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ASSESSING THE EFFECT OF NALOXEGOL ON OPIOID-INDUCED BOWEL DYSFUNCTION

BY
DEBBIE GRØNLUND

DISSERTATION SUBMITTED 2018

AALBORG UNIVERSITY
DENMARK

Assessing the effect of naloxegol on opioid-induced bowel dysfunction

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3. **Grønlund D**, Olesen AE, Mark EB, Krogh K, Frøkjær JB, Drewes AM. Effects of naloxegol on gastrointestinal transit time and colonic fecal volume in healthy participants receiving oxycodone. Submitted to *J Neurogastroenterol Motil* (2018)

4. Kalsi GK, **Grønlund D,** Martin P, Drewes AM, Scott M, Birch MJ. Technical report: Inter- and intra-rater reproducibility of regional gastrointestinal transit times measured using the 3D-Transit electromagnet tracking system. *Neurogastroenterol Motil* (2018); [in press]

5. Olesen AE, **Grønlund D**, Gram M, Skorpen F, Drewes AM, Klepstad P. Prediction of opioid dose in cancer pain patients using genetic profiling - not yet an option with support vector machine. *BMC Res Notes* 11,78 (2018)

6. Poulsen JL, Brock C**, Grønlund D**, Krogh K, Drewes AM. Prolonged-release oxycodone/naloxone improves anal sphincter relaxation compared to oxycodone plus Macrogol 3350. *Dig Dis* Sci 62, 3156 (2017)

7. **Grønlund D**, Poulsen JL, Sandberg TH, Olesen AE, Madzak A, Krogh K, Frøkjær JB, Drewes AM. Established and emerging methods for assessment of small and Large Intestinal Motility. *Neurogastroenterol Motil* 7, 29 (2017)

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II. **Grønlund D**, Poulsen JL, Krogh K, Brock C, Liao D, Gregersen H, Drewes AM, Olesen AE. The impact of naloxegol on anal sphincter function – using a human experimental model of opioid-induced bowel dysfunction. *Eur J Pharm Sci* 17, 187-192 (2018)

III. **Grønlund D**, Olesen AE, Mark EB, Krogh K, Frøkjær JB, Drewes AM. Effects of naloxegol on gastrointestinal transit time and colonic fecal volume in healthy participants receiving oxycodone. Submitted to *J Neurogastroenterol Motil* (2018)

IV. Kalsi GK, **Grønlund D,** Martin P, Drewes AM, Scott M, Birch MJ. Technical report: Inter- and intra-rater reproducibility of regional gastrointestinal transit times measured using the 3D-Transit electromagnet tracking system. *Neurogastroenterol Motil* (2018); [in press]

ABBREVIATIONS

BSFS	The Bristol Stool Form Scale
ENS	Enteric nervous system
FDA	The Food and Drug Administration
GI	Gastrointestinal
IAS	Internal anal sphincter
MRI	Magnetic resonance imaging
OIBD	Opioid-induced bowel dysfunction
PAC-SYM	The Patient Assessment of Constipation Symptoms questionnaire
PAMORA	Peripherally acting μ-opioid receptor antagonist
PR	Prolonged-release
RAIR	Recto-anal inhibitory reflex
WMC	Wireless motility capsule

ENGLISH SUMMARY

Treating acute and chronic pain often require opioids, one of the most potent and effective classes of analgesic drugs. However, their use is plagued by numerous and potentially severe side effects of the gastrointestinal (GI) system. Constipation is probably the most prevalent and bothersome symptom, but as opioids affect the whole gut, symptoms such as gastrointestinal reflux, nausea, bloating, abdominal pain, and straining during evacuation are all frequently reported by opioid users. Collectively, these side effects are termed opioid-induced bowel dysfunction (OIBD). The mechanisms behind OIBD rely on μ-opioid receptor activation in the enteric nervous system, which negatively affects GI motility, GI fluid secretion/absorption, and function of GI sphincters. Conventional laxatives are considered the golden standard in treating OIBD. Nevertheless, the efficacy of laxatives remains debatable, and many patients consider them insufficient in reliving their problems. Over the last years, newer pharmacological treatment options for OIBD has emerged, including co-administrated peripherally acting μ-opioid receptor antagonists (PAMORAs). Whereas laxatives merely are considered a symptomatic treatment, PAMORAs specifically target the underlying mechanism of OIBD, by blocking μ-opioid receptors in the GI tract. To assess the effect of new pharmacological treatments of OIBD, e.g. PAMORAs, and to gain new insights into the pathological mechanisms of OIBD, validated outcome measures are essential. The purpose of this PhD project was to explore the applicability of subjective and objective methods to assess OIBD in clinical and research settings. This was done by evaluating the effect of the PAMORA naloxegol on experimentally induced OIBD. Thereby, we gained new insights into the pharmacodynamics of PAMORAs, in which part of the GI tract the effects of opioids and naloxegol are most profound, and what methods can be used show these effects.

Three studies compile this thesis. Study I (a literature review) discuss the strengths and limitations of currently applied and newer upcoming methods to assess the small bowel and colon in an objective manner. Study II (an experimental study divided into Study IIa and IIb) investigates the underlying mechanisms of naloxegol on OIBD by assessing GI symptoms via questionnaires, GI transit time and motility patterns via the 3D-Transit system, colonic fecal volume via magnetic resonance imaging (MRI), and anal sphincter function via anorectal manometry and the EndoFLIP system. Finally, Study III (a validation study) evaluates reliability of the 3D-Transit system.

In Study II, 24 healthy participants were included in a 6-day treatment of oxycodone co-administered either naloxegol or placebo, in a double-blind randomized crossover design. Thus, we used an experimental OIBD model to assess the effect of a pharmacological compound to reverse OIBD symptoms. Compared to placebo, naloxegol significantly improved GI symptoms and stool form, decreased total GI- and colonic transit times, and improved response of the recto-anal inhibitory reflex (RAIR). There was no effect of naloxegol on colonic fecal volume, anal resting pressure or anal canal distensibility. Study III showed a good reliability of manually analyzed segmental transit times extracted from the 3D-Transit system, provided that the research staff who analyze the recordings were well trained and experienced in doing so.

In summary, self-assessed questionnaires, the 3D-Transit system, and anorectal manometry were useful and sensitive methods to quantify an effect of naloxegol on experimentally-induced OIBD. Future studies may apply these results in choosing the appropriate methods in the design of studies that evaluate OIBD, and the effect of pharmacological interventions to treat this condition. Our studies also indicate that further refinement of the MRI method may be needed in order to expand its applicability in studies of OIBD, and that it may be worth focusing on the assessment of RAIR when investigating how opioids and other pharmacological compounds affects anal sphincter function.

DANSK RESUMÉ

Opioider er en vigtig del af den farmakologiske behandling af moderate og stærke smerter. Desværre er behandling med opioider forbundet med flere potentielt alvorlige gastrointestinale bivirkninger. Forstoppelse er den hyppigst forekommende bivirkning, men patienterne plages også ofte af mavesmerter, oppustethed, halsbrand, kvalme, og smerter ved afføring, idet opioider påvirker hele mavetarmsystemet. Samlet set kaldes disse bivirkninger for opioid-induceret tarmdysfunktion (OIBD). OIBD opstår når opioider binder til μ-opioid receptorerne i det enteriske nervesystem, hvilket har en negativ indvirkning på gastrointestinal motilitet, gastrointestinal væskeabsorption og sekretion samt funktionen af de gastrointestinale sfinktere.

Forebyggelse og behandling af OIBD tager som regel udgangspunkt i laksantia. Ofte er behandling med laksantia dog ikke tilstrækkeligt effektivt, og kan i sig selv give bivikninger såsom oppustethed og mavesmerter. I de senere år er der udviklet flere behandlingsmuligheder af OIBD, blandt andet perifert virkende μ-opioid antagonister. Hvor laksantia udelukkende regnes for at være symptombehandling, blokerer disse antagonister μ-opioid receptorerne i det enteriske nervesystem, og er derved målrettet de underliggende patofysiologiske mekanimser af OIBD. Både i kliniske og forskningmæssige sammenhænge er valide subjektive og objektive metoder vigtige for at kunne undersøge effekten af nye farmakologiske behandlingsmuligheder af OIBD. Formålet med de gennemførte studier var at få ny indsigt i den farmakodynamiske virkning af naloxegol (en perifert virkende μ-opioid antagonist), samt at få ny viden omkring hvilke metoder der bedst kan bruges til at vurdere de patofysiologiske mekanismer bag OIBD og effekten af farmakologiske behandlinger heraf.

Studie I (et review) diskuterer fordele og ulemper ved objektive metoder der kan benyttes til at måle motilitet i tynd- og tyktarm. Studie II undersøger effekten af naloxegol på eksperimentelt induceret OIBD, ved hjælp af validerede spørgeskemaer og følgende objektive effektmål; transit tid og motilitet i tyktarmen, volumen af fæces i tyktarmen samt funktionen af analkanalen, målt med henholdsvis 3D-Transit systemet, MR og anorektal manometri. Studie III undersøger reproducerbarheden af transit tider målt med 3D-Transit systemet.

I Studie II modtog 24 raske forsøgspersoner en 6-dages behandling med oxycodon co-administreret enten naloxegol eller placebo, i et dobbelt-blindet, randomiseret overkrydsningsstudie. Forsøgspersonerne havde færre gastrointestinale symptomer,

oplevede mindre hård afføring, havde kortere transit tid i tyktarmen samt havde en øget afslapning af den interne anale sfinkter i forbindelse med rektal udvidelse (og dermed et øget respons af den anorektale inhibitoriske refleks) under naloxegol behandlingen, sammenlignet med placebo. Der var ingen effekt af naloxegol på fæcesvolumen i tyktarmen, og heller ingen effekt på hviletrykket i analkanalen eller på analkanalens eftergivelighed. Studie III viste en god reproducerbarhed af manuelt analyserede transit tider optaget med 3D-Transit systemet, forudsat at disse blev analyseret af erfarent forskningspersonale.

Disse studier viser at spørgeskemaer, 3D-Transit systemet og anorektal manometri var brugbare og sensitive metoder til at kvantificere effekten af naloxegol på eksperimentelt induceret OIBD. Fremtidige studier kan gøre brug af disse resultater i studiedesignet af nye forsøg der undersøger OIBD. Derudover lægger studierne op til at videreudvikle MR metoden til at undersøge fæcesvolumen i OIBD patienter, samt at fokusere på metoden til at måle den anorektale inhibitoriske refleks når man ønsker at se på lægemidlers effekt på analkanalens funktion under opioid-påvirkning.

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Debbie Grønlund, May 2018, Aalborg

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CHAPTER 1 INTRODUCTION

Pain is one of the most frequent symptoms presented in the primary and secondary health care system. It is estimated that around 20% of the general adult population suffer from chronic pain, and treating chronic pain is notoriously difficult.[1,2] Moderate to severe pain often require opioids, one of the most potent classes of drugs used for pain management. The past few decades has seen an alarming rise in opioid prescriptions, a fact commonly referred to as the "opioid epidemic".[3] The escalating amount of opioid prescriptions increase the risk of patients experiencing numerous side effects. The more serious side effects relates to the central nervous system, and include sedation, respiratory depression, and impaired cognition.[4] However, opioids also affect the periphery, and perhaps the most common side effects of all are the gastrointestinal (GI)-related ones. Opioid-induced constipation is considered the most prevalent and bothersome side effect, occurring in 40-86% of all chronic opioid users (depending on opioid dose, type and formulation).[5,6] Nevertheless, as opioids affect the entire GI tract, more uncharacteristic symptoms such as gastro-oesophageal reflux, nausea, abdominal pain, bloating, and defecation problems are just as common.[7] Collectively, all GI side effects related to opioid treatment are termed opioid-induced bowel dysfunction (OIBD). Despite a very common phenomenon, health care providers seems to underestimate the high incidence rate of OIBD,[8] probably due to lack of awareness and, until now, absence of a universal diagnostic criteria.[9] OIBD was recently defined by the Rome IV criteria as a worsening in bowel habits after initiating opioid therapy, characterized by two or more of the following; reduced stool frequency, development or worsening of straining, a feeling of incomplete evacuation, and harder stool form.[10]

1.1 PATIENT BURDEN OF OIBD

Tolerance towards OIBD rarely develops over time, and may therefore be an undesirable travelling companion throughout the course of opioid treatment,[11] and OIBD severity seems to increase with age.[12] These GI side effects may reduce health-related quality of life, and burden patient's daily activities and social life to the extent of opioid dose reduction, non-adherence, and treatment discontinuation.[13,14] In fact,

an internet-based survey from 2009, reported that 33% of patients felt the need to decrease the dose or stop using opioids due to OIBD.[5] GI dysfunction is generally considered a taboo in the Western World and unfortunately, the severe psychological burden of OIBD is often misjudged by health care providers which may compromise patient care and medical compliance.[15,16] Persistent constipation in relation to OIBD may have serious consequences due to the risk of colonic distension, gut perforation, and ileus, and is also associated with increased mortality.[17] The socioeconomic implications of OIBD are correspondingly significant.[18] A recent register-based cohort study of 97.169 opioid users in Denmark showed that non-cancer patients with OIBD had 34% higher healthcare costs compared to those without.[19] Despite all this, a strong reliance on opioids for pain management for various acute and chronic pain conditions remain.

