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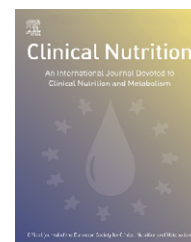


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## REVIEW

# Standardized concept for the treatment of gastrointestinal dysmotility in critically ill patients—Current status and future options

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**Summary**

Inhibition of gastrointestinal motility is a major problem in critically ill patients. Motor stasis gives rise to subsequent complications including intolerance to enteral feeding, enhanced permeability of the atrophic intestinal mucosa and conditions as severe as systemic inflammatory response syndrome, sepsis and multiple organ failure. Although the diagnosis of motility disturbances in critically ill patients is difficult, the type and site of the disturbance are important to consider in the analysis of the condition and in the choice of therapeutic approach. The pharmacological treatment of impaired gastrointestinal motility is difficult to handle for the clinician, because the underlying mechanisms are complex and not fully understood and the availability of pharmacological treatment options is limited. In addition, there is a lack of controlled studies on which to build an evidence-based treatment concept for critically ill patients. Notwithstanding this situation, there has been remarkable progress in the understanding of the integrated regulation of gastrointestinal motility in health and disease. These advances, which largely relate to the organization of the enteric nervous system and its signaling mechanisms, enable the intensivist to develop a standardized concept for the use of prokinetic agents in the treatment of impaired gastrointestinal motility in critically ill patients.

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## Introduction

Although long neglected, dysmotility of the gastrointestinal tract is a major complication in critically ill patients in intensive care units (ICUs).<sup>1,2</sup> In most cases this dysmotility manifests itself as inhibition of propulsive gastrointestinal motility, and rarely as hypermotility accompanied by diarrhoea or emesis. Inhibition of motility may extend over the entire gastrointestinal tract or affect only regional functions of the gut, such as gastric emptying and/or peristalsis in the small intestine, motility of the colon or evacuation of the sigmoid and rectum.

## Gastrointestinal dysmotility: symptoms, reasons and pathophysiology

Approximately half of all mechanically ventilated patients have been shown to exhibit antral hypomotility, decreased gastric emptying and diminished migrating motor complexes.<sup>1-4</sup> Impaired gastrointestinal motility leads to a multitude of subsequent complications in critically ill patients, with intolerance of enteral feeding as one of great importance.<sup>1,2,5</sup> Enteral nutrition is one of the major factors that determines the outcome and length of stay of critically ill patients in the ICU.<sup>6-8</sup> Feeding the patients by the oral route protects the intestinal mucosa from atrophy

and thus prevents the development of increased mucosal permeability for endoluminal mediators and bacteria. Translocation of microbes and transition of mediators into the systemic circulation can initiate the development of a systemic inflammatory response syndrome (SIRS) and sepsis, and in the worst case may lead to multiple organ failure.<sup>9,10</sup> Further complications due to intolerance of intragastric enteral nutrition in critically ill patients are manifold and well known and have been reviewed in detail elsewhere.<sup>11,12</sup>

There are numerous processes that can account for the disturbed gastrointestinal motility in critically ill patients, such as abdominal surgery, head or spinal injuries, SIRS, sepsis, systemic or regional hypoperfusion and hypoxaemia, imbalance of acid-base, glucose and electrolytes, and fluid status.<sup>5,13–17</sup> Many mediators, such as 5-hydroxytryptamine (5-HT; serotonin), catecholamines, calcitonin-gene-related peptide and nitric oxide (NO), which are physiologically involved in complex regulatory pathways, can depress propulsive motility when released in excess and/or under pathological conditions. Substances released in response to stress, e.g. corticotropin-releasing factor (CRF) and catecholamines, or as a consequence of surgical manipulation of the intestines impair gastric emptying and disturb intestinal motility.<sup>16,18</sup> In addition, a broad spectrum of drugs which are indispensable for the treatment of critically ill patient causes or augments gastrointestinal dysmotility. These drugs include anesthetics and sedatives, opioids, catecholamines, and alpha-adrenoceptor agonists such as clonidine and dexmedetomidine.<sup>12,19–24</sup>

In the evaluation of the clinical relevance of disturbed motility it is important to keep in mind that the physiological stool frequency varies widely from one or two evacuations per day to one evacuation every third or fourth day.<sup>25–28</sup> Usually the patient's normal bowel habits are not known to the intensivist. Furthermore, it makes a difference whether a patient regularly uses laxatives or suffers from concomitant internal and neurological diseases, such as neuropathy, diabetes mellitus, functional gastrointestinal motility disorders, Parkinson's disease, familial and non-familial visceral myopathies, muscular dystrophies, amyloidosis, thyroid disease or collagen disease, which by themselves impair gastrointestinal motility.<sup>29–33</sup> Independent of pre-existing diseases, gastrointestinal motility is also affected by the consumption of alcohol and nicotine, as high doses of alcohol delay gastric emptying and small bowel motility, whereas nicotine stimulates evacuation of the sigmoid and rectum.<sup>34</sup> Chronic abuse of alcohol and nicotine promotes the development of peripheral neuropathies, with an inhibitory effect on gastric emptying.

An unsolved problem in every-day practice is the measurement and evaluation of impaired gastrointestinal motility with non-invasive or minimally invasive techniques that do not compromise the critically ill patient, are cost-effective and generate reliable information. The quantity of gastric reflux collected over a defined period of time or of gastric aspirates collected at fixed intervals via a nasogastric tube enables the intensivist to estimate the quantity of gastric juice passing through the pyloric sphincter, given that the daily gastric secretion is assumed to be about 1 l. Hence a gastric reflux volume of 500 ml over 24 h indicates impaired but not completely inhibited gastric emptying.

Defaecation is a rough but reliable indicator of propulsive function of the sigmoid and/or rectum. However, non-invasive monitoring of propulsive peristalsis or of atonia in the small intestine and colon remains a great challenge. Auscultation of bowel sounds is often practiced, but difficult to interpret. What does it really mean if no bowel sounds are audible or, as a corollary, do bowel sounds indicate coordinated propulsive peristalsis? Current methods used to record gastrointestinal motility disturbances in humans are listed in Table 1.

