descending routes (Ossipov et al., 2005; Drossman et al., 2009). The RVM also stimulate descending routes through dorsolateral funiculus (DVF) and increases nociceptive input in spinal cord (Porreca et al., 2002). These responses have been found to occur by 'on' and 'off' cells activation or inactivation in RVM (Fields, 1992). In addition release of dynorphin that is an endogenous opiate at spinal cord level, produce pain conditions by increasing the excitatory effect of afferent neurons which are also seen in peripheral nerve injury and chronic inflammation (Vanderah et al., 2000; Bian et al., 1999; King et al., 2005). Release of large doses of morphine cause the sensitization of sensory neurotransmission which leads to the paradoxical pronociception (Larcher et al., 1998). Systemic injection of morphine/heroine after Anti-nociceptive effects that have damaged, can produce a rebound hyperalgesia (Larcher et al., 1998). Furthermore, CCK and CCK receptors have similar mechanism of pain (Ghilardi et al., 1992; Heinricher et al., 2001; Kaplan and Fields, 1991; Song and Zhao, 2001; Nichols et al., 1997).

Effects produced by activation of Glial cells on pain: In spinal cord glial cells have intensifying pathological pain (Watkins et al., 2001). Specific glial cells such as astrocytes and microglia present in dorsal horn produce hyperalgesia upon activation by inflammation or any injury (Watkins et al., 2005). Noxious substances activate the glial cells which produces neuropathic pain its inhibition decreased the pain. Neuromodulators and neurotransmitters produced IL-6, TNF and IL-1 which increases pain intensification and pain transmission (Watkins et al., 2001; Watkins et al., 2005).

A) When glial cells become activated they release nitric oxide, prostaglandins different growth factors and stimulate spinal neurons. b) Activation of glial cells causes the release of substances which increase the discharge of pain transmitters. c) Activation of glial cells causes the release of neuromodulators and pain neurotransmitters (glutamate, nitric oxide, ATP, prostaglandins, substance –P and calcitonin). So the nociceptive activity of glial cells is preserved (Watkins et al., 2001). d) Neuron-to-glia chemokine (fractalkine) also activates glial cells. This (fractalkine) chemokine is present on extracellular surface of spinal neurons (Watkins et al., 2005). These neurons upon activation release this bound chemokine, which activates nearly present glia cells. Fractalkine also stimulate the release of pro-inflammatory cytokines (Watkins et al., 2001; Chapman et al., 2000; Johnston et al., 2004; Saab et al., 2006; Rattan and Tejwani, 1997).

Symptoms: Opioids causes an effect on GIT (gastrointestinal) motility (Table 2). It is known as gastrointestinal dysfunction or opioid bowel. Symptoms of this disease includes constipation, nausea, bloating, weight loss, pain sometimes, potentiating of abdominal distention and visceral pain (Grunkemeier et al., 2007). When the major symptom is pain then it is known as narcotic bowel syndrome. One of the symptoms of NBS is inconsistent increase of abdominal pain in spite of constant or increasing dosages of prescribed narcotics to relieve pain (Sandgren et al., 1984; Geoerger et al., 2001; Fogel and Perlman, 2007).

Diagnosis: In NBS upon X-rays, their may be the signs of intestinal obstruction which may be due to pseudo-obstruction or A-dynamic ileus fecal material may also be observed in X-rays. Lab tests such as lipase test, urinalysis, blood count test and amylase are normal. Patients who are admitted in hospital with severe abdominal pain may not have any diagnosis after many interventions (MRIs, endoscopies, multiple blood tests, CTs and colonoscopies) (Rogers and Cerda, 1989; Sandgren et al., 1984; Wong et al., 1994; Kurlander and Drossman, 2014).

Identification features of NBS: Symptoms of NBS and GI disorder are different from each other. Excessive use of opioids cause abdominal pain which is the distinctive feature of NBS (Pappagallo, 2001; Rogers and Cerda, 1989; Grunkemeier et al., 2007).

How narcotic bowel syndrome can be treated?: Antidepressants are mostly preferred for this treatment. Antidepressants are used for the treatment of severe abdominal pain. After using antidepressants, narcotics and medications are discontinued by which withdrawal effects such as nausea, anxiety, restless, abdominal pain, aching of muscles and vomiting are reduced. Doctor can also help to reduce the withdrawal effects so the patients can also be satisfied by visiting the psychologist. Patients should go for their checkup regularly after withdrawal effects of narcotics. Once narcotics use is off then during the period of withdrawal despite of discomfort, most of the patients feel better and their need of narcotics will be no longer (Grunkemeier et al., 2007).