1.2 PATHOPHYSIOLOGY OF OIBD

The GI tract is composed of smooth muscle arranged in a longitudinal and circular layer, both innervated through the enteric nervous system (ENS). The ENS regulates sensory, motor, and secretory effects of the whole GI tract. Opioid receptors are localized at the myenteric and submucosal neurons in the ENS.[20] Three main opioid receptor classes are expressed; μ (mu), κ (kappa), and δ (delta), all of which are G-protein-coupled receptors. Of these, the μ-opioid receptors are the most widely distributed, and also the most important receptor in relation to OIBD.[21] The main effect of μ-opioid receptor activation is thought to be decreased formation of cyclic adenosine monophosphate, which leads to decreased neuronal excitability, and thereby, inhibition of cell activity.[22] Under normal physiological conditions, endogenous opioids regulate and coordinate normal GI functions via these mechanisms; however, opioid receptors are also affected by exogenously administered opioids.[21] Exogenous opioids affect GI motility in multiple negative ways. In the stomach, opioids are believed to increase tonic contraction of the antrum and impair muscle tone of the gastric reservoir,[23] leading to delayed gastric emptying as demonstrated in multiple studies.[24–26] In the small bowel and colon, opioids directly induce non-propulsive contractions by inhibition of neurotransmitters in the smooth muscle cells. In the circular muscle layer this facilitates stronger and more frequent phasic, non-migrating muscle contractions called “spike bursts”, which leads to an increased contractile tone and reduced propulsive contractions of the longitudinal

muscle layer.[27] Furthermore, opioids possibly cause GI dysmotility through the suppression of local acetylcholine release via central nervous system-stimulated sympathetic overflow to the intestines.[23,28] All together, these effects delay oro-cecal and colonic transit time as confirmed by several studies. [25,29–31] Furthermore, a recent study found that opioids reduce the number of mass movements in colon.[32] Water and electrolyte secretion is also decreased as opioids inhibit the formation of cyclic AMP, acetylcholine and vasoactive peptide production. This inactivates chloride channels causing a disruption in the osmotic gradient across the gut lumen leading to less water secretion.[33] This makes fecal content dry and difficult to pass. Opioids also cause less gastric- and pancreatico-bilary secretion leading to altered digestion and decreased bioavailability of drugs.[34] Lastly, opioids may also increase the tone of GI sphincters, although the mechanisms behind this are not fully understood.[35] Opioids have been associated with increased lower esophageal sphincter resting pressure,[36] and increased tone of the Sphincter of Oddi which may give rise to colicky upper abdominal pain.[37,38] Studies on how opioids affect the anal sphincter are scarce and inconsistent, however associations to increased rectal threshold volumes for minimum perception, and diminished recto-anal inhibitory reflexes (RAIR) have been found.[39] The RAIR is an important part of defecation which is severely impaired in the absent of RAIR as in e.g. Hirschprungs' disease.[40] The theory of opioids diminishing RAIR is supported by the experiences of opioid users who often complain about straining, incomplete evacuation, and a sensation of anal blocking.[41] All these opioid effects in the GI tract may manifest as the previously described diverse and multifaceted OIBD symptoms.

1.3 PREVENTION AND TREATMENT OF OIBD

As OIBD covers a group of various GI side effects, and is not a condition in itself, the treatment regimen is often difficult. Lifestyle changes such as increasing daily fibre intake and physical activity are often recommended, although there is little evidence that these factors may improve constipation in general.[42] Thus the prophylaxis and management of OIBD rely heavily on conventional laxatives.[43] When this is ineffective or insufficient, peripherally acting μ-opioid receptor antagonists (PAMORAs), a fixed dose of oxycodone:naloxone,[44] or the secretagogue lubiprostone (activator of the chloride channel) may be considered.[45] Furthermore, Prucalopride, a 5-HT4 agonist, also seems to improve OIBD symptoms, although not currently

approved for this indication.[46] In the next chapters, the use of conventional laxatives and PAMORAs to treat OIBD is discussed.

1.3.1 LAXATIVES

The primary effects of laxatives are to increase the osmotic gradient (e.g. lactulose and sorbitol), and/or stimulate the colonic musculature (e.g. bisacodyl and sessosides). Laxatives are the standard treatment for constipation, although their efficacy often is unsatisfactory.[47] The efficacy of laxatives on OIBD is also debatable. Thus, some patients do benefit from them, but for a large group of patients, the GI symptoms remain a persistent struggle that increases the ongoing burden of chronic pain.[13,48] This became clear in a multinational survey of 322 chronic opioid users, in which 81% still reported numerous GI side effects despite concomitant laxative use.[49] Likely, the explanation is that opioids affect the entire GI tract whereas laxatives mainly exert their effect in the colon. Hence, laxatives have no effect on dysmotility and secretory changes in the stomach and small bowel, and do not exert any effect on GI sphincter function. Overall, laxatives are merely considered a symptomatic treatment of OIBD, as the underlying pathology is not targeted. Furthermore, laxatives are known to worsen GI symptoms, and in itself cause abdominal pain, bloating, gas and reflux symptoms.[50]

1.3.2 PERIPHERAL OPIOID ANTAGONISTS

PAMORAs is a group of newer pharmacological agents designed to relive or reverse undesired opioid GI side effects. Currently, four PAMORAs are marketed; alvimopan, methylnatrexone, naldemedine, and naloxegol. These are all drugs that specifically block μ-opioid receptors in the periphery with preservation of central analgesia (Figure 1).[51] All have been approved for the indication of OIBD in patients with chronic non-cancer pain, except alvimopan, which is merely approved in the US to decrease the time to GI recovery following partial bowel resection surgery.[52] Methylnaltrexone is a derivative of naltrexone and the first PAMORA to be approved in 2008 by the US Food and Drug Administration (FDA) as a subcutaneous injection, and very recently as an oral formulation. It has been proved efficacious in terms of decreasing morphine-induced delay in oro-cecal transit time, increasing weekly stool

frequency, and overall improving defecation difficulties.[53–56] Due to a quite strong effect, the drug must be used carefully, especially in patients with preexisting GI disease. Naldemedine, also a derivate of naltrexone, was recently approved in March 2017 by FDA as an oral tablet. It has been found to increase the rate of stool frequencies per week in OIBD patients.[57,58] Naloxegol is the drug of interest of this thesis, hence the pharmacodynamics and implications for this is described in details in the next section.

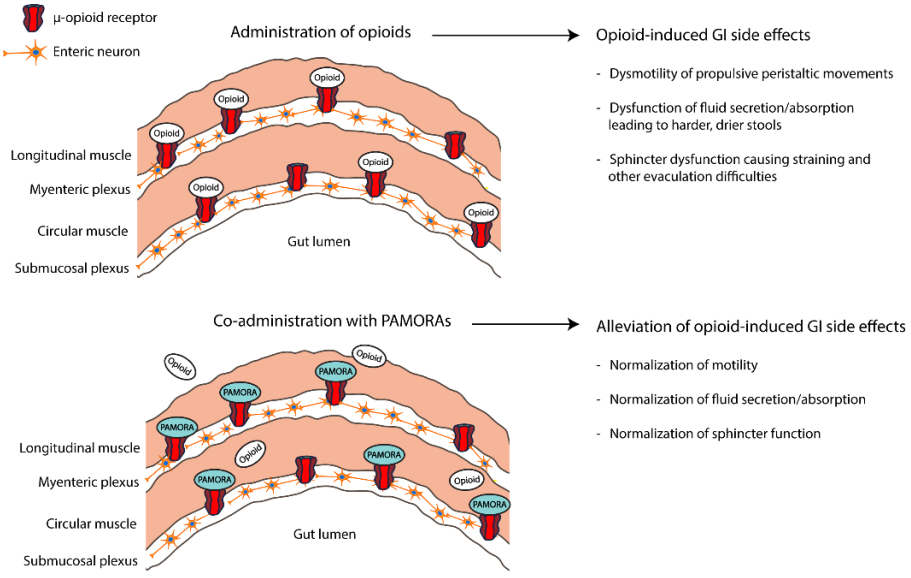

Figure 1. μ-opioid receptors are present in the myenteric and submucosal plexuses of the enteric nervous system. When these receptors are activated, various gastrointestinal (GI) functions are affected. Peripherally acting μ-opioid receptor antagonists (PAMORAs) may alleviate these side effects by blocking opioids from the μ-opioid receptors.

1.3.2.1 NALOXEGOL

Naloxegol is a polyethylene glycol conjugated derivative of naloxone, restricted to the periphery via two mechanisms; 1) a large molecule size limits passive permeability through the blood-brain barrier, and 2) it is a substrate of the P-glycoprotein transporter, a gatekeeper in the blood-brain barrier.[59] Thereby naloxegol molecules stay for a long time in the systemic circulation. In 2014, the FDA approved naloxegol as treatment of OIBD in patients with chronic non-cancer pain, and the

European Medicines agency approved it for patients with inadequate response to laxatives. Naloxegol was approved following a series of large clinical trials in patients with OIBD (called the KODIAC studies), showing a dose-dependent therapeutic efficacy in terms of increasing weekly stool frequency, improving time to first bowel movement, and decreasing patient-reported GI symptoms.[60–62] The latter revealed improvements in straining, stool form, feeling of evacuation completeness, and not at least, improvement in psychical and social functioning. In general, naloxegol is considered well-tolerated, and is proven safe in relation to e.g. cardiac side effects and mild-moderate renal/hepatic failure.[63–66] An overview on efficacy and safety outcomes in clinical trials of naloxegol is provided in Table 1.

Author	Phase	H/P, n	Study design	Safety/efficacy outcomes
Gottfridsson et al. [2013][67]	1	H, 45	DB, randomized, crossover 2 days of naloxegol or placebo	Naloxegol doses up to 150 mg did not induce QT/QTc interval prolongation
Bui et al. [2014][66]	1	P, 16 H, 8	OP Single naloxegol dose	Hepatic impairment had no impact on pharmacokinetics and safety of naloxegol
Bui et al. [2014][65]	1	P, 24 H, 8	OP Single naloxegol dose	Renal impairment had no impact on pharmacokinetics and safety of naloxegol
Bui et al. [2016][68]	1	H, 87	OP, non-randomized, crossover 1-17 days of naloxegol co-adm. ketoconazole, diltiazem or rifampin	Ketoconazole and diltiazem (CYP3A inhibitors) increased naloxegol plasma exposure, while a CYP3A inducer (rifampin) reduced it
Bui et al. [2016][69]	1	H, 38	DP, randomized, crossover Single naloxegol dose co-adm. quinidine or placebo	Quinidine (a CYP3A inhibitor) increased naloxegol plasma exposure
Webster et al. [2013][60]	2	P, 207	DB, randomized, parallel 4 weeks of naloxegol or placebo	Naloxegol increased stool frequency, improved time to first bowel movement, and induced less symptoms
Eldon et al. [2015][63]	2	H, 46	DB, randomized, crossover Single naloxegol dose or placebo	Morphine-induced delay in oro-cecal transit time was reversed by naloxegol
Halawi et al. [2017][70]	2	H, 72	DB, randomized, parallel 3 days of codeine, naloxegol, codeine+naloxegol or placebo	Codeine-induced delay in whole gut transit was not reversed by naloxegol
Chey et al. [2014][61] Tack et al. [2015][62] Lawson et al. [2016][71]	3	P, 652	DB, randomized, parallel 12 weeks of naloxegol or placebo	Naloxegol increased stool frequency and form, improved time to first bowel movement, induced less GI symptoms, and improved straining
Webster et al. [2014][64]	3	P, 804	OP, randomized, parallel 52 weeks of naloxegol or usual care	Long-term administration of naloxegol was safe and well- tolerated

Table 1. Overview on studies on the safety and efficacy of naloxegol. H: Healthy participants; P: Patients; DB: Double-blind; OP: Open-label; PGP: P-glycoprotein; PAC-SYM: The patient assessment of constipation symptoms questionnaire; PAC-Qol: The patient assessment of constipation quality of life questionnaire; SF-36: The Short Form (36) Health Survey.