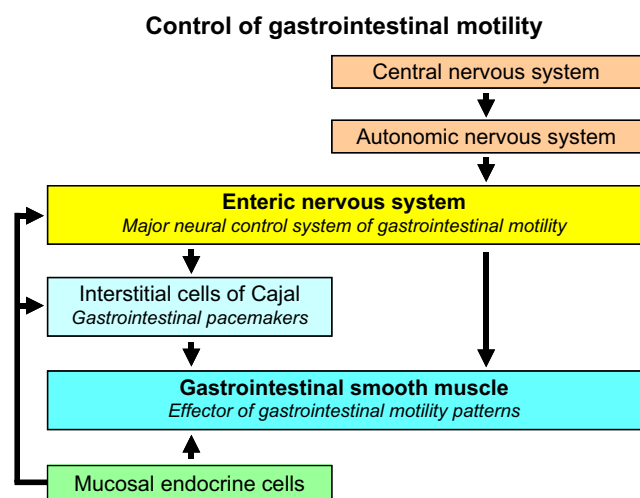
The pharmacological treatment of impaired gastrointestinal motility in critically ill patients is difficult to handle for the clinician, because the mechanisms underlying dysmotility are usually complex, the pre-existing patient's characteristics in terms of gastrointestinal function are diverse and the availability of pharmacological tools is limited. Nevertheless, the last decade has seen remarkable progress in the understanding of the integrated regulation of gastrointestinal motility in health and disease. These advances relate to the organization of the enteric nervous system and its signalling mechanisms that control gastrointestinal motility,<sup>35–38</sup> the pathophysiology and characteristics of gastrointestinal diseases associated with compromised motility or of conditions such as postoperative ileus that secondarily disturb propulsive transport,<sup>15,39–41</sup> and the pharmacological treatment options.<sup>42–44</sup>

The physiological regulation of gastrointestinal motility depends primarily on the functionality of integrated reflex circuits in the enteric nervous system and the activity of the interstitial cells of Cajal and the smooth muscle cells themselves.<sup>22,32,35,37–40</sup> The basic patterns of gastrointestinal motility are modulated by endocrine messengers released from mucosal cells as well as by inputs from the brain via autonomic pathways. For instance, 5-HT released from enterochromaffin cells in the mucosa acts on enteric neurons bearing 5-HT<sub>3</sub> and 5-HT<sub>4</sub> receptors and in this way stimulates enteric reflex circuits relevant to gastrointestinal propulsion and secretion. In addition, 5-HT acts on 5-HT<sub>3</sub> receptors expressed by vagal and spinal afferent neurons and in this way gives rise to nausea, emesis and pain, respectively.<sup>22,39,40,42</sup> A scheme of the physiologically and pathophysiologically relevant control systems is presented in Figure 1. The relative contribution of the control systems to the regulation of gastrointestinal motility varies along the alimentary canal and changes in disease, given that local immune mechanisms stimulated by infection or inflammation may have an important impact on nerve and muscle. Since alterations in any of the complex control systems may result in disturbances of gastrointestinal motility, it is unrealistic to assume that one single drug alone is able to promote propulsive motility over the entire gastrointestinal tract. The therapeutic benefit of promotility (prokinetic) agents is based on their ability to stimulate, either directly or indirectly, smooth muscle contractions. However, propulsive motility occurs only when there is a coordinated pattern of contraction and relaxation along the length of the gut. This type of motor activity depends essentially on the presence of integrated neural control mechanisms. While propulsive motility involves phasic contractions and relaxations, an increase in muscle tone, e.g. in sphincters, provides resistance and thus impairs propulsion.<sup>42</sup>

**Table 1** Current methods used to record gastrointestinal motility disturbances.

Method	Parameter and gastrointestinal region
High-frequency intraluminal ultrasound imaging	Motility of oesophagus
Intraluminal impedance measurement	Bolus transport in oesophagus
Quantitation of gastric reflux (ICU)	Indirect measurement of gastric emptying
Radiology	Qualitative recording of wall movements in oesophagus, stomach, small and large intestine
Gamma scintigraphy of labelled meal	Quantitation of gastric emptying, regional and total transit through gastroduodenal region, small and large intestine
Barostat/tensostat	Muscle tone in stomach and colorectum
3-D ultrasonography	Gastric motility
Single photon emission computerized tomography	Gastric motility
Electrogastrography	Electrical activity in stomach
<sup>13</sup> C test	Gastric emptying
Perfusion manometry	Oesophagus, oesophagogastric motility, stomach, antroduodenal region, small intestine, colon, anorectum
Sleeve manometry	Sphincter motility
Ambulatory manometry with solid state transducers	Oesophagus, oesophagogastric motility, stomach, antroduodenal region
High resolution manometry	Oesophagus, oesophagogastric motility, stomach, antroduodenal region
Capsule manometry	Manometry throughout oesophagus and gastrointestinal tract
Magnetic resonance imaging	Motility in stomach, small and large intestine
Lactulose hydrogen test	Orocaecal transit time
Radiopaque solid marker test	Colonic transit time
Auscultation of bowel sounds (ICU)	Motor activity
Anorectal manometry and balloon expulsion	Anorectal evacuation
Defaecation (ICU)	Motility in colorectal region

This table lists a selection of methods that are used clinically and/or experimentally to study gastrointestinal motility. Only some of them are applicable in the intensive care unit (ICU). For further reading see references 161–163.

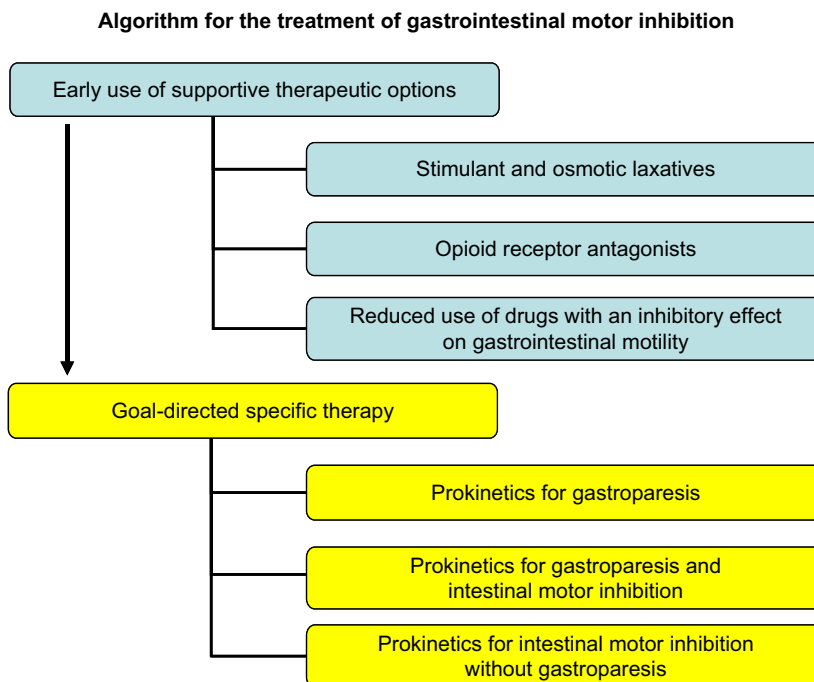


**Figure 1** Scheme of the major control systems regulating gastrointestinal motility.

The recommendation of pharmacological treatment options should ideally be based on evidence-based concepts derived from systematic reviews of the use of promotility

drugs in critically ill patients. However, to date there is only one systematic review of this topic,<sup>45</sup> which discloses the major drawback in this field, namely the lack of an appropriate number of studies, since over a time period of 20 years only 18 studies met the inclusion criteria for the review. Moreover, the results of the studies examining the effect of erythromycin, cisapride and metoclopramide on gastrointestinal transit and feeding tolerance were controversial. The majority of studies found a significant increase, or at least a positive trend, in gastrointestinal motility when a promotility agent was used. The negative studies obviously were hampered by small sample size and inadequate power to detect treatment effects. In general, the heterogeneous population of critically ill patients even in specialized ICUs makes it difficult to perform a study with well-defined inclusion and exclusion criteria.