Patients, NBS and pharmacist: Doctors, who do not have any knowledge about this disease, try to relief the pain by using excessive doses of opioids which cause the increase in pain (Grunkemeier et al., 2007; Drossman, 2009). NSAIDs such as topical, oral, selective and non-selective COX-2 agents, warfarin, aspirin and PPIs (proton pump inhibitors) or H2-RAs (***H2*** receptor agonists) are also used. It is thought that some patients who are suffering from gastric pain or NBS can be treated by H2-RAs and PPIs to relief the pain. Medicines which suppress the acidity of stomach are safe for this treatment (Ali et al., 2009; Thomson et al., 2010).

Bio psychosocial approach for treatment of NBS

Physician-patient relationship: For the successful treatment, an effective therapeutic relationship is necessary. However, relationship with patients of NBS may be at risk and can lead to aggressive behavior of patient whenever doctor asks about the plans to withdraw narcotics. First of all the doctor should

Table 2: Distinctive characteristics of some GI Disorder

IBS	Gastritis	Chronic Pancreatitis	NBS
Flatulence, diarrhea, constipation, mucous in stool, abdominal pain and cramping.	Nausea and Vomiting, burning pain in upper abdomen, weight loss, loss of appetite, bloating, belching.	Intermittent/persistent mid abdominal pain, weight loss, foul-smelling, greasy stools.	Chronic/intermittent ‘’cotikey’’ abdominal pain, pain aggravated by eating, bloating, constipation, N/V, abdominal distention, increased pain with increased opioids use.

N/V: Nausea and Vomiting; NBS: Narcotic Bowel Syndrome; IBS: Irritable Bowel Syndrome; GI: gastrointestinal.

empathasize the patient for the treatment. (Stewart et al., 1999). Then doctor should provide informational care to the patient (Stewart et al., 1999; Clouse et al., 2006). Then the doctor should wait for the response of the patient that is if the patient is agree to undergo the treatment or not. Doctor should answer to all the questions of the patient regarding the treatment. He should also provide appropriate responses. The treatment plan should also be discussed with family member or care taker of patient for the purpose of understanding the treatment process and support the patient during difficult times. Emotional support should be provided to the patient and the doctor should be available to the patient all the time (Grunkemeier et al., 2007).

Management of NBS patient: Patients suffering from NBS and using narcotics should withdraw narcotics slowly but completely. Doctor patient communication should be essential and effective. Advantages of narcotics withdrawal should be described completely. This should also include the pathophysiology of this disease. Non-narcotics such as SNRIs and TCAs can be used for the relief of pain. A proper schedule is made for the withdrawal of narcotics and the doctor should be available for those patients who take excessive narcotics. Verbal reassurance is also necessary. The therapy leads to completion in those patients who are motivated if all the issues are addressed properly. For the progress of detoxification process regular meetings with the patient are important. Willpower of patient has a central role in the success of this process. Before starting the treatment protocols, family support is beneficial for the patient (Longstreth and Drossman, 2005).

Pain management: For the management of psychological co-morbidities and for quick and long term pain relief the tricyclic antidepressants (desipramine) or serotonin reuptake inhibitor (duloxetine) must be given. This treatment can be started with low dose which would be increased during the duration of detoxification therapy and after that. Possibly this treatment should begin at least a week before the detoxification therapy (before hospitalization) and may remained in use in order to manage the patient after discharge.

(a). Use of antihistamines and anti cholinergic can cause orthostasis and constipation. TCA (tricyclic antidepressants), secondary amines have advantage over tertiary amines because they have less side effects. Inorder to produce the analgesic effect, 50 to 75mg can be beneficial. It is the advantage of serotonin reuptake inhibitor e.g. duloxetine to relief the pain through noradrenergic action, and it also does not have any side effect with respect of bowel. Since it is found that there are very less benefit of selective serotonin reuptake inhibitors (e.g. paroxetine, fluoxetine, citalopram) in the treatment of pain, they are generally not suggested (Maizels and McCarberg 2005; Brannan et al., 2005; Grover and Drossman 2009).

(b). In case of nausea mirtazepine can be given in conjugation with serotonin reuptake inhibitor or TCA.

The single dose of quetiapine (Seroquel; 25-100 mg) can be given at night for treatment of pain. For the treatment of sleep problems, anxiety and also to relief the pain, this is a very useful medication and can be used after discharge from hospital (Drossman, 2009; Grover and Drossman, 2009).