CHAPTER 2 RATIONALS AND AIMS

At present, there is no consensus as to which tool should be used for the assessment of OIBD, either in clinical practice or in research. Choice of approach also reflects the somewhat different purposes of the two settings. In clinical practice, the diagnosis and evaluation of OIBD severity is usually based on the patient's perception of symptoms, i.e. anamnesis of defecation difficulties, abdominal pain, and health-related quality of life.[43] Often, stool frequency is evaluated by the physician via e.g. the Bristol Stool Form Scale (BSFS), however this is primarily used as an affirmative diagnostic criteria for constipation, defined as less than three stools per week.[72] In research, we seek to understand the underlying mechanisms of OIBD and/or efficacy of a pharmacological agent to treat it, instead of merely focusing on the treatment goal (i.e. reduction of OIBD-related pain, burden etc.). In the majority of research studies, efficacy outcomes like time to first bowel movement, change in laxative use, and stool frequency and is often used, the latter being the most common approach. Also, self-reported questionnaires and more objective measures can provide a clearer picture on the diversity of GI symptoms, and work as valuable tools to assess pharmacological effects. A combination of the two is often considered, as there seems to be low correlation between subjectively assessed symptoms and objective evaluations such as transit time.[73–75]

Meaningful and valid objective methods to quantify degree of constipation and other OIBD symptoms remain elusive. The lack of validated outcome measures has been a great limitation in evaluating the efficacy of treatments that alleviate OIBD. By investigating the pharmacological effects of a PAMORA on OIBD, we may gain valuable insights into two main areas: 1) The utility of methods to assess OIBD, and 2) PAMORA specific pharmacodynamics, i.e. how does this type of drug affect GI peristaltic patterns, GI secretion, and function of GI sphincters in the opioid-affected gut. Hence, the overall purpose of this PhD project was to explore the applicability of objective and subjective methods to assess the effect of naloxegol on experimentally induced OIBD.

The thesis is based on four peer-reviewed papers compiling data from three studies; a literature review, an experimental study, and a validation study (Figure 2). The literature review (Study I) discusses strengths and limitations of established and emerging methods for evaluating GI motility. The experimental study investigates the

underlying mechanisms of naloxegol on OIBD, by assessing anal sphincter function (Study IIa), GI transit time, motility, and fecal load in colon (Study IIb). Finally, a validation study evaluates the repeatability of subjectively estimated GI transit times obtained from the 3D-Transit system (Study III). The four papers will from heron be referred to as named above.

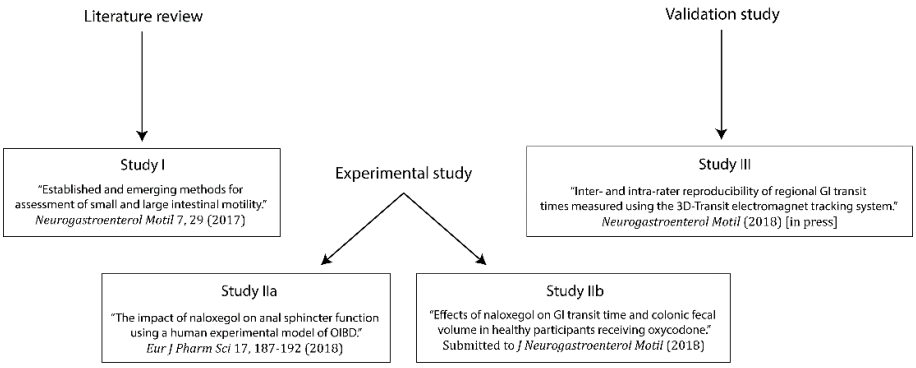

Figure 2. Overview on studies implemented in the thesis, and titles of corresponding papers.

The study aims were:

Study I: To summarize procedures, indicattions, advantages, and disadvantages of currently available and upcoming methods for evaluation of small bowel and colonic motility.

Study II: To evaluate how naloxegol affected 1) anal resting pressure, 2) RAIR-induced sphincter relaxation, 3) anal canal distensibility, 4) total and segmental GI transit times, 5) total and segmental colonic fecal volumes, and 6) self-assessed GI symptoms, during experimentally induced OIBD.

Study III: To assess the inter- and intra-rater repeatability of segmental GI transit times from the 3D-Transit system, and evaluate how the experience of the rater influences the identification of these time points.

CHAPTER 3 METHODS AND RESULTS

Section 3.1 sums up the essence of Study I. The rationale behind Study II is followed by a short description of methods (section 3.2.1) and key results (section 3.2.2). Lastly, for Study III, rational, methods (section 3.3.1), and key results (section 3.3.2) are presented. Details are found in the corresponding papers.

3.1 STUDY I

GI dysmotily is a vague descriptive term used to describe disruption of normal contractility of the gut. In a broad sense, any alterations in the transit of food and GI secretions may be considered an intestinal motility disorder, which may have several, complex, underlying causes. In a large proportion of patients presenting with symptoms from the GI tract, it may be possible to detect and quantify dysmotility using various available methods, and thereby optimize treatment for these patients. Also, valid objective methods to assess the GI tract are highly important in research settings. This review outlined established and emerging methods to assess small bowel and colonic motility for clinical and research purposes. For the upper GI tract (esophagus and stomach), several standardized methods to evaluate motility exist; however assessing the more unapproachable small bowel and colon is quite cumbersome. In clinical settings, radiopaque markers, hydrogen breath tests and scintigraphy are commonly used for this purpose. Radiopaque markers are small pellets which are ingested, followed by an abdominal x-ray after a few days. By counting the number of remaining markers, colonic transit time may be estimated in a seemingly quick and inexpensive way. However, radiation exposure of the patient is a major drawback. Hydrogen breath tests may determine oro-cecal transit time through the measurement of hydrogen gases excreted in the breath after ingestion of a loading dose of lactulose. Data interpretation may however be difficult, as lactulose has a natural accelerating effect on small bowel transit. Scintigraphy is based on the oral ingestion of a radiolabeled meal followed by a gamma camera image of the abdomen to particularly determine colonic transit time. However, this method also include radiation expose of the participant. In addition, for all three methods applies that only transit time and not details on GI motility patterns is be assessed. In contrast, the wireless motility capsule (WMC, SmartPill®) and the 3D-Transit system represent

newer alternative approaches to assess both segmental transit times and motility patterns in an ambulatory and much less invasive way. The WMC qualifies regional GI transit time and GI motility patterns by measuring pH and intraluminal pressure. The former is highly useful clinically when classifying constipation, and the latter is predominantly used as a research tool to study dysmotility patterns. Nonetheless, WMC only provides a measure of whole colonic transit time and not regional. This is on the other hand possible with the 3D-Transit system. Here, changes in capsule rotations can be studied in respect to the anatomical position, which provides a direct measure of peristalsis and information about the direction, velocity and lengths of bowel contractions. The system is, at present, merely used in basic research. Other emerging techniques are high-resolution manometry for colonic dysmotility (which may replace conventional manometry in pending years), and magnetic resonance imaging (MRI) motility assessments. MRI is an exciting novel technique which has the potential to quantify both small bowel and colonic motility; however, these techniques are still in their infancies. A better understanding of several GI dysmotility disorders is highly needed, and therefore, data quality optimization, standardization, and patient-safety of both established and emerging techniques are warranted.

3.2 STUDY II

Many aspects on the underlying pathology and mechanism of treatment options on OIBD have yet to be described in detail. In the logic sense, restrictive blocking of peripheral μ-opioid receptors whilst undergoing opioid treatment would abolish the side effects related to the gut. Unfortunately, it is not that simple, as various factors may affect this outcome. By investigating the effect of naloxegol on many different subjective and objective aspects, a clearer picture of OIBD pathology may arise. This may also provide a better understanding of which methods are most relevant and sensitive to assess OIBD. An explorative crossover study employing an experimental model of OIBD in healthy males was chosen as the best possible way of addressing this. The OIBD model was previously established by our research group in which a 5-day treatment of prolonged-release (PR) oxycodone in healthy participants increased GI transit time, increased colorectal volume, and induced substantial symptoms of OIBD, compared to placebo. These studies will from heron also be referred to as the studies by Poulsen et al.[77] and Nilsson et al.[78]

3.2.1 METHODS

3.2.1.1 STUDY DESIGN

The study was conducted in compliance with the ICH-GCP principles of the European Union, and approved by the Danish Medicines Agency (reference no. 2015021429) and The North Denmark Region Committee on Health Research Ethics (reference no. N-20150014). It was designed as a double-blind, randomized, crossover trial. Twenty-four healthy males from the age of 20-60 years with neither current GI symptoms, history of GI disease, previous or current drug abuse, or daily nicotine or alcohol consumption were included. They were randomized to receive either 1) oral PR oxycodone (10 mg twice on day 1 and 15 mg twice on day 2-5) and co-administered 25 mg oral naloxegol (oxycodone+naloxegol) or matching placebo tablets (oxycodone+placebo). A flowchart of events in each treatment period is provided in Figure 3, and an overview on all experimental assessments and procedures is given in Figure 4.

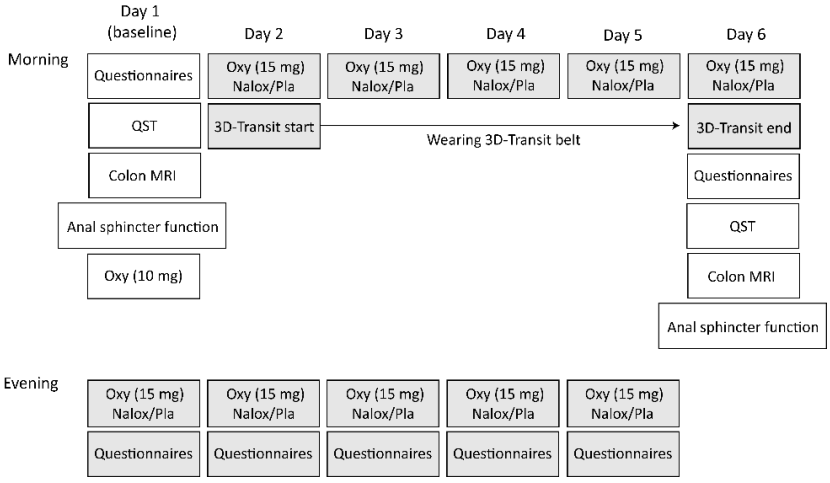

Figure 3. Overview on events in a treatment period of Study II. The grey fields represent events occurring outside of the research facilities. QST: quantitative sensory testing; MRI: magnetic resonance imaging; Oxy: oxycodone; Nalox: naloxegol; Pla: placebo.

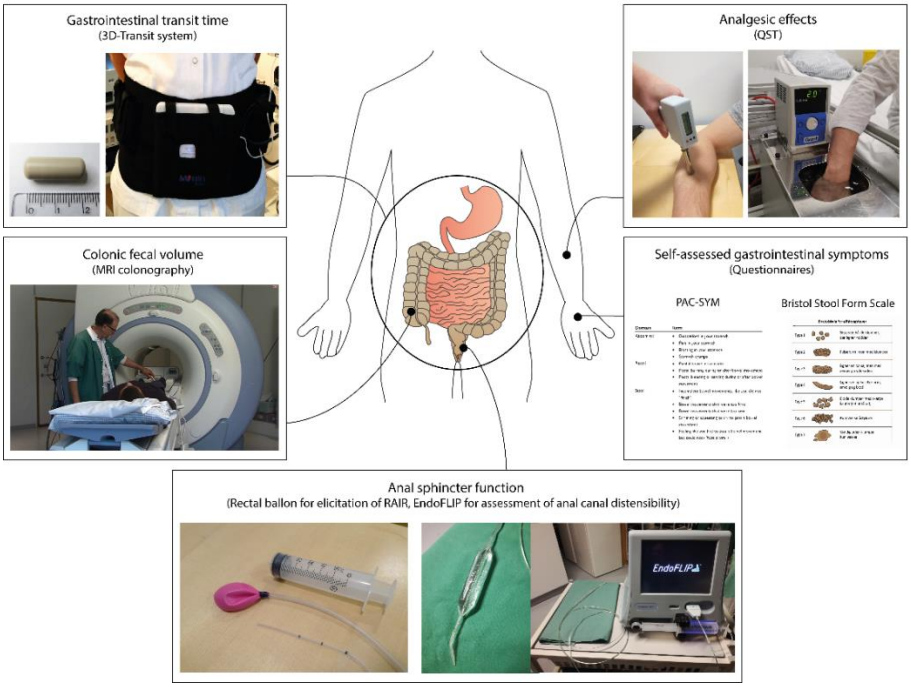

Figure 4. Overview on all assessments and experimental procedures in Study II. MRI: magnetic resonance imaging; QST: Quantitative sensory testing; PAC-SYM: Patient assessment of constipation symptoms questionnaire; RAIR: Recto-anal inhibitory reflex.