Despite this lack of evidence-based information, improved understanding of the signalling mechanisms controlling gastrointestinal motility enables the intensivist to develop a rational standardized concept for the use of prokinetic agents in the treatment of impaired gastrointestinal motility in adult critically ill patients (Figure 2, Table 2). It appears reasonable to analyse not only the studies performed in intensive care patients, but also to



**Figure 2** Standardized concept for pharmacological treatment of gastrointestinal motor inhibition.

**Table 2** Summary of the pharmacological options to treat gastrointestinal motor inhibition.

Therapeutic strategy	Therapeutic options	Individual drugs
Early use of supportive therapeutic options	Stimulant laxatives	Bisacodyl Sodium picosulfate
	Osmotic laxatives	Magnesium salts
	Polyethylene glycol plus electrolytes	Macrogol 3350
	Opioid receptor antagonists	Naloxone
	Reduced use of drugs with an inhibitory effect on gastrointestinal motility	Anaesthetics, sedatives, opioids, and adrenoceptor agonists
Goal-directed specific therapies	Prokinetics for gastroparesis	Erythromycin Metoclopramide Domperidone
	Prokinetics for gastroparesis and intestinal motor inhibition	Erythromycin Metoclopramide plus neostigmine
	Prokinetics for intestinal motor inhibition without gastroparesis	Ceruletide Metoclopramide plus neostigmine

take into consideration the therapeutic approaches currently used for the treatment of postoperative ileus,<sup>41</sup> acute colonic pseudo-obstruction,<sup>46-48</sup> constipation-predominant irritable bowel syndrome and diabetic gastropathy.<sup>49</sup> Analogously, patients in intensive care with a history of functional bowel disorders and non-ulcer dyspepsia may profit from therapeutic strategies developed for these entities,<sup>42,50,51</sup> regardless of their treatment in ICUs of surgical subspecialties, neurosurgery, neurology

or internal medicine. Although neonates and infants in ICUs may, similarly to adults, suffer from inhibition of gastrointestinal propulsion, the therapeutic scheme presented here must not be extrapolated to children. This group of patients is likely to differ considerably in the susceptibility to motility-modifying drugs and, owing to their particular physiological and pharmacological characteristics, must not be considered as small adults.

## Algorithm for the pharmacological treatment of inhibited gastrointestinal motility

### Early use of supportive therapeutic options

#### Laxatives

Independent of the underlying pathology and the patient's bowel habit, the early use of oral or rectal (preferred) laxatives is highly recommended, e.g. at

*Day 2 or at least at day 3 after admission to an ICU:*

1st line medication	Bisacodyl	10–20 mg, as suppository
2nd line	Bisacodyl Sodium picosulfate	10–20 mg, orally 10–20 mg, orally
3rd line	Magnesium salts	0.1 mg/kg b.w., orally

#### Polyethylene glycol: Macrogol 3350

Polyethylene glycol (PEG) 3350 is an osmotic laxative and works by causing water to be retained with the stool. PEG increases faecal bulk and passes virtually unchanged through the whole gastrointestinal tract.

PEG	20–30 g/day, orally (in about 250 ml water)
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#### Opioid receptor antagonists

Naloxone	3 × 3–3 × 12 mg/day, orally
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### Goal-directed specific therapy

#### Impaired gastric emptying

1st line medication	Erythromycin	3 × 100 mg/day, i.v., maximum use for 3 days
2nd line	Metoclopramide	10 mg, i.v.
3rd line	Domperidone	30–40 mg, orally

#### Gastroparesis and impaired intestinal motility

1st line medication	Erythromycin	3 × 100 mg/day, i.v., maximum use for 3 days
	<i>and 24 h later</i>	
	Combination of metoclopramide +Neostigmine	10–30 mg 0.5–1.5 mg Once per day, i.v., in 250 ml saline, over 1–2 h

#### Impaired intestinal motility without gastroparesis

1st line medication	Ceruletide	40 µg once per day, i.v., in 100 ml saline, over 30–60 min
	Or	
	Combination of metoclopramide	10–30 mg

+Neostigmine	0.5–1.5 mg Once per day, i.v., in 250 ml saline, over 1–2 h
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### Principal considerations for the use of prokinetics

- Reduce the dose of drugs with an inhibitory potential, such as opioids, sedatives, alpha-adrenoceptor agonists and catecholamines as much as possible.
- Perform only one stimulation per day.
- The dose of prokinetics should not be increased, since higher doses bear the risk of iatrogenic inhibition of propulsive motility (see below).
- If the use of prokinetics over several consecutive days remains without benefit, consider a pause of one day without any pharmacological stimulation.

### Rationale for the use of prokinetics and their mechanisms of action

#### Laxatives in general

The terms laxatives and cathartics are often used interchangeably. There is a distinction, however, between the term laxation, which describes the evacuation of formed faecal material from the rectum, and the term catharsis, which relates to the evacuation of unformed, usually watery, faecal material from the entire colon.

The rationale for the use of laxatives in the intensive care setting is to improve intestinal motility by correcting a disturbed water input/output balance. Under physiological conditions about 7–8 l of fluid enter the small intestine from exogenous and endogenous sources or are secreted by intestinal epithelial cells on a daily basis. Absorption of water and nutrients occurs in the small intestine, with only 1–1.5 l of fluid crossing the ileocecal valve into the large intestine. The colon then extracts most of the remaining fluid, leaving about 100 ml of faecal water daily. There are hints that the secretion of fluid in the intestine is reduced under intensive care conditions. In addition, opioids are known to cause a hyperpolarization of gastrointestinal secretomotor neurons and thus to reduce intestinal ion and water secretion, which together with a slowing of intestinal transit will lead to enhanced dehydration of the stool and pronounced constipation.<sup>42</sup> For this reasons, the early use of laxatives is recommended to improve the intestinal fluid balance by promoting water secretion and preventing excessive water absorption.

Laxatives generally work by

- enhancing retention of intraluminal fluid by hydrophilic and osmotic mechanisms
- decreasing net absorption of fluid by effects on fluid and electrolyte transport in the small and large bowel
- enhancing fluid secretion and motility
- altering motility by either inhibiting segmenting non-propulsive contractions or stimulating propulsive contractions.

According to their mechanism of action, laxatives can be classified into stimulant laxatives (e.g. diphenylmethane derivatives), osmotic laxatives (saline laxatives, non-digestible sugars and alcohols, polyethylene glycol electrolyte solutions), bulk-forming laxatives (methylcellulose, bran) and surfactant laxatives (lactulose). Many of these compounds, in particular osmotic and stimulant laxatives, increase the activity of NO synthase and the biosynthesis of platelet-activating factor. NO stimulates intestinal secretion and inhibits segmenting contractions, thereby stimulating laxation. Platelet activating factor is a proinflammatory phospholipid mediator that stimulates colonic secretion and gastrointestinal motility.<sup>52</sup> Magnesium-containing laxatives may also increase the release of cholecystokinin (CCK), which leads to intestinal fluid accumulation and stimulates motility in the small intestine.