Constipation: Solution of PEG (polyethylene glycol) is used for the treatment of constipation and its dose includes 1-3 glasses per day. In case of severe constipation a complete flush is recommended before the daily dosing. Alternate option of treatment is methylnaltrexone (Relistor) and it is used when constipation is very severe and there is no response of PEG solution. Osmotic preparations which contain Mg and phosphates or stimulant laxatives are not given because they disturb electrolyte balance. N-methylnaltrexone is under research, it may relieve from opioid induced constipation and ileus. However, it blocks the GI (gastro intestinal) sites of action and preserve the central analgesic effects (Quigley et al., 2006; Camilleri and Alvimopan 2005; Paulson et al., 2005; Reimer et al., 2008; Lembo,2006).

To reduce anxiety: For the treatment of anxiety benzodiazepine should be given on 1st day. Another choice besides this is lorazepam 1mg orally after every 6 hours and if necessary then IV can be given. The dose can be decreased (in case of unnecessary sedative effect) or increased (in case of uncontrollable anxiety) suitably. At the end of narcotic tapering this benzodiazepine should also be stopped (Drossman et al., 2003; Jackson et al., 2000; Thiwan and Drossman, 2006).

Psychological treatments: Many studies have done for the treatment of pain. Regular checkup with psychologist can be very helpful for the patient. Psychologist use non pharmacological methods in order to manage the symptoms (distraction, focused attention and relaxation). Psychologist also helps in solving the problems of patients that may account towards the improvement of understanding the symptoms. Eventually, psychologists sometimes prove to be helpful for the patient in formulating strategies which explain the effect of NBS on relationship employment and associated problems. There are a few patients those may be feared by the suggestion of getting help from a psychologist. It should be explained to them that this suggestion does not mean that they have a mental disorder or narcotic addiction. Besides, it is the part of a broad technique for the management of their situation and is developed for the reduction of their negative symptoms (Lackner et al., 2004).

Table 3: Narcotic bowel syndrome treatment:

Class	Drugs	Doses
Anxiolytic	Clonazepam	Start with 0.25 mg q 8 hr
	Lorazepam	Start with 1mg q 6 hr
Spasmolytic	Hyoscyamine	Sublingual 0.25mg q4 hr
Anti-depressent	TCA-Desipramine OR Nor-Tryptyline	5=mg qhs then titrated to 150 mg qhs
	SSRTs-Duloxitine	30 mg qd then titrated to 60 mg qd
	Venlafaxine	37.5 mg qd then titrated to 225 mg qd
Sympatholytic	Clonidine	Start with 0.1-0.2 mg q4 hr
Spasmolytic	Hyoscyamine	0.25mg sublingual q 4hrs prn

Narcotic bowel syndrome treatment: At the start of treatment Benzodiazepines is prescribed for many days and then dose must be reduced when withdrawal is completed (Table 3). In hospital when there is a rapid withdrawal then initially patients clinical condition is rapidly evaluated after every hour in order to check the urinary retention, cardiac arrhythmias, syncope or orthostatic hypotension (Grunkemeier et al., 2007).

Issues interfering with a successful result: During detoxification, main obstacles which affect the outcomes are:

1. Lack of communication: Poor patient-physician interaction or communication- when physician is not able to validate pain, not able to explain the benefits of treatment or have lack of sympathy.
2. Initial dose is very low on first day (Opioid-equivalence conversion must accurate).
3. An uninterested patient needs better counseling from physician.
4. Rapid reduction in dose.
5. Not following the schedule for narcotic administration.
6. Not able to identifying the root causes: withdrawal symptoms and anxiety.

Patient acceptance to narcotics is very important for success of treatment (Joishy and Walsh 1998; Pereira et al., 2001). Program must stop in case if patient is not interested in the communication with physician. Time must be taken to confer the outcomes of prior treatment before discussing value of change. To increase the motivation of the patient and for the success of treatment patient must b given the chances of open discussion with physician.

In case if patient does not know the withdrawal, procedure and patient seems that drug is not working he may abruptly discontinue the narcotic OR taper the narcotic. So, in this case the motivation of the patient should be increased and physician must provide informational care to the patient. Patient may consult with many doctors in order to find the best one. This is due to lack of proper communication among doctor and the patient. So, the patient may consult another doctor who again starts to treat the patient with narcotics. So therefore, it is necessary to provide informational care to the patient about withdrawal program (DiClemente et al., 1985).

Conclusions: NBS occurs in patients who are suffering from severe pain and many GIT disorders due to excessive use of narcotics. Diagnosis of this disease along with the symptoms is discussed here.

In this article, we have described the clinical features, pathophysiology, treatment protocol and diagnostic features for NBS. Early diagnosis of the disease along with its treatment protocols can lead to better satisfaction of patient and can help the physician as well as health care system. However, the treatment also depends upon doctor patient relationship.

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