3.2.1.2 ANALGESIC EFFECTS

Quantitative sensory testing was applied to assess whether naloxegol influenced the analgesic effect of oxycodone, hence this was measured on day 1 and day 6. A handheld algometre was used to apply pressure to the dorsal forearm until participants reached their pain detection threshold. Furthermore, in a cold pressor test the dominant hand was immersed in cold water (2 ºC) in 2 min, while participants continuously rated their pain intensity on a scale from 1-10.

3.2.1.3 SELF-ASSESSED GASTROINTESTINAL SYMPTOMS

Two questionnaires were used to provide continuous information on GI symptoms; The Patient assessment of Constipation Symptoms questionnaire (PAC-SYM) to

assess participant's experience of constipation over time,[78] and the BSFS to assess stool frequency and form.[79] The participants filled in these questionnaires in the morning of day 1, every evening the next five days, and again in the morning of day 6.

3.2.1.4 ANAL SPHINCTER FUNCTION

Anal sphincter function on day 1 and day 6 was evaluated by three assessments; anal resting pressure, the RAIR, and anal canal distensibility. A water-perfused pressure catheter was placed in the internal anal sphincter (IAS), and a latex balloon, composed as previously described and attached to a syringe was placed in the rectum.[80] The balloon was inflated from 10 – 100 mL in a stepwise matter to elicit and measure the magnitude of RAIR, and anal resting pressure was measured as the IAS pressure five seconds before each distension (Figure 5A).[81] The EndoFLIP, encountering a cylindrical distensible bag, measured anal canal distensibility as the bag was filled with a saline solution to reach a maximum level of 50 mL (Figure 5B).[82] The bag pressure and anal canal diameter during the distension was used to assess pressure-strain elastic modulus (a measure of stiffness) and yield pressure.

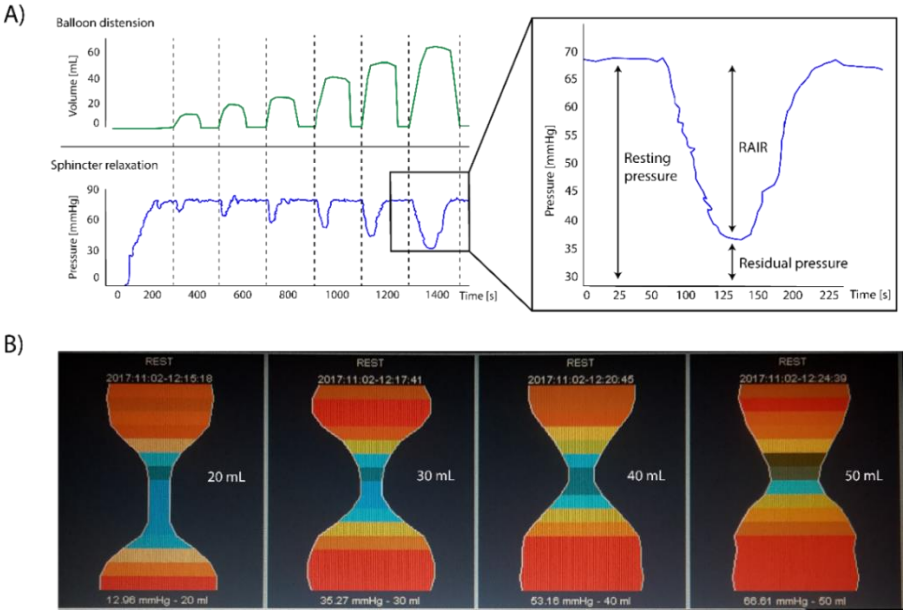

Figure 5. (A) Graphical illustration of measuring anal resting pressure and the recto-anal inhibitory reflex (RAIR) in relation to rectal balloon distension. The dotted lines represent start of balloon distensions. RAIR-induced sphincter relaxation was quantified as the difference in resting and residual pressure. **(B)** Screenshot from a typical EndoFLIP recording, here showing anal canal distensibility at 20-50 mL. Blue color indicates more pressure and thereby more constriction of the anal sphincter.

3.2.1.5 COLONIC FECAL VOLUME

To quantify total and regional volume of non-gaseous colonic content (feces) on day 1 and day 6, an MRI scan of the lower abdomen was taken. Contiguous images (35-40) were obtained using Dixon-type liver accelerated volume acquisition (LAVA-flex) water-only scans during a single inspired breath hold of 20 sec. The scans were analyzed by an in-house semi-automatic data analysis software in which colonic regions of interests were manually outlined by the researcher (Figure 6).[83,84] Subsequently, a statistical classification approach was used to refine the segmentation of the colon, and determine the colonic fecal volume.

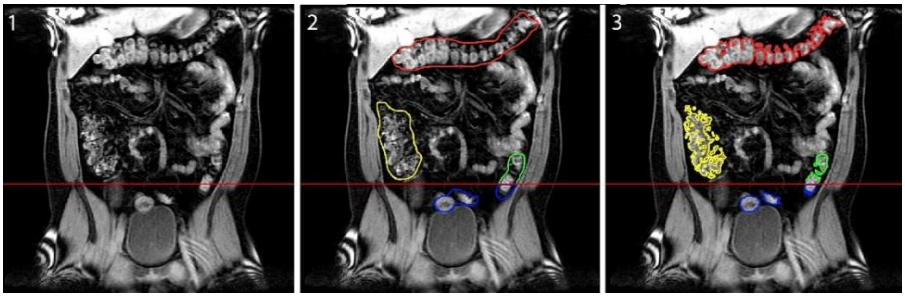

Figure 6. The procedure on outlining colonic regions to determine segmental colonic fecal volume. (1) The transition between the descending and recto-sigmoid colon was defined at the level of the left anterior superior iliac spine (red line). (2) Colonic regions were manually outlined, and (3) the automatic software crops the pixels to include only what is believed to be fecal matter, and volume was determined for each segment on each image.

3.2.1.6 GASTROINTESTINAL TRANSIT TIME

On day 2, the 3D-Transit electromagnetic capsule was swallowed and the abdominal belt was mounted to measure total and regional GI transit time and colonic motility patterns until day 6. Transit times were determined manually using analysis software in which capsule rotations and anatomical position of the capsule could be observed via 2D tracing (Figure 7A).[85] Colonic segmental transit times were assessed using a graphical user interface. Furthermore, five colonic motor patterns were identified using an automatic algorithm; 1) mass movements; 2) fast antegrade movements; 3) slow antegrade movements; 4) slow retrograde movements; and 5) fast retrograde movements (Figure 7B), as previously described.[86]

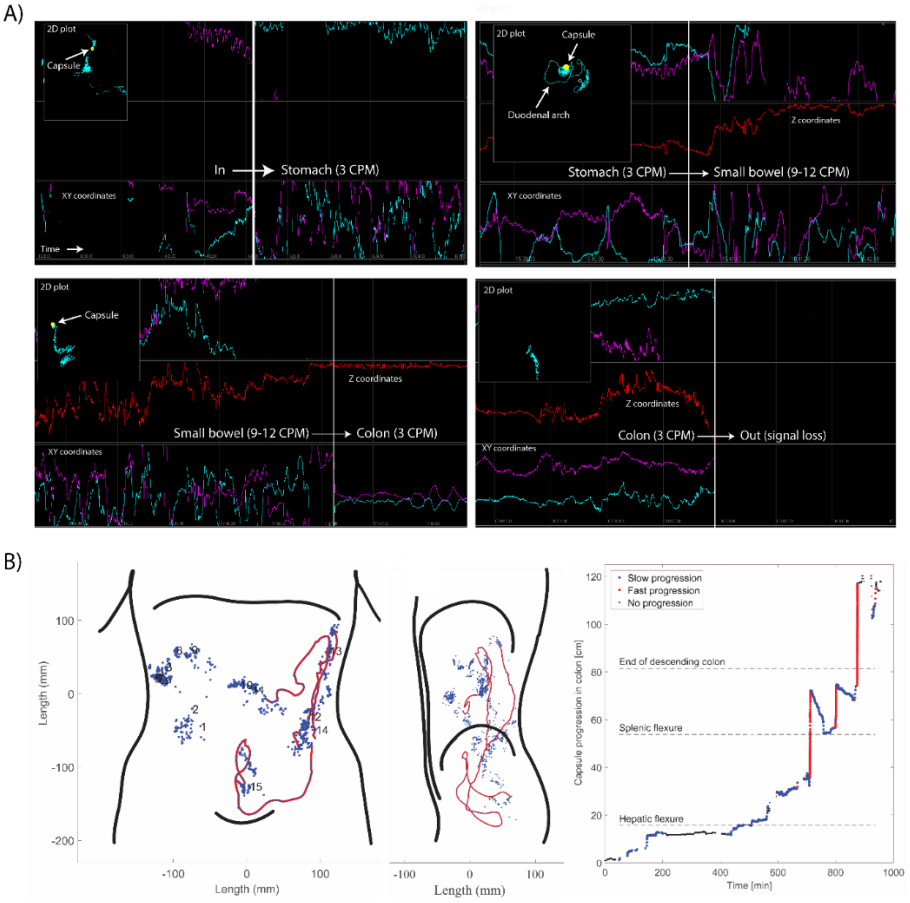

Figure 7. (A) Screenshots from a typical 3D-Transit recording. Segmental transit times are determined by evaluating capsule rotations (as a proxy for contractions/minute, and the anatomical position as seen on the 2D plot. **(B)** Capsule progression through the colon. Blue dots indicate slow progression (1 dot/minute) and red lines indicate fast propulsions (mass movements of colonic content). CPM: Contractions/minute.

3.2.2 KEY RESULTS

Fifty-six responded to the recruiting material and 31 of these were found non-eligible (Figure 8). In total, 25 participants were screened and randomized. One participant was excluded after the first treatment period due to non-compliance, and replaced by mirror-randomization and thus, 24 participants (median age of 25 years) completed the study.

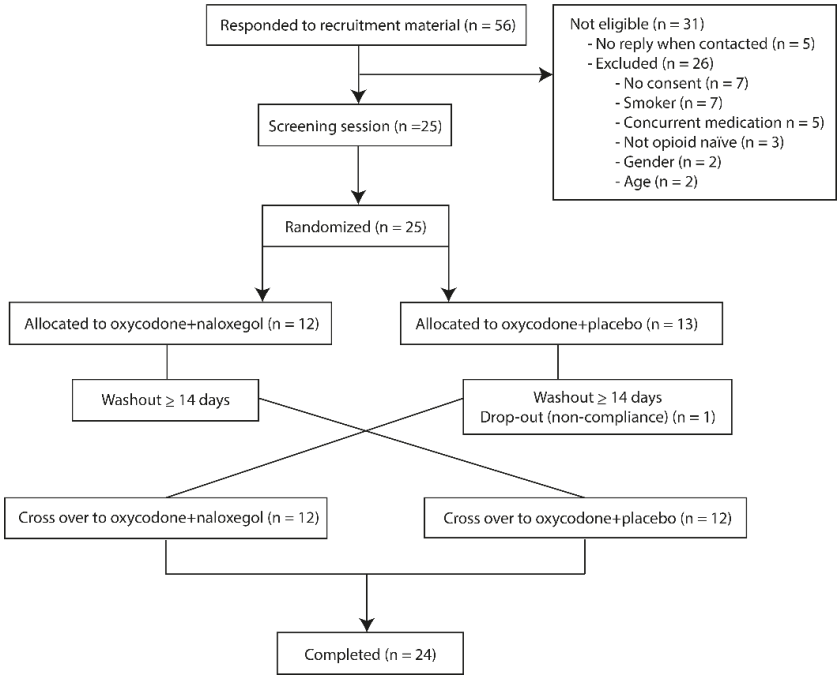

Figure 8. Flowchart for disposition of participants in Study II.