### Stimulant laxatives (diphenylmethane derivatives): bisacodyl and sodium picosulfate

It has been proposed that stimulant laxatives induce a limited low-grade inflammation in the small and large bowel to promote accumulation of water and electrolytes. *Sodium picosulfate* is hydrolysed by colonic bacteria to its active form and acts locally in the colon. Effective doses of sodium picosulfate vary considerably between 5 and 30 mg/day in individual patients. Consequently, recommended doses may be ineffective in some patients or may produce abdominal cramps and excessive fluid secretion in others.<sup>53</sup>

*Bisacodyl* needs to be activated by the hydrolytic activity of endogenous esterases in the bowel. As a consequence, the laxative effect of an oral dose of bisacodyl requires usually some 6–12 h to occur.<sup>54,55</sup> It has recently been shown that routine administration of bisacodyl has a beneficial effect in critically ill patients on a medical ICU.<sup>24</sup> When given as a rectal suppository, bisacodyl induces laxation within 30–60 min, since by this route the enterohepatic circulation of the drug is circumvented.

### Osmotic laxatives

*Magnesium salts* (magnesium sulfate, magnesium hydroxide, magnesium chloride) decrease intestinal transit time by mechanisms of action that are typical of laxatives. The magnesium salts are used in a wide range of doses from 0.1 mg/kg b.w. to a total of 15 g.<sup>56,57</sup> The recommended dosage is 0.1 mg/kg b.w., since the prolonged use of higher doses leads to sufficient absorption of magnesium into the systemic circulation and bears the risk of renal and other organ toxicity.<sup>58</sup> Particular care should be taken in patients with increased gastric residual volumes, because magnesium chloride and magnesium sulphate can slow gastric emptying.<sup>56,59</sup>

*Lactulose* is a synthetic disaccharide that is non-absorbable in the small intestine but fermentable in the colon. Its use in intensive care is recommended only with some restrictions, because it may induce massive fluid and fat loss, cause extensive bloating and subsequently increase intra-abdominal pressure.<sup>56</sup>

### PEG plus electrolytes: macrogol 3350

PEG administered in an electrolyte-balanced solution is an osmotic laxative that is used for the management of chronic functional constipation and of chronic pain patients with opioid-induced constipation. Although the working principle is convincing, there is still limited clinical experience in critically ill patients. Through its property to bind water, PEG dissolved in an electrolyte solution creates a watery bulk that passes through the gastrointestinal tract without absorbing additional water from the intestinal lumen. The PEG bulk distends the bowel wall and is likely to trigger mechanisms that promote peristalsis. PEG passes through the gastrointestinal tract virtually unchanged, because it is not metabolized and because its action is independent of the colonic microflora.<sup>60,61</sup> Impaired renal function and electrolyte imbalances are contraindications for the use of PEG plus electrolytes.

### Opioid receptor antagonists: naloxone

Gastrointestinal motor stasis and constipation are the most frequent and debilitating adverse effects of opioid analgesics.<sup>21</sup> Inhibition of gastrointestinal motility by opioid analgesics is primarily due to activation of opioid receptors in the enteric nervous system,<sup>22</sup> whereas their analgesic action is predominantly mediated by mu-opioid receptors in the brain. Given this situation, a rational approach to prevent opioid-induced bowel dysfunction would be to combine opioid analgesics with opioid receptor antagonists whose action is limited to the gut. This approach has been validated by the use of opioid receptor antagonists such as naloxone whose systemic bioavailability following oral administration is as low as 2% because of extensive first-pass metabolism in the liver. For this reason, oral naloxone has been found to improve opioid-induced bowel dysfunction without compromising opiate-induced analgesia.<sup>62</sup>

It needs to be realized, however, that naloxone will cross the blood-brain barrier and reverse analgesia if given at oral doses that exceed the hepatic capacity for first-pass metabolism of the drug. As a consequence, oral naloxone needs to be titrated in an individually controlled manner. In a study with 22 chronic pain patients on oral opioid treatment it was found that individual titration of oral naloxone between  $3 \times 3$  and  $3 \times 12$  mg/day significantly ameliorated constipation and reduced the use of laxatives but did not affect pain intensity.<sup>62</sup> There is also a limited number of small studies showing that naloxone may be beneficial in gastrointestinal motor disturbances that are unrelated to opiate use. Thus, naloxone has been reported to ameliorate idiopathic chronic constipation, intestinal pseudo-obstruction and constipation-predominant irritable bowel syndrome, but these effects need to be confirmed by larger controlled trials.<sup>63</sup>

### Erythromycin

Erythromycin is a macrolide antibiotic that stimulates gastric and intestinal motility through a direct action at motilin receptors on enteric neurons and smooth muscle cells<sup>64–66</sup> and increases the pressure of the lower esophageal

sphincter (LES) by stimulation of cholinergic nerves.<sup>67</sup> A systematic meta-analysis of prokinetics used in the treatment of gastroparesis has revealed that the effect of erythromycin on gastric emptying is greater than that of other prokinetic drugs.<sup>68</sup> Erythromycin administered i.v. is more potent to relieve gastroparesis than following oral administration.<sup>69,70</sup> The effects of erythromycin to facilitate gastric emptying and to improve tolerance to enteral feeding have been confirmed in two double-blind, placebo-controlled studies in critically ill and mechanically ventilated patients.<sup>71,72</sup> In contrast, the impact of erythromycin on colonic transit has remained controversial, given that the transit time of radio-opaque markers in the proximal and distal colon was found to be reduced or unchanged in healthy volunteers.<sup>73,74</sup>

I.v. erythromycin is used therapeutically under the assumption that it supplements the lack of, and mimics the action of, endogenous motilin to facilitate neurotransmitter release from enteric neurons. Experimental and clinical experience confirms that a dose of 100 mg erythromycin given i.v. three times per day is sufficient to restore the interdigestive motility pattern in the gastrointestinal tract and to improve gastric emptying in most cases.<sup>75</sup> It is important to note that erythromycin should not be given for periods longer than 3 days, because the therapeutic effect of the drug is known to undergo desensitization and because a persistent failure of erythromycin to stimulate gastrointestinal motility could be due to a defect in erythromycin-activated transmitter mechanisms.<sup>42</sup> In prospective, randomized trials erythromycin was found to lack any beneficial action on postoperative ileus.<sup>76,77</sup>

The use of erythromycin as a motility agent in the ICU might be considered problematic, given the rising incidence of microbial resistance<sup>78</sup> and the association of erythromycin with torsade de pointes and ventricular dysrhythmias.<sup>79</sup> However, there is no evidence in the literature that microbial resistance develops following short-term treatment with a low-dose regimen of erythromycin. A prolongation of the QT-interval is a common adverse effect of macrolide antibiotics,<sup>80</sup> and the majority of such arrhythmias have been reported to occur after i.v. administration of erythromycin resulting in plasma levels of approximately 30 mg/ml (41  $\mu$ M),<sup>79,81</sup> which are above the levels that can be reached by i.v. administration of 100 mg erythromycin. The arrhythmias are caused by a block of HERG K<sup>+</sup> channels<sup>82</sup> and are augmented by comorbidities such as cardiomyopathy, congestive heart failure, coronary artery disease, atrial fibrillation and/or bradycardia, hypokalaemia and hypomagnesia.<sup>83</sup>

### Metoclopramide

Metoclopramide, a substituted benzamide structurally related to procain amide, has been used as a prokinetic agent for at least 35 years. Pharmacologically, metoclopramide is an antagonist of dopamine D<sub>2</sub> receptors, a partial 5-HT<sub>4</sub> receptor agonist and a weak antagonist of vagal and central 5-HT<sub>3</sub> receptors.<sup>43,84</sup> Activation of 5-HT<sub>4</sub> receptors enhances the release of acetylcholine from enteric motor neurons, and there is evidence that this mechanism of action predominates in determining the gastrointestinal prokinetic

effect of metoclopramide.<sup>85</sup> The ability to release enteric acetylcholine is the rationale for combining metoclopramide with a blocker of acetylcholine esterase such as neostigmine, because this addition will enhance and prolong the availability of acetylcholine at its receptors and thus enforce the prokinetic activity of endogenous acetylcholine. Further aspects of this combination therapy are discussed below under the heading 'neostigmine'.

The prokinetic properties of metoclopramide are limited to the upper gastrointestinal tract where the drug enhances LES tone, stimulates antral and small intestinal contractions and improves antropyloroduodenal coordination, whereas no clinically significant effects on large bowel motility have been reported.<sup>43,86</sup> In critically ill patients metoclopramide has a beneficial effect on gastrointestinal transit and feeding tolerance when it is given i.v.,<sup>87</sup> but the drug is ineffective when it is administered through the nasogastric tube.<sup>88,89</sup> The duration of postoperative ileus remains unaltered by metoclopramide.<sup>90,91</sup>

The main limiting factor in the use of metoclopramide is its adverse effect profile. All prokinetics with central D<sub>2</sub> receptor antagonist properties have been found to induce extrapyramidal motor reactions. The symptoms which include drowsiness, agitation, irritability, fatigue, dystonic reactions and tardive dyskinesia occur primarily after chronic treatment over several months and are usually reversible.<sup>92</sup> In addition, these extrapyramidal effects appear to occur more commonly in children and young adults and at higher doses.<sup>93</sup> Metoclopramide may also cause galactorrhea by blocking the inhibitory effect of dopamine on prolactin release, but this adverse effect is relatively infrequent. Very rare complications comprise menstrual irregularity and the neuroleptic malignant syndrome.<sup>43</sup>

### Neostigmine

Neostigmine is a reversible acetylcholine esterase inhibitor that transiently increases the concentration of acetylcholine at its receptors and in this way facilitates the parasympathetic and enteric stimulation of gastrointestinal contractility. I.v. neostigmine has a quick onset of action within about 5 min; the duration of its action is determined by the relatively short elimination half-life of approximately 25 min.<sup>94,95</sup> The effect of i.v. injected neostigmine to stimulate gastrointestinal motility has remained somewhat controversial. Thus, neostigmine was found to be ineffective in patients with postoperative intestinal paralysis when given at the third postoperative day at the low dose of 0.5 mg intramuscularly 3 times at intervals of 3 h.<sup>96</sup> In contrast, patients with postoperative ileus after orthopedic spinal surgery experienced a prompt colonic decompression after i.v. injection of 2 mg neostigmine.<sup>97</sup> Similarly, colonic motility, colonic tone and colonic motility index measured by a manometry/barostat system were increased by 5  $\mu$ g/kg neostigmine on day 3 after left colonic or rectal resection.<sup>98</sup>

This prokinetic effect of neostigmine in the colon is in line with the observations of a case report<sup>99</sup> and the results of several controlled studies in patients suffering from acute colonic pseudo-obstruction, in whom neostigmine injected i.v. at doses of 2–2.5 mg over 3–30 min caused resolution of colonic pseudo-obstruction with a success rate

of 80–90%.<sup>46,47,61,100–104</sup> Although the pathophysiology of acute colonic pseudo-obstruction as a severe form of adynamic ileus is poorly understood, this obstruction occurs without mechanical cause and shares some similarities with the state of intestinal hypomotility or atonia under intensive care conditions. Electrolyte imbalances and the use of drugs that inhibit gastrointestinal motility such as postoperative anesthetics, opioids and anti-Parkinson's drugs are factors associated with a poor response to neostigmine, whereas postoperative patients usually show a good response to neostigmine.<sup>104</sup>

Opioids, which in critically ill patients are required for analgesia and sedation to enable mechanical ventilation or painful procedures to be performed, are among the factors that inhibit gastrointestinal motility at least in part by depressing the release of acetylcholine in the enteric nervous system.<sup>22</sup> Against this background it is reasonable to argue that a successful therapy of gastrointestinal hypomotility will depend on the combination of a drug that stimulates the release of acetylcholine from enteric neurons, e.g. metoclopramide, with a drug that inhibits acetylcholine breakdown, e.g. neostigmine. The administration of these two drugs at a moderate but effective dosage (metoclopramide up to 30 mg, neostigmine up to 1.5 mg) via infusion over a period of 1–2 h is successful in at least 50% of the patients treated (unpublished observations). Drug administration by continuing infusion enables titration of the treatment until defecation occurs, after which the infusion is stopped. It has been found that the dosage of metoclopramide and neostigmine needed to stimulate gastrointestinal motility varies among individual critically ill patients as does the efficacy of the treatment, which is probably due to a multitude of factors that determine gastrointestinal hypomotility. Despite these uncertainties it is strongly recommended that the doses of metoclopramide and neostigmine are kept within the indicated range and the duration of infusion is limited to 2 h, because prokinetics by themselves may inhibit peristalsis when given at too high a dosage.<sup>105</sup> Clinical experience confirms that, if a treatment trial fails, pharmacological stimulation of gastrointestinal motility should not be continued before the next day and limited to one trial per day.