3.2.2.1 ANALGESIC EFFECTS

For both treatments, the analgesic effect of oxycodone was validated with a 15-19% increase in pain detection threshold to muscle pressure on day 6, compared to baseline (all $P < 0.02$). Naloxegol did not reverse this analgesic effect, as there was no difference in pain detection threshold on day 6 between treatments ($P > 0.1$). For the cold pressor test, it was not possible to detect an analgesic effect of oxycodone in either treatment-arms (all $P > 0.05$) (Study IIa-IIb).

3.2.2.2 SELF-ASSESSED GASTROINTESTINAL SYMPTOMS

GI symptoms increased over days in both treatments. Compared to placebo, naloxegol decreased PAC-SYM questionnaire scores, and improved stool form (i.e. induced

softer stools), a significant difference confined to day 3 (Figure 9A-B). There was no difference in stool frequency between treatments ($P > 0.05$) (Study IIa-IIb).

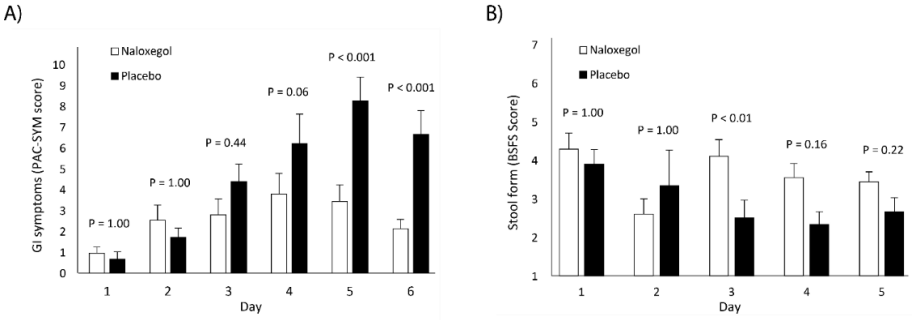

Figure 9 (A). Progression of GI symptoms over the course of 6 days in each treatment arm, assessed by The Patient assessment of Constipation Symptoms questionnaire (PAC-SYM) The differences reached statistical significance at days 5-6. **(B) Results** from the Bristol Stool Form Scale (BSFS) depicting stool form (lower scores represent harder, drier stools, i.e. 1 = constipation; 7 = diarrhea). Data are presented as means ± SEM.

3.2.2.3 ANAL SPHINCTER FUNCTION

Neither anal resting pressure nor anal canal distensibility were affected by either treatment (all $P > 0.05$). Compared to baseline, RAIR was diminished after 6 days of oxycodone treatment, and this effect was reversed by naloxegol, an effect significant at rectal balloon volumes of 60-100 mL (Figure 10) (Study IIa).

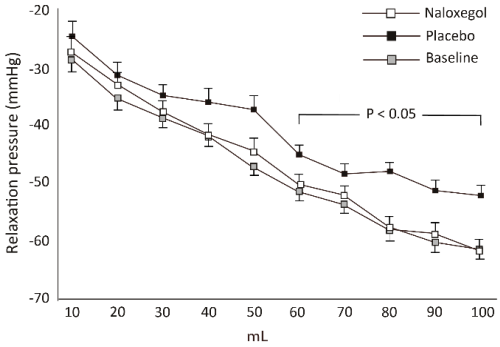

Figure 10. The effect of the two treatments on relaxation pressure (i.e. drop in internal anal sphincter pressure following balloon distension), in which naloxegol treatment normalized oxycodone-induced diminish of the recto-anal inhibitory reflex. The P-value represents differences between the two treatment arms, and data are presented as means ± SEM.

3.2.2.4 COLONIC FECAL VOLUME

Compared to baseline, colonic fecal volume was higher on day 6 in both treatments (all $P < 0.001$), and naloxegol did not reduce this volume on day 6, compared to placebo ($P > 0.2$) (Figure 11A) (Study IIb).

3.2.2.5 GASTROINTESTINAL TRANSIT TIME

3D-Transit capsule retention on day 6 occurred in 3 out of 24 cases during oxycodone+naloxegol treatment and 8 out of 24 cases during oxycodone+placebo. Compared to placebo, naloxegol reduced oxycodone-induced prolongation of total GI transit time (P=0.02) and colonic transit time (P<0.01) in which the significant difference was confined to the recto-sigmoid segment (Figure 11B). No difference in colonic motility parameters were found (all $P > 0.1$) (Study IIb).

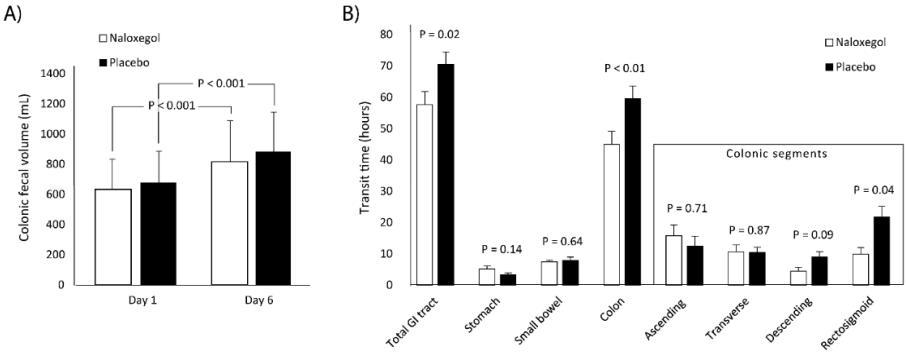

Figure 11. (A) Differences in total colonic fecal volume from day 1-6. **(B)** Total and segmental transit times. Data are presented as means ± SEM.

3.2.2.6 ASSOCIATIONS BETWEEN MEASURES

There were no significant associations between PAC-SYM scores, stool frequency or form, segmental transit times, colonic fecal volumes, or the anal sphincter measurements in either of the two treatments (Study IIa-IIb).

3.3 STUDY III

Regional transit times obtained by the 3D-Transit system is determined by visually observing changes in capsule rotation, along with shifts in position, as it passes the GI tract. However, mostly due to motion artefacts, these time points can be very difficult to identify, especially for the untrained eye. The 3D-Transit system possesses great potential in assessing GI motility, however, the validity of this manual method has not yet been addressed in detail. Hence, in this study we evaluated the inter-and intra-rater reliability of segmental transit times and addressed how the experience of raters influenced the identification of transit times.

3.3.1 METHODS

An overview on the study design of Study III is provided in Figure 12. Three researchers from Aalborg and London with different levels of experience in analyzing 3D-transit system data took part in this study. From a local research database, 36 recordings of healthy participants were randomly selected for analysis. All raters used a standardized procedure to place landmarks in the 3D-Transit System software to identify the time points when the ingestible capsule progresses from the stomach to the small bowel (gastric emptying), to the cecum (small bowel transit time), and out (colonic transit time). The analyses were repeated after a minimum time gap of two weeks. For each time point identified, the time taken, and difficulty of placing the landmarks were documented. Inter- and intra-rater reliability were determined using the intraclass correlation coefficient.

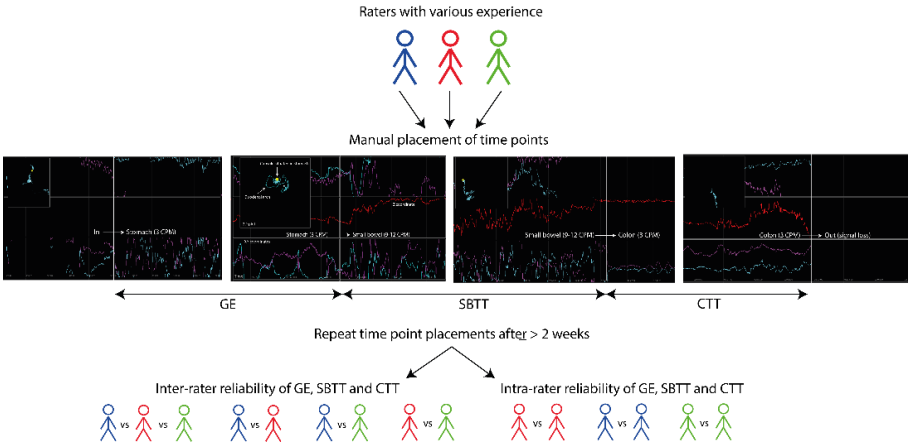

Figure 12. Simplified design of Study III.

3.3.2 KEY RESULTS

Inter-rater reliability comparing measurements for all three raters was poor for gastric emptying and small bowel transit time, although, fair between the two most experienced raters (ICC = 0.41 – 0.47) (Figure 13). For colonic transit time, inter-rater reliability was excellent for all measurements and in between raters (ICC = 0.94). For the two experienced raters, good to excellent intra-rater reliability was found for gastric emptying and small bowel transit time (ICC = 0.84 -1.00), while agreement was poor for the least experienced rater (0.20-0.48). Excellent intra-rater reliability was found for all three raters for colonic transit time (ICC = 0.97-0.99) (Study III).

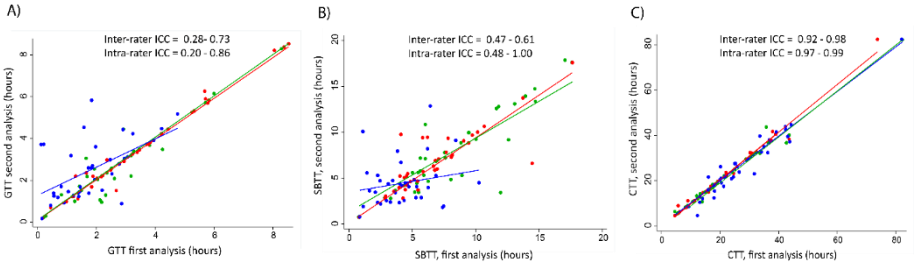

Figure 13. Combined scatterplots for inter-and intra-rater reliability across raters for (A) gastric emptying transit times (GTT), (B) small bowel transit times (SBTT), and (C) colonic transit times (CTT). Green color is the most experienced rater, red color is the mid-experienced rater, and blue color is the least experienced rater.

CHAPTER 4 DISCUSSION

Section 4.1 discusses the establishment of an experimental model to mimic OIBD, and the potential of such a model to clarify underlying mechanisms of OIBD and how pharmacological agents may treat it. Hereafter, a discussion on feasibility, advantages and limitations of subjective and objective assessments to evaluate OIBD is provided in section 4.2 and 4.3, undertaking the results from Study II and III.

4.1 HUMAN EXPERIMENTAL OIBD MODELS

In general, the purpose of experimental models is to mimic a specific symptom or disease in a reversible manner. This generates a controlled setting in which underlying pathological mechanisms, or responses to pharmacological interventions can be thoroughly investigated as in Study II. In animal models, the primary usage is in pharmacological studies to evaluate the safety and efficacy of novel and existing compounds in e.g. the opioid-affected rodent or primate gut.[87] However, due to the substantial species differences, interpolation of findings from animal studies to man is not always feasible. Human experimental models are therefore an important tool in translation from animal research into clinical implications. A valid human model must induce the same or similar symptomatology associated with the relevant disease, and this also applies with GI models. Various *in vivo* models of GI symptoms exist, e.g. for gut hyperalgesia, acid-related esophageal diseases, and diarrhea.[88–90] In contrast, inflammatory GI diseases are very difficult to mimic in humans, partly due to their multifactorial etiology and complex symptomatology, but also due to ethical reasons. This vastly limits models of e.g. irritable bowel syndrome, Crohn's disease, and ulcerative colitis to be induced in animals.[91]

As OIBD is not a disease in itself, but induced GI side effects to an intervention, the establishment of a human experimental OIBD model may seem straightforward. As previously mentioned, such a model was recently established by Poulsen et al. and Nilsson et al.[76,77] Lately, this model was employed in a comparative study to assess the efficacy of two treatments; Combined PR oxycodone and PR naloxone (an non-selective opioid antagonist) *vs* macrogol 3350 (a conventional laxative), on GI motility and anal sphincter function.[92,93] A very similar model was applied in Study II, in which the dose of oxycodone was slightly higher (30 mg instead of 20 mg pr.

day), and treatment period was six days instead of five. These changes were applied to ensure sufficient OIBD manifestation in order to detect a possible effect of naloxegol. As various GI symptoms were induced, and GI transit time in both treatment periods were considerably longer than placebo values from the study by Poulsen et al, we concluded that an OIBD model was indeed established in Study II. Not only oxycodone can be used to induce symptoms of OIBD in healthy participants for the purpose of measuring a pharmacological effect of a PAMORA. Thus, a 3-day treatment period of 12 mg b.i.d codeine in healthy has been used to show a reversal of codeine-induced prolongation of small intestine and colonic transit by alvimopan.[26] The same approach was used by another research group in which methylnaltrexone was found to have no effect on codeine-induced prolongation of colonic transit.[94] The authors of the latter study suggested that a higher dosage of methylnaltrexone may be needed to induce a detectable effect on transit in opioid-naïve healthy participant, however they did not question the model itself.