An adverse effect of neostigmine and the combination of neostigmine plus metoclopramide is symptomatic bradycardia in a few patients,<sup>46,104</sup> which can be controlled with atropine. Increased bronchotracheal secretion and hypersalivation due to neostigmine plus metoclopramide can likewise be reduced by atropine. Additional vagal stimulation, e.g. through tracheal suctioning, should be avoided during the infusion of neostigmine plus metoclopramide. Contraindications to the use of neostigmine plus metoclopramide include bowel obstruction, gastrointestinal ischemia or perforation, pregnancy, uncontrolled cardiac arrhythmias and severe bronchospasm.<sup>48</sup> In patients with renal dysfunction it is recommended to adjust the dose of neostigmine because the serum half-life of the drug is prolonged.<sup>106</sup>

### Ceruletide

Ceruletide, which is the international non-proprietary name of cerulein, is a synthetic decapeptide and potent analogue. This peptide is potent in causing contraction of the

gallbladder and bile ducts, in stimulating coordinated propulsive motility from the duodenum to the ileum and in inducing segmenting activity of the colon.<sup>107</sup> These actions are primarily mediated by CCK<sub>1</sub> (or CCK<sub>A</sub>) receptors. Ceruletide was approved by the FDA for use as an adjunct in the X-ray examination of the gall bladder and small bowel. However, because of its prokinetic effect, ceruletide is also a useful therapeutic for the treatment of postoperative ileus and intestinal atonia.<sup>107</sup> Ceruletide has been demonstrated to alleviate postoperative adynamic ileus in two randomized double-blind studies and to augment audible bowel sounds even at the low dose of 2.5 ng/kg min for 1 h.<sup>108,109</sup>

Since ceruletide induces contraction of sphincter smooth muscle cells including those of the pyloric sphincter, gastric emptying is reduced during infusion of the peptide. Other adverse effects of ceruletide might be nausea and vomiting, abdominal pain and cramps, but rarely hypotension and tachycardia. For this reason, ceruletide should be used solely in patients with sufficient analgosedation who, in addition, have a nasogastric tube. Experimental studies in rats have shown that subcutaneous injection of ultra high doses of ceruletide (50 µg/kg b.w.) induces acute pancreatitis.<sup>110,111</sup> However, this dose of ceruletide is far beyond that used therapeutically in humans and, to the best of our knowledge, no complication of pancreatitis due to therapeutic use of ceruletide has ever been reported to occur in humans.

### Domperidone

Domperidone, a butyrophenone derivative, displays prokinetic properties that are related to its ability to block peripheral dopamine receptors. This compound increases esophageal peristalsis and facilitates gastric emptying by augmenting gastric peristalsis and improving antroduodenal coordination.<sup>112–114</sup> An additional asset in the pharmacological profile of domperidone is its anti-emetic property which is due to blockade of dopamine D<sub>2</sub> receptors both at the chemoreceptor trigger zone in the area postrema and at the gastric level.<sup>114,115</sup> Domperidone is available for oral administration, because it is rapidly absorbed from the intestine to reach peak plasma concentrations 30 min after oral intake. The compound does not readily cross the blood-brain barrier and displays a high rate of plasma protein binding (up to 93%). An i.v. formulation was voluntarily withdrawn by its manufacturer more than 20 years ago, because the preparation exhibited cardiotoxicity due to prolongation of the QT interval and predisposed patients to ventricular tachycardia when combined with other medications of a similar cardiac adverse effect profile.<sup>114,116–118</sup> Importantly, there are no literature or adverse drug reports that the oral preparations of domperidone would cause sudden death due to prolongation of the QT interval.<sup>114</sup>

Numerous clinical studies attest to the gastroprokinetic efficacy of domperidone and support its use in patients with gastroparesis.<sup>114,119</sup> Similar to other pharmacological strategies in gastrointestinal dysmotility, however, most of the studies were conducted in patients suffering from diabetic gastroparesis.<sup>114</sup> Although it is a disadvantage that domperidone can be used only in patients who are able to swallow

the liquid form or have a nasogastric tube, the drug has some advantages in particular groups of intensive care patients. Thus, slightly sedated patients without a nasogastric tube who suffer from delayed gastric emptying, nausea and/or vomiting may profit from domperidone's potent antiemetic properties. Furthermore, domperidone is of benefit to patients with Parkinson's disease, in whom dopaminergic drugs used for the therapy of the underlying disease decrease gastric motility through stimulation of peripheral dopamine receptors in the gastric wall. In these patients, domperidone selectively counteracts the peripheral adverse effects of the dopaminergic therapeutics.

Although domperidone is similar in efficacy to metoclopramide, domperidone causes fewer extrapyramidal side effects because it does not cross the blood-brain barrier. There are case reports that domperidone has even been used to treat extrapyramidal symptoms caused by metoclopramide.<sup>120</sup>

### Prokinetic drugs withdrawn from the market or development

There are a number of prokinetic drugs that either has been withdrawn from the market in most countries or whose development was suspended because of adverse effects that cannot be justified (Table 3). It is useful to briefly consider these compounds and their underlying mechanisms of action, because this enables us to better appreciate the problems of prokinetic therapy in terms of pharmacological approaches, drug interactions and adverse effect profile. It is also important to realize that some of these drugs, e.g. cisapride, can still be obtained in certain countries (e.g. Mexico), even without a physician's prescription, and through the internet sites.<sup>121</sup>

#### Cisapride

Cisapride, a 5-HT<sub>3</sub> receptor antagonist and 5-HT<sub>4</sub> receptor agonist, is effective in stimulating motility throughout the gastrointestinal tract,<sup>122,123</sup> but does not shorten the duration of postoperative ileus after gastrointestinal or colonic surgery.<sup>124</sup> Since 2000 cisapride has been withdrawn from the US market and most European countries because of its potential to induce serious and occasionally fatal cardiac arrhythmias, including ventricular tachycardia, ventricular fibrillation, and torsades de pointes.<sup>43,125</sup> These arrhythmias result from prolongation of the QT interval through an interaction with the pore-forming subunits of the HERG K<sup>+</sup> channel. The HERG channel conducts the delayed rectifier K<sup>+</sup> current that is important for normal repolarization of the

ventricle. Cisapride-induced ventricular arrhythmias occur most often when the drug is combined with other drugs that inhibit CYP3A4, because blockade of this enzyme delays the metabolism of cisapride and results in high plasma concentrations of the drug.<sup>43</sup>

#### Itopride

The prokinetic effects of itopride are thought to arise from antagonism of dopamine D<sub>2</sub> receptors and inhibition of acetylcholine esterase.<sup>126</sup> Although itopride is already marketed in Japan and in some countries of Eastern Europe, its further development was stopped by Axcan Pharma in September 2006, because both a North American and international Phase III clinical trial on patients with functional dyspepsia failed to show a significant improvement of the *individual* co-primary endpoints pain and fullness. However, analysis of the *combined* endpoint of pain and fullness revealed a greater response rate for itopride than for placebo.<sup>127</sup>

#### Prucalopride

Prucalopride is a full 5-HT<sub>4</sub>-receptor agonist and has been shown to enhance colonic contractility, to improve stool frequency and to decrease total gut transit time in healthy volunteers and in patients with therapy-resistant constipation.<sup>128,129</sup> Although prucalopride is in general well tolerated, its development was halted because of carcinogenicity in animals.<sup>130</sup>

#### Tegaserod

Tegaserod is a partial 5-HT<sub>4</sub> receptor agonist which, in addition, can block 5-HT<sub>2b</sub> receptors, but does not bind to 5-HT<sub>3</sub> receptors.<sup>131,132</sup> The compound does not cross the blood-brain barrier and can be administered safely to patients with either liver or renal impairment, since it does not affect the pharmacokinetics of CYP2D6 and other CYP P450 substrates.<sup>132</sup> Tegaserod accelerates orocecal transit and stimulates interdigestive small bowel motility as well as postprandial antral and intestinal motility in healthy volunteers<sup>133,134</sup> and has a beneficial effect in women with constipation-predominant irritable bowel syndrome.<sup>135</sup> The drug has been approved in some countries (e.g. Switzerland) for the treatment of constipation-predominant irritable bowel syndrome and functional constipation (<http://www.novartis.com>). Apart from its effect to cause diarrhea, tegaserod is in general well tolerated. However, postmarketing surveillance has revealed that tegaserod carries a risk to develop ischemic colitis.<sup>136</sup> In the US, marketing of tegaserod was suspended in 2007 after a safety review of 29

**Table 3** Prokinetic drugs withdrawn from the market or from development.

Drug	Pharmacological action	Reason for withdrawal
Cisapride	Full 5-HT <sub>4</sub> receptor agonist, 5-HT <sub>3</sub> receptor antagonist	Cardiotoxicity
Prucalopride	Full 5-HT <sub>4</sub> receptor agonist	Carcinogenicity in animals
Tegaserod	Partial 5-HT <sub>4</sub> receptor agonist	Adverse cardiovascular effects
Itopride	Dopamine D <sub>2</sub> receptor antagonist, acetylcholinesterase inhibitor	Lack of efficacy
Panthenol	Not known	Lack of efficacy

studies involving more than 11,600 patients had shown that 13 patients on tegaserod experienced ischemic cardiovascular events (including 1 death) as compared with only 1 subject out of more than 7000 subjects on placebo.<sup>136</sup>

#### Panthenol (dexpanthenol)

In some countries the combination of panthenol or dexpanthenol plus neostigmine, given i.v., was used by surgeons to resolve postoperative ileus under the assumption that panthenol/dexpanthenol releases acetylcholine in the gastrointestinal wall and neostigmine inhibits the breakdown of acetylcholine. The injectable form of panthenol/dexpanthenol was withdrawn from the market, because there is no evidence that the drug exerts any prokinetic effect. *In vitro* experiments have likewise failed to reveal any effect of dexpanthenol on peristalsis in the guinea-pig ileum (unpublished observations by MKH and PH).

#### Future options: drugs under development (Table 4)

##### Levosulpiride

The benzamide derivative levosulpiride selectively inhibits D<sub>2</sub> receptors and has a stimulant effect on 5-HT<sub>4</sub> receptors and to a lesser extent on 5-HT<sub>3</sub> receptors.<sup>43,137,138</sup> Its action on 5-HT receptors is thought to account for the ability to stimulate gastric and small bowel motility<sup>138</sup> and to accelerate gastric emptying in patients suffering from functional dyspepsia and diabetic gastroparesis.<sup>139,140</sup> Levosulpiride is more effective than domperidone, metoclopramide and at least as effective as cisapride. A disadvantage of its use in the ICU is that the drug has to

be given orally and crosses the blood-brain barrier,<sup>137</sup> which together with its antidopaminergic activity explains why the use of levosulpiride is associated with extrapyramidal symptoms.<sup>43</sup>

##### Renzapride

Renzapride is a substituted benzamide that is a full 5-HT<sub>4</sub> receptor agonist and at the same time a 5-HT<sub>3</sub> receptor antagonist. It is 10-fold less potent than cisapride in blocking HERG K<sup>+</sup> channels, an adverse effect that is responsible for cisapride's propensity to cause cardiac arrhythmias.<sup>43,141</sup> Renzapride has been found to have a beneficial effect in patients with constipation-predominant irritable bowel syndrome, in whom it increases overall gastrointestinal motility, and in diabetic patients in whom it accelerates gastric emptying.<sup>43,142</sup>

##### Mosapride

Mosapride is a benzamide derivative that, like renzapride, acts as a 5-HT<sub>4</sub> receptor agonist and a 5-HT<sub>3</sub> receptor antagonist. This compound which is already commercially available in Japan is devoid of any adverse effect on the HERG K<sup>+</sup> current. Mosapride is effective in the treatment of upper gut motility disorders such as gastroesophageal reflux disease (GERD), but does not improve symptoms of functional dyspepsia.<sup>143,144</sup>

##### Dexloxiglumide

Dexloxiglumide, the R-isomer of loxiglumide, is an antagonist of CCK<sub>1</sub> (or CCK<sub>A</sub>) receptors and blocks these receptors with enhanced potency and selectivity compared with the

**Table 4** Future options in the pharmacological treatment of gastrointestinal motor inhibition.

Drug	Pharmacological action
<i>5-HT receptor ligands</i>	
Levosulpiride	Dopamine D <sub>2</sub> receptor antagonist, 5-HT <sub>4</sub> receptor agonist, weak 5-HT <sub>3</sub> receptor agonist
Renzapride	Full 5-HT <sub>4</sub> receptor agonist, 5-HT <sub>3</sub> receptor antagonist
Mosapride	Full 5-HT <sub>4</sub> receptor agonist, 5-HT <sub>3</sub> receptor antagonist
<i>CCK receptor ligands</i>	
Dexloxiglumide	CCK <sub>1</sub> receptor antagonist
<i>First generation motilides</i>	
Alemcinal (ABT-229)	Motilin receptor agonist
Mitemcinal (GM 611)	Motilin receptor agonist
KC 11458	Motilin receptor agonist
<i>Second generation motilides</i>	
Atilmotin	Motilin receptor agonist
BM-591348	Motilin receptor agonist
KOS-2187	Motilin receptor agonist
<i>Ghrelin analogues</i>	
TZP-101	Ghrelin receptor agonist
<i>Peripheral opioid receptor antagonists</i>	
Alvimopan	μ-Opioid receptor antagonist
Methylnaltrexone	μ-Opioid receptor antagonist

racemic mixture.<sup>42</sup> Although dexloxiglumide was found to ameliorate abdominal pain and discomfort in female patients with constipation-predominant irritable bowel syndrome, it failed to enhance gastrointestinal transit in these patients.<sup>145</sup>

#### Motilin receptor agonists (motilides)

**First generation motilides:** *ABT-229 (alemcinal)*, *GM 611 (mitemcinal)* and *KC 11458*. The motilin receptor agonists *ABT-229 (alemcinal)*, *GM 611 (mitemcinal)*, and *KC 11458* are devoid of antibacterial activity but 10–1000 times more potent as prokinetics than erythromycin.<sup>146,147</sup> All substances accelerated gastric emptying in healthy volunteers, but failed to improve diabetic gastroparesis or functional dyspepsia<sup>147–149</sup> and in one study even increased the severity of dyspeptic syndromes.<sup>150</sup> This therapeutic failure may be explained by the ability of motilides to reduce both antral contraction and gastric accommodation and by rapid tachyphylaxis to motilide action.<sup>65,151</sup>

**Second generation motilides:** *BM-591348*, *KOS-2187* and *atilmotin*. *Atilmotin*, a peptide analogue of the 1–14 fragment of human motilin, *BM-591348*, a synthetic non-peptide agonist of motilin receptors, and *KOS-2187*, a non-peptide derivative of a natural motilin agonist, are members of a second generation of motilides.<sup>152</sup> Intravenous bolus injection of *atilmotin* has been found to accelerate gastric emptying of liquids and solids in human volunteers.<sup>153</sup> This short duration of action (about 30 min) is most likely due to the short half-life of the peptide.