4.1.1 ADVANTAGES AND LIMITATIONS OF OIBD MODELS

The application of experimental models for the study of pharmacological effects on OIBD symptoms has several important advantages. For example, the influence of confounding diseases, psychological factors, and other administrated drugs is eliminated, and we are able to study OIBD in a much more controlled setting. In clinical settings, patients with OIBD always has one or more disorders associated with severe pain, demanding the initial opioid analgesic treatment. However, patients (especially in the elderly generation) may not only be suffering from pain, but also have other disorders known to induce GI dysfunction and chronic constipation, e.g. type 2-diabetes and Parkinson's disease.[95,96] Furthermore, patients with OIBD are highly susceptible to psychological distress including both global distress and anticipatory anxiety.[97,98] Psychological distress is known to induce GI symptoms in itself, possibly creating a vicious circle. In general, pain and stressful states is known to evoke both short- and long-term influences on function of the GI tract.[99] Finally, many OIBD patients are likely treated with additional drugs known to affect GI motility, such as NSAIDs, antihypertensive agents, and tricyclic antidepressants.[100,101] All these comorbidities are vastly avoided in experimental OIBD models (Figure 14). Nevertheless, several limitations need to be addressed as the degree to which a very short-term model can mimic processes involved in clinically OIBD is debatable. First

of all, OIBD patients are often treated with higher opioid doses and for a much longer period of time than what is feasible and ethical in studies with healthy participants. Opioids are highly addictive substances, and several ethical considerations needs to be taken into account when administrating these drugs to healthy participants. Hence, in study II, strict exclusion criteria concerning present or previous use of addictive substances (nicotine, alcohol, illegal drugs) were applied. Moreover, early signs of opioid dependency were assessed by the study personal three days after a treatment period was ended (no participants showed any initial dependency signs during or after any treatment period). An experimental model involving the GI tract also needs to sustain from causing prolonged alterations in either intestinal histology of GI motility. For the time however, we do not know whether a short-lasting treatment period of opioids cause long-term alterations in gut motility function, however we do consider the dosage and length of treatment in Study II to be completely reversible and safe.

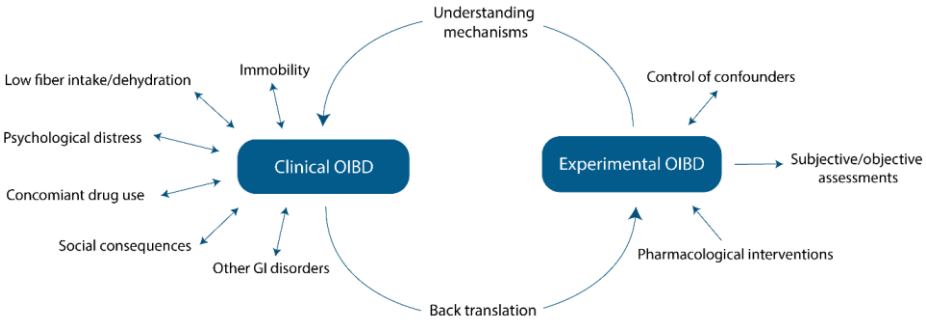

Figure 14. Schematic overview on the most important confounders in clinical studies of OIBD, and how these are avoided in experimental OIBD models. In experimentally induced OIBD, the response to pharmacological interventions can be assessed with subjective/objective methods like in Study II.

4.2 SUBJECTIVE ASSESSMENTS OF OIBD

Pain and discomfort are personal, subjective experiences influenced by the situation, cultural background, and various psychological variables.[102] This also applies to the patient's view on opioid-induced GI side effects. In clinical practice, knowledge on patient experience of OIBD symptoms is crucial in all aspects of diagnostics and choice of treatment, and several self-assessed questionnaires and rating scales for evaluating constipation/OIBD in the clinic have been developed over the past years. All are primarily focusing on self-reports on constipation intensity/severity,

ease/difficulty of defecation, incomplete evacuation, straining and satisfaction (i.e. satisfaction with stool frequency or pharmacological treatment).[103] The most widely used questionnaire is probably the Bowel Function Index, which is very straightforward and easy to use in daily clinical practice.[104] Some questionnaires are more time-consuming and prone to non-compliance thus primarily adapted for research purposes. These include the Cleveland Clinic Constipation Score, Constipation assessment scale, the Patient Assessment of Constipation-Quality of Life, Gastrointestinal Symptom Rating Scale, and PAC-SYM, all well-validated and assessing a wide range of GI symptoms related to OIBD.[105] For multiple reasons, the PAC-SYM questionnaire was chosen as the single subjective measure in Study II. First of all, the PAC-SYM has high internal consistency and high test-retest reliability.[78] Second of all, as a distinct advantage, the PAC-SYM questionnaire is divided into three symptom domains; abdominal symptoms (four questions), rectal symptoms (three questions), and stool symptoms (five questions), and therefore provides a broad picture on all aspects of OIBD. Third of all, several studies have found PAC-SYM to efficaciously detect not only negative opioid-effects on GI symptoms, but also efficacy of various pharmacological agents to treat it.[46,76,106] In Study II, we found progressively increasing GI symptoms during the course of oxycodone treatment, and comparing naloxegol and placebo, participants receiving naloxegol had fewer GI side effects. This supports the clinical efficacy of naloxegol to treat OIBD symptoms, and the results are also in line with a previous comparable study in which naloxegol improved PAC-SYM scores of non-cancer pain patients receiving high doses of opioids.[62] However, as with all other questionnaires to evaluate OIBD, the PAC-SYM only provide a snapshot of a very subjective feeling, and results rely heavily on the participants understanding of the terminology utilized in the questionnaires. A limitation regarding Study II was that GI symptoms were not recorded prior to start of each study period, which could have increased the validity of the PAC-SYM results.

Several attempts have been made to prove a correlation between self-reported GI symptoms and objective measures such as transit time. Such correlations could, in the long run, justify that clinicians and researchers merely use subjective measures, thereby probably increasing compliance and reducing clinical trial costs. In Study II, the PAC-SYM results did not correlate to the length of transit times (or RAIR-induced sphincter relaxation), which is in line with previous studies investigating the association between PAC-SYM and transit time in constipated individuals.[73,74,107] This indicates that the individual perception of OIBD is independent of objective

findings, which reflects the multifactorial clinical representation of OIBD. Thus valid, easy applicable, and low-cost objective methods are still needed in both clinical settings and research trials to assess OIBD.

4.3 OBJECTIVE ASSESSMENTS OF OIBD

4.3.1 STOOL FREQUENCY AND FORM

The BSFS is a visual scale allowing the patient/participant to identify form of stool using seven different images with anchored words.[79] If used over a longer period of time, the BSFS may also be used to evaluate daily/weekly stool frequency. As touched upon in Chapter 2, stool frequency and form are often applied in the clinic to evaluate OIBD severity, and these outcomes continue to be used as surrogate markers of bowel transit/motility, despite limited validation. Especially in research, stool frequency is not recommended as the sole outcome when evaluating OIBD, for three overlapping reasons: Firstly, stool frequency is likely affected by multiple factors that are difficult to control for i.e. dietary intake, activity level, psychological state etc. Secondly, stool frequency does not always associate with symptom burden, and may be normal in even heavily constipated patients.[5] Thirdly, stool frequency rarely correlates with other more objective measures, e.g. whole-gut transit as found in studies with patients with chronic constipation and irritable bowel syndrome.[79,108] On the other hand, stool form may be a much better predictor of whole-gut transit (and indicator of general bowel health), although patients may find evaluating stools via the BSFS difficult.[109] Altogether, because stool frequency is very variable even in healthy (3-11 stools per week in adults[110]), and stool characteristics also can vary substantially, BSFS outcomes should always be accompanied by other more objective testing modalities.

In Study II, we found a mean stool frequency of 0.5 pr. day for participants receiving oxycodone+placebo treatment. As the most common bowel habit is considered once daily, these results indicate that oxycodone decreased stool frequency.[111] Our results are also comparable to the preceding study by Nilsson et al., who reported a frequency of 0.8 after 5 days of oxycodone treatment.[77] The small difference may reflect the slightly higher oxycodone dosage and longer treatment period in Study II. Although a trend was present, we found no significant effect of naloxegol on stool frequency (0.68 *vs* 0.5 daily spontaneous bowel movements). This conflicts earlier studies in which 4-12 weeks of naloxegol treatment increased weekly

stool frequency in OIBD patients.[61,112] As these studies employed chronic opioid users, it is very plausible that such a short-term treatment applied in Study II is too small to affect stool frequency. On the other hand, naloxegol did induce softer stools, as the mean daily BSFS score was 3.6 compared to 2.9 for placebo. The physiological explanation is probably linked to improvement of motility and reduced passive absorption of gut fluids. A recent paper on data from the KODIAC studies also reported that naloxegol improved stool form over a course of 12 weeks.[71] Our findings can be considered very clinically relevant, as patients often relate their OIBD burden to uncomfortable passing of dry, hard stools.[41]

4.3.2 THE 3D-TRANSIT SYSTEM

As mentioned in Section 3.2, commonly used methods for assessing GI motility are scintigraphy, radiopaque markers, and hydrogen breath tests, all mainly applied for the measurement of whole gut transit time. The purpose of Study II was to explore the exact motility changing effects of a PAMORA, and where in the GI tract these changes were most pronounced. For this purpose, the 3D-Transit is currently the most advanced tool on the marked, hence this methods was applied. This system accurately tracks and measures the position of up to three ingestible electromagnetic capsules throughout the GI tract, via an external detector plate carried on the abdomen.[85,113] As depicted in Figure 7A, regional transit times are hereafter manually identified by visually observing changes in the orientation angles of the capsule, reflecting gut peristalsis. However, due to external movements and external noise, it can be very difficult to identify the time points from when a capsule progresses from one GI segment to the other. The inter-rater reliability of manually assessed GI transit times has been reported to be very good.[85] However, the raters in this study were not blinded to each other's analyses, and helped each other analyze difficult recordings. Study III was conducted to assess the intra-and inter-rater reliability of regional GI transit times in a blinded fashion, between raters with various experiences. This was done to validate the results on transit time outcomes from Study II, and to provide recommendation for future studies using the 3D-Transit system. Our results showed that raters need adequate and long-term training in identifying the transition from one GI segment to the other, as the inexperienced rater provided transit times with very low reliability.