#### Ghrelin analogues

Ghrelin is a 28 amino acid peptide that is produced in endocrine cells of the stomach.<sup>154</sup> Via activation of ghrelin (GRLN) receptors, the peptide stimulates appetite and food intake as well as postprandial and interdigestive motility in the gut.<sup>154</sup> Experimental studies have shown that ghrelin induces the migrating motor complex in the fasted state and stimulates gastric emptying and gastrointestinal transit in rats and dogs. Furthermore, ghrelin is able to reverse postoperative, septic and morphine-induced ileus in the stomach of mice, rats, and dogs.<sup>154,155</sup> Since the effect of ghrelin to accelerate gastric emptying is also seen in healthy volunteers and in patients with diabetic, idiopathic, or neurogenic gastroparesis,<sup>154,156</sup> ghrelin analogues are currently developed as a new class of prokinetics.

#### Peripheral opioid receptor antagonists: methylnaltrexone and alvimopan

As referred to before, gastrointestinal motor stasis and constipation are adverse effects that limit the usefulness of opioid analgesics. A rational approach to prevent these unwanted effects is to combine opioid analgesics with opioid receptor antagonists whose action is restricted to the gut. Based on this concept, opioid receptor antagonists with a peripherally restricted site of action have been developed.<sup>63</sup>

*Methylnaltrexone* is a quarternary mu-opioid receptor antagonist which has low oral bioavailability and does not cross the blood-brain barrier.<sup>157</sup> Subcutaneous, i.v. or oral administration of *methylnaltrexone* prevents the adverse effects of opioid analgesics on gastrointestinal function without attenuation of analgesia.<sup>157</sup> At therapeutic doses

(0.3–0.45 mg/kg i.v. and up to 19 mg/kg per os) *methylnaltrexone* is well tolerated and able to relieve constipation in methadone-maintained, opioid-dependent subjects as well as in patients with advanced medical illness requiring high doses of opiates for pain control.<sup>157</sup> Opiate-medicated patients with postoperative ileus following open segmental colonic resection have also been reported to benefit from treatment with *methylnaltrexone*.

*Alvimopan* is another mu-opioid receptor antagonist that has low oral bioavailability and does not enter the brain but is almost 100-fold more potent than *methylnaltrexone*.<sup>158</sup> Several clinical studies have proved that oral *alvimopan* (12 mg) prevents opiates such as morphine or codeine from delaying gastrointestinal transit in healthy subjects without compromising analgesia.<sup>63</sup> *Alvimopan* is likewise efficacious in ameliorating constipation in patients on chronic opioid therapy for non-malignant pain or opioid addiction.<sup>63,158</sup> In addition, *alvimopan* showed significant advantages over placebo in shortening postoperative ileus, with acceptable side effects.<sup>63,158,159</sup> Further testing of *alvimopan* was halted after a numerical imbalance in the number of ischemic cardiovascular events and neoplasm cases had been observed among patients on *alvimopan*, relative to placebo (<http://www.formkit.com/Daily/Daily-Detail.cfm?chosen=65062>).

Clinical studies in healthy subjects show that both *methylnaltrexone* and *alvimopan* have prokinetic actions in the gut unrelated to opiate use. Thus, *methylnaltrexone* can stimulate gastrointestinal transit as measured by the lactulose hydrogen breath test<sup>160</sup> and *alvimopan* is able to accelerate colonic transit as measured by scintigraphy.<sup>161</sup> This action is likely to result from inhibition of endogenous opioid peptides which may physiologically dampen gastrointestinal propulsion.<sup>63</sup>

#### Impact of enteral nutrition formulae and pre-, pro-, and synbiotics

##### Enteral nutrition and nutrition formulae

Enteral nutrition via a nasogastric tube, jejunal catheter or needle catheter jejunostomy seems to have advantages in critically ill patients compared to nutrition by the parenteral route. Thus, enteral nutrition improves wound healing and reduces the incidence of infectious complications, the length of stay at the ICU and the overall costs<sup>164,165</sup> and, for this reason, is highly recommended in the ESPEN Guidelines on Enteral Nutrition.<sup>164</sup> However, up to now there is no evidence from controlled studies that impaired intestinal motility in the critically ill does in fact benefit from enteral nutrition, either in the form of standard enteral formulae, particular immune-modulating formulae, formulae with antioxidant supplementation, or fibre-enriched diets. In contrast, fibre-supplemented enteral formulae slow intestinal transit by a complex inhibitory feedback from the distal gut<sup>166</sup> and have an anti-diarrheal effect in ICU patients with pre-existing diarrhea.<sup>167,168</sup>

##### Pre-, pro-, and synbiotics

Apart from gastrointestinal secretions, probiotics (gut flora), prebiotics (external fibers) and synbiotics (products generated by fermentation) are important for the function

of the gastrointestinal tract.<sup>169</sup> Similarly to the lack of a prokinetic effect of enteral nutrition formulae in ICU patients, there is no evidence for a direct or indirect action of pre-, pro-, and synbiotics to reverse gastrointestinal motor inhibition. However, numerous studies have shown that a supply of lactic acid bacteria provides a simple, inexpensive, and effective tool for the prevention and management of all forms of diarrhea, with no or only minor side effects.<sup>169–171</sup>

## Conclusions

The multiplicity of gastrointestinal motor control systems poses a challenge to the pharmacological modulation of gastrointestinal motility, especially the treatment of motor inhibition. This is because the ultimate goal is not simply to increase the tone of the muscle but to improve the coordination of the stationary and propulsive motor patterns in the gut. These motor patterns consist of a temporally and spatially coordinated alternation of muscle contraction and relaxation. Against this background, this article presents an algorithm for the treatment of gastrointestinal motor activity, based on a careful analysis of the mode of action of the available prokinetic drugs and their efficacy in distinct motor disturbances. Our standardized concept for the treatment of impaired gastrointestinal motility in critically ill patients is open to refinement by newly developed drugs. For this reason, we also discuss drug classes that have been withdrawn from the market because of serious unwanted effects but hold promise of therapeutic efficacy once safe substitutes have been found. The pipeline of new developments also promises a significant extension in the pharmacological armamentarium to treat gastrointestinal motor inhibition and attests to the multiple pharmacological approaches that need to be considered in the therapeutic algorithm.

## Conflict of Interest statement

None declared.

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