The 3D-Transit system has previously been used to gain insights into regional GI dysmotility in patients with carcinoid diarrhea, severe ulcerative colitis and Parkinson's disease.[75,114,115] Regarding experimental OIBD, the 3D-Transit system was also used in the study by Poulsen et al., to prove the prolongation of transit by oxycodone.[76] Comparing the total GI transit time for oxycodone+placebo treatment in that study and Study II, transit time was considerable longer in the latter (71.3 hours *vs* 43.9 hours). This emphasizes that we succeeded in establishing an OIBD model in terms of prolonging transit. Only a few studies have investigated the effect of naloxegol on opioid-induced prolongation of transit time, as the main focus until now has been to prove a more clinical-related effect of the drug, e.g. increased stool frequency. In Study II, naloxegol treatment significantly reduced total GI transit time, compared to placebo (56.8 hours *vs* 71.3 hours). Compared to placebo treatment in the study by Poulsen et al, which did not include oxycodone administration, naloxegol did not completely reverse transit time to "normal levels" (56.8 hours *vs* 22.2 hours). However, to verify this comparison we would need a strict placebo-arm in Study II, which was not included in the study design. Our findings are in line with a study employing the hydrogen breath test to conclude that naloxegol reduce morphine-induced prolongation of transit time in healthy participants.[63] In contrast, our result are in conflict with a very recent study by Halawi et al. finding that 3 days of 25 mg naloxegol treatment in healthy participants does not reverse codeine-induced prolongation of whole gut transit as measured with scintigraphy.[70] This might question whether a higher dose of naloxegol may be needed to treat OIBD resulting from acute opioid administrations, reinforced by a previous study showing that morphine-prolongation of transit time in healthy participants was significantly reduced by naloxegol only when administered as dosages of 125 mg or higher.[116] The discrepancies between our studies could also lie within the study designs, as the study by Halawi et al. used a relatively low dose of the pro-drug codeine, and only for 3 days. Furthermore, although scintigraphy is considered the golden standard for transit measurements, a limitation for this method is that transit time is based on snapshot images of the colon obtained after 24 and 48 hours of ingesting a radiolabeled solid. In Study II, most transit times were in the range of 60-90 hours, and therefore scintigraphy likely underestimates transit times for the most constipated participants, who might also have the greater effect of naloxegol treatment. This problem is eliminated with methods employing ingestible capsules like the 3D-Transit system. Furthermore, with this system it is possible to assess regional transit times, not only for the stomach, small bowel, and colon, but also for the four colonic segments. In

Study II, naloxegol significantly reduced transit time in the recto-sigmoid segment (9.2 hours *vs* 23 hours in the placebo treatment). This may be because naloxegol promotes colonic motility, leading to less stasis of stool in this GI region thereby making stool less dry and hard easing defecation. Also, it may point to that opioid-induced anal sphincter dysfunction is somewhat reduced by naloxegol which will be discussed in section 4.3.4.

The 3D-Transit system has the potential to measure various colonic motility patterns, e.g. number of colonic mass movements, proportion of antegrade, retrograde, fast and slow peristaltic movements. Colonic transit time presumably reflects underlying motility, hence, as naloxegol decreased colonic transit time, we expected to find increased colonic motility parameters as well. However, no differences between the two treatments were found. The method to evaluate colonic motility patterns with the 3D-Transit system is still in its infancy. However, from a very recent study employing the 3D-Transit system we know that oxycodone does cause colonic dysmotility, in that a 5-day oxycodone treatment induced less colonic mass movements in healthy participants.[32] Colonic motility parameters has previously been addressed in a study by Hiroz et al., which was designed to capture colonic responses to stimuli known to enhance gut motility in healthy participants.[117] Compared to this study, we found considerably less values for colonic activity in Study II. However, in the Hiroz et al. study, colonic motility was assessed in immobilized healthy participants, using the preceding stationary MTS-1 system. Hence, whether the discrepancy ascribes the presumed dampening effect on motility by oxycodone, or differences in methodology, cannot be known for sure.

4.3.3 MRI COLONOGRAPHY

Like stool frequency and GI transit time, colonic volume may also be considered a surrogate marker for underlying GI motility. Theory is, the less forward propulsive motility, a larger volume of fecal matter accumulates in colon which leads to more constipation. In the clinic, assessment of colonic volume may be beneficial to evaluate constipation in terms of assessing the degree of fecal retention and the need for disimpaction before therapy. For this, a standard abdominal x-ray is often used.[118] Furthermore, abdominal CT imaging can provide a more virtual colonography which is useful for evaluating colonic content in relation to bloating and abdominal

distension.[119] However, a CT requires either colonic gas filling or contrast enhancement, and therefore exposes the patient to substantial discomfort and potentially harmful ionizing radiation.[120] MRI produces images without the use of contrast-enhancing agents in the unprepared colon, which facilitates the quantification of segmental colonic volumes in a non-harmful manner. MRI has previously been used to measure fasting and postprandial small and colonic volumes in healthy and patients with IBS.[121–124] Although not applied in the clinical evaluation of OIBD (to our knowledge), MRI colonography represents a valuable tool for the evaluation of OIBD in research. For this purpose, our research group has recently developed an in-house semi-automatic software capable of calculating segmental colorectal volumes from T2-weighted MRI images, a method shown to have a high degree of validity.[65,106] This was applied to show an increase in colonic volume after 5 days of oxycodone treatment in healthy participants in the study by Nilsson et al. (a 41% increase in cecum/ascending colon compared to placebo treatment).[77] Also, the same method was used in a recent study in which oxycodone-treated participants receiving the osmotic laxative macrogol had a significantly higher colorectal volume, than those receiving naloxone.[92] However, using T2-weighted MRI images has limitations in that colonic gas and the colon wall itself are also interpreted as colon volume. Thus these images are unable to determine the "true" volume of fecal matter. This may however be obtained using LAVA-Flex MRI sequences, which eliminates the possibility of interpreting gas and intestinal wall erroneously as feces.[125,126] This method has been shown to offer a superior and more homogenous fat suppression of the abdomen compared to a standard T1-weigthed MRI.[127] Thus, the MRI images obtained in Study II was analyzed as LAVA-Flex sequences. In line with the previous study by Nilsson et al. using T2-weghted images,[77] we found a significant increase in colonic fecal volume after 6 days of oxycodone treatment in Study II. We assumed that colonic fecal volume would be somewhat reliant on GI transit time, however volume did not differ between naloxegol and placebo treatment. An explanation for this may be that naloxegol simply doesn't affect colonic volume to an extent that is measureable with MRI. Another possible explanation however is linked to the proposed effect of naloxegol on opioid-induced fluid secretion/absorption dysfunction as explained in section 1.3. Thus, colonic fecal volume could be counterbalanced to the level of placebo treatment as naloxegol may increase the amount of water in colonic contents, which may be interpreted as high fecal load on the MRI images. However, colonic volume obtained by LAVA-Flex sequences is not (yet) a validated method, and the MRI results from Study II should therefore be considered preliminary. Further

refinement on the analysis of colonic water content is also necessary to confirm this theory. For this, texture analysis of MRI images could be the way forward as applied in a study investigating the effect of loperamide (an opioid sold as an anti-diarrhoeal agent) on small bowel water content.[128] Another explanation for the MRI findings in Study II is methodological limitations. Several MRI scans were missed due to retention of the 3D-Transit capsule (as the capsule is not approved for the MRI scanner), thus only 15/24 and 19/24 scans on day 6 were obtained for the naloxegol and placebo treatment, respectively. This probably systematically underestimates colonic fecal volume in especially the placebo treatment arm, as the participants in this group would likely the more constipated.

4.3.4 ASSESSMENT OF ANAL SPHINCTER FUNCTION

Anal sphincter function in relation to constipation may be assessed with a variety of objective methods. In the clinic, an underlying evacuation disorder is often confirmed or ruled out using a defecography, endo-anal ultrasound, or a balloon expulsion test to assess anorectal and pelvic floor motion[129] In addition, anorectal manometry (conventional, high-resolution, and 3D-high definition) is the most widely used technique for the detection of abnormalities of sphincter function or recto-anal coordination.[130] With this, anal resting pressure, maximal pressure during sustained voluntary contraction, duration of sustained voluntary contraction, and pressure during cough reflex can be assessed.[131] Sphincter function is rarely a part of the clinical evaluation of OIBD although straining and discomfort during evacuation are common symptoms. Thus, a study in opioid-treated patients, one-third had the sensation of anal blocking and often felt the need to use digital maneuvers to complete defecations.[41] A part of the explanation as to why clinicians rarely focus on opioid-induced anal sphincter dysfunction may be that studies on this area are highly inconclusive and relatively old. Thus, two studies report that opioids elevate anal sphincter tone[132,133], while all others conclude that opioids have no effect.[39,93,132–135] All these studies used simple anorectal manometry which was also applied in Study II. Here, we also found no effect of oxycodone on anal resting pressure, and thus also no effect of naloxegol compared to placebo. The distribution and physiological importance of opioid receptors in the structures of the IAS and external anal sphincter is not clarified.[136] Thus, a simple reason for this finding may be that opioid receptors are not present in the myogenic structures of the smooth muscle that produce the basal

tone of the anal sphincter.[137] Other explanations for these results are that such a short duration of treatment is not enough to affect anal pressure, or that the differences in anal resting pressure between baseline and 6 days pharmacological treatment may be too small to detect using simple anorectal manometry. An effect was however observed on the RAIR in that 1) oxycodone treatment significantly diminished the RAIR, and 2) naloxegol returned this to normal level. The former is in line with a study by Poulsen et al. who found oxycodone to diminish RAIR after 5 days treatment,[31] and with an older study using loperamide.[116] The physiological explanation behind this effect on RAIR may be that opioids hyperpolarize the intramural enteric neurons,[33] or due to an effect of opioids on the conscious perception of stool in the rectum.[39] This dampening effect of opioids on perception of rectal filling and ability of IAS relaxation may contribute to the symptomatology of OIBD and hinder normal defecation. The normalizing effect of naloxegol on RAIR is likely explained by the elimination of oxycodone molecules from the high density of opioid receptors in the neural structures of the IAS.[138] The method used to assess RAIR in Study II is inspired from the study by Musial et al., as a very quick and simple way to quantify the drop in IAS pressure following a rectal distention.[39] However, limitations with this method are difficulties in manually securing the correct placement for the rectal balloon, and that position of the participant and the presence or absence of the perception of the desire to defecate possibly have an influence on the absolute values obtained. Also, these measurements are performed in the unprepared rectum which means that accumulating stool could prevent the filling of the balloon in especially the most constipated participants, which could provide erroneously pressure data. A better and more standardized method to assess both anal resting pressure and the RAIR would have been high-resolution anorectal manometry which can provide a much better visualization and direct assessment of the recto-anal coordination.[139] This method may be more sensitive to clinically relevant pathology than anorectal manometry.[140] In addition to manometry evaluating anal sphincter tone and RAIR we applied the EndoFLIP to evaluate distensibility of the entire sphincter apparatus following the pharmacological treatments. However, our group has yet been unsuccessful in proving an effect of opioids on anal canal distensibility using the EndoFLIP,[93] and this was also the case for Study II. These findings suggest that opioids does not affect distensibility and stiffness of the anal canal, and thereby this method was not appropriate to detect effects on naloxegol on this either. Most likely, the EndoFLIP system is a more suitable method in the detection of large distensibility deficiencies, and is not suitable to detect very small changes in distensibility as a 6

day opioid treatment probably would produce. Thus, the EndoFLIP system has previously been used to evaluate anal sphincter function in patients with profound defactory disorders such as fecal incontinence and systemic sclerosis affecting the smooth muscle cells of the IAS.[141,142]

CHAPTER 5 CONCLUSION

Naloxegol not only improved GI symptoms, but also reversed opioid-induced dysmotility and opioid-induced dampening of the RAIR. Thus, self-assessed questionnaires, the 3D-Transit system, and assessment of RAIR through anorectal manometry were all methods sensitive enough to detect an effect of a PAMORA on experimentally induced OIBD. When setting up future studies investigating OIBD, in which one wants to comprehend many different areas of the GI tract, researchers could beneficially focus on these methods. Especially the 3D-Transit system holds great potentials within obtaining detailed information on intestinal motility, and results from Study III validates and supports the current methodology for the extraction of segmental transit time from its software. The EndoFLIP system does not seem suitable for these kind of experimental studies. On the other hand, RAIR seems to account for a part of the defactory problems seen in OIBD, and the method using anorectal manometry and balloon distension of the rectum appears feasible. Although no effect of naloxegol was seen on colonic fecal volume, the method of MRI colonography holds potential for improvement and may be a suitable method when investigating how opioids affects colonic fecal volume.

5.1 FUTURE PERSPECTIVES

This thesis provides the framework for further development of methods to assess OIBD, and for various types of new studies. As mentioned in the introduction, the efficacy outcome in previous studies of naloxegol has primarily been change in number of bowel movements, and not much is known on the underlying mechanisms of this drug. Thus, the next natural step would be to evaluate the effect of naloxegol in chronic opioid users using questionnaires, the 3D-Transit system, and assessment of RAIR as applied in Study II. These methods could also be applied in studies investigating other conditions where GI dysmotility or anal sphincter dysfunction is suspected, e.g. in patients with irritable bowel syndrome or Crohn's disease. Moreover, we intend to further examine the possibilities within MRI to assess water content in colon, not only to be applied for the MRI data in Study II, but to be used as a general elucidative and diagnostic tool when assessing OIBD in clinical settings.

Also, for the 3D-Transit system, we intend to advance data analysis of the colonic motility parameters obtained with this system, and possibly conduct new studies on how naloxegol affect specific motility patterns in colon. Refinement of the MRI method and the 3D-Transit system could provide important knowledge regarding how gut secretory and motility mechanisms are affected by opioids, and how this is modulated/normalized by e.g. PAMORAs.

LITERATURE LIST

1. Reid, K. J. et al. Epidemiology of chronic non-cancer pain in Europe: narrative review of prevalence, pain treatments and pain impact. Curr. Med. Res. Opin. 27, 449–462 (2011).

2. Breivik, H., Collett, B., Ventafridda, V., Cohen, R. & Gallacher, D. Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. Eur. J. Pain 10, 287–333 (2006).

3. Skolnick, P. The Opioid Epidemic: Crisis and Solutions. Annu. Rev. Pharmacol. Toxicol. 58, annurev-pharmtox-010617-052534 (2018).

4. Khademi, H., Kamangar, F., Brennan, P. & Malekzadeh. Opioid Therapy and its Side Effects: A Review. Arch. Iran. Med. Arch Iran Med 19, 870–876 (2016).

5. Bell, T. J. et al. The prevalence, severity, and impact of opioid-induced bowel dysfunction: Results of a US and European patient survey (PROBE 1). Pain Med. 10, 35–42 (2009).

6. Abramowitz, L. et al. Prevalence and impact of constipation and bowel dysfunction induced by strong opioids: a cross-sectional survey of 520 patients with cancer pain: DYONISOS study. J. Med. Econ. 16, 1423–1433 (2013).

7. Brock, C. et al. Opioid-induced bowel dysfunction: Pathophysiology and management. Drugs 72, 1847–1865 (2012).

8. Pottegård, A. et al. Information on risk of constipation for Danish users of opioids, and their laxative use. Int. J. Clin. Pharm. 36, 291–294 (2014).

9. Nelson, A. D. & Camilleri, M. Opioid-induced constipation: advances and clinical guidance. Ther. Adv. Chronic Dis. 7, 121–134 (2016).

10. Simren, M., Palsson, O. S. & Whitehead, W. E. Update on Rome IV Criteria for Colorectal Disorders: Implications for Clinical Practice. Curr. Gastroenterol. Rep. 19, (2017).

11. Swegle, J. M. & Logemann, C. Management of common opioid-induced adverse effects. American Family Physician 74, 1347–1354 (2006).

12. Gupta, A., Coyne, K. S., Datto, C. & Venuti, C. The Burden of Opioid-Induced Constipation in Younger Patients with Chronic Noncancer Pain. Pain Med. 1–10 (2018).

13. Coyne, K. S. et al. Opioid-Induced Constipation Among Patients with Chronic Noncancer Pain in the United States, Canada, Germany, and the

United Kingdom: Laxative Use, Response, and Symptom Burden Over Time. Pain Med 16, 1551–1565 (2015).

14. Rauck, R. L., Hong, K.-S. J. & North, J. Opioid-Induced Constipation Survey in Patients with Chronic Noncancer Pain. Pain Pract. Off. J. World Inst. Pain (2016).

15. LoCasale, R. J., Datto, C., Wilson, H., Yeomans, K. & Coyne, K. S. The Burden of Opioid-Induced Constipation: Discordance Between Patient and Health Care Provider Reports. J. Manag. Care Spec. Pharm. 22, 236–245 (2016).

16. Müller-Lissner, S. et al. Opioid-Induced Constipation and Bowel Dysfunction: A Clinical Guideline. Pain Med. 7, 121–34 (2016).

17. Holzer, P. et al. Opioid-induced bowel dysfunction in cancer-related pain: causes, consequences, and a novel approach for its management. J. Opioid Manag. 5, 145–51 (2009).

18. Hjalte, F., Berggren, A.-C., Bergendahl, H. & Hjortsberg, C. The Direct and Indirect Costs of Opioid-Induced Constipation. J. Pain Symptom Manage. 40, 696–703 (2010).

19. Søndergaard, J., Christensen, H. N., Ibsen, R., Jarbøl, D. E. & Kjellberg, J. Healthcare resource use and costs of opioid-induced constipation among non-cancer and cancer patients on opioid therapy: A nationwide register-based cohort study in Denmark. Scand. J. Pain 15, 83–90 (2017).

20. Holzer, P. Pharmacology of Opioids and their Effects on Gastrointestinal Function. Am. J. Gastroenterol. Suppl. 2, 9–16 (2014).

21. Holzer, P. Opioid receptors in the gastrointestinal tract. Regulatory Peptides 155, 11–17 (2009).

22. Sharma, S. K., Nirenberg, M. & Klee, W. a. Morphine receptors as regulators of adenylate cyclase activity. Proc. Natl. Acad. Sci. U. S. A. 72, 590–4 (1975).

23. Wood, J. D. & Galligan, J. J. Function of opioids in the enteric nervous system. Neurogastroenterology and Motility 16, 17–28 (2004).

24. Crighton, I. M. et al. A comparison of the effects of intravenous tramadol, codeine, and morphine on gastric emptying in human volunteers. Anesth. Analg. 87, 445–449 (1998).

25. Jeong, I. D. et al. A randomised, placebo-controlled trial comparing the effects of tapentadol and oxycodone on gastrointestinal and colonic transit in healthy humans. Aliment. Pharmacol. Ther. 35, 1088–1096 (2012).

26. Gonenne, J. et al. Effect of alvimopan and codeine on gastrointestinal

transit: A randomized controlled study. Clin. Gastroenterol. Hepatol. 3, 784–791 (2005).

27. Kurz, A. & Sessler, D. I. Opioid-induced bowel dysfunction: Pathophysiology and potential new therapies. Drugs 63, 649–671 (2003).

28. De Luca, A. & Coupar, I. M. Insights into opioid action in the intestinal tract. Pharmacology and Therapeutics 69, 103–115 (1996).

29. Yancey-Wrona, J. et al. 6β-Naltrexol, a Peripherally Selective Opioid Antagonist that Inhibits Morphine-Induced Slowing of Gastrointestinal Transit: An Exploratory Study. Pain Med. 12, 1727–1737 (2011).

30. Smith, K. et al. Naloxone as part of a prolonged release oxycodone/naloxone combination reduces oxycodone-induced slowing of gastrointestinal transit in healthy volunteers. Expert Opin. Investig. Drugs 20, 427–439 (2011).

31. Kaufman, P. N. et al. Role of opiate receptors in the regulation of colonic transit. Gastroenterology 94, 1351–6 (1988).

32. Mark EB , Poulsen JL, Haase AM, Espersen M, Scchlageter V, Scott M, Krogh K, D. A. The effect of opioid treatment on colorectal motility assessed by electromagnetic capsules. in Neurogastroenterol Motil 106 (2017).

33. Galligan, J. J. & Akbarali, H. I. Molecular Physiology of Enteric Opioid Receptors. Am. J. Gastroenterol. Suppl. 2, 17–21 (2014).

34. Kromer, W. Endogenous and exogenous opioids in the control of gastrointestinal motility and secretion. Pharmacol. Rev. 40, 121–62 (1988).

35. Rangan, V. & Lembo, A. Reduction in pain : Is it worth the gain ? The effect of opioids on the GI tract. 1–4 (2018).

36. Kraichely, R. E., Arora, A. S. & Murray, J. A. Opiate-induced oesophageal dysmotility. Aliment. Pharmacol. Ther. 31, 601–606 (2010).

37. Sharma, S. S. Sphincter of Oddi dysfunction in patients addicted to opium: An unrecognized entity. Gastrointest. Endosc. 55, 427–430 (2002).

38. Torres, D., Parrinello, G., Trapanese, C. & Licata, G. Sudden severe abdominal pain after a single low dose of paracetamol/codein in a cholecystectomized patient: Learning from a case report. Am. J. Ther. 17, 133–134 (2010).

39. Musial, F., Enck, P., Kalveram, K. T. & Erckenbrecht, J. F. The effect of loperamide on anorectal function in normal healthy men. Journal of clinical gastroenterology 15, 321–4 (1992).

40. Loening-Baucke, V., Pringle, K. C. & Ekwo, E. E. Anorectal manometry for the exclusion of Hirschsprung's disease in neonates. Journal of pediatric

gastroenterology and nutrition 4, 596–603 (1985).

41. Tuteja, A. K., Biskupiak, J., Stoddard, G. J. & Lipman, A. G. Opioid-induced bowel disorders and narcotic bowel syndrome in patients with chronic non-cancer pain. Neurogastroenterol Motil 22, 424–30, e96 (2010).

42. Dorn, S., Lembo, A. & Cremonini, F. Opioid-Induced Bowel Dysfunction: Epidemiology, Pathophysiology, Diagnosis, and Initial Therapeutic Approach. Am. J. Gastroenterol. Suppl. 2, 31–37 (2014).

43. Drewes, A. M. et al. Definition, diagnosis and treatment strategies for opioid-induced bowel dysfunction-Recommendations of the Nordic Working Group. Scandinavian Journal of Pain 11, 111–122 (2016).

44. Sanders, M. et al. New Formulation of Sustained Release Naloxone Can Reverse Opioid Induced Constipation Without Compromising the Desired Opioid Effects. Pain Med. (United States) 16, 1540–1550 (2015).

45. Jamal, M. M., Adams, A. B., Jansen, J.-P. & Webster, L. R. A Randomized, Placebo-Controlled Trial of Lubiprostone for Opioid-Induced Constipation in Chronic Noncancer Pain. Am. J. Gastroenterol. 110, 725–732 (2015).

46. Sloots, C. E. J. Efficacy and Safety of Prucalopride in Patients with Chronic Noncancer Pain Suffering from Opioid-Induced Constipation. (2010).

47. Miles, C., Fellowes, D., Goodman, M. L. & Wilkinson, S. S. in Cochrane Database of Systematic Reviews (ed. Candy, B.) (John Wiley & Sons, Ltd, 2006).

48. Epstein, R. S., Teagarden, J. R., Cimen, A., Sostek, M. & Salimi, T. When People with Opioid-Induced Constipation Speak: A Patient Survey. Adv. Ther. 34, 725–731 (2017).

49. Drewes, A. M. Opioids and the gut; not only constipation and laxatives. Scandinavian Journal of Pain 15, 81–82 (2017).

50. Xing, J. H. & Soffer, E. E. Adverse effects of laxatives. Dis. Colon Rectum 44, 1201–1209 (2001).

51. Mozaffari, S., Nikfar, S. & Abdollahi, M. Investigational opioid antagonists for treating opioid-induced bowel dysfunction. Expert Opin. Investig. Drugs 27, 235–242 (2018).

52. Kirk Ludwig, Warren E. Enker, Conor P. Delaney, Bruce G. Wolff, Wei Du, John G. Fort, Maryann Cherubini James Cucinotta, L. T. Gastrointestinal Tract Recovery in Patients Undergoing Bowel Resection. 143, 1098–1105 (2008).

53. Yuan, C.-S. et al. Effects of subcutaneous methylnaltrexone on morphine-induced peripherally mediated side effects: a double-blind randomized

placebo-controlled trial. J. Pharmacol. Exp. Ther. 300, 118–123 (2002).

54. Webster, L. R., Michna, E., Khan, A., Israel, R. J. & Harper, J. R. Long-term safety and efficacy of subcutaneous methylnaltrexone in patients with opioid-induced constipation and chronic noncancer pain: A phase 3, open-label trial. Pain Med. (United States) 18, 1496–1504 (2017).

55. Michna, E. et al. Subcutaneous methylnaltrexone for treatment of opioid-induced constipation in patients with chronic, nonmalignant pain: a randomized controlled study. J. Pain 12, 554–62 (2011).

56. Rauck, R., Slatkin, N. E., Stambler, N., Harper, J. R. & Israel, R. J. Randomized, Double-Blind Trial of Oral Methylnaltrexone for the Treatment of Opioid-Induced Constipation in Patients with Chronic Noncancer Pain. Pain Pract. 17, 820–828 (2017).

57. Webster, L. R., Yamada, T. & Arjona Ferreira, J. C. A Phase 2b, Randomized, Double-Blind Placebo-Controlled Study to Evaluate the Efficacy and Safety of Naldemedine for the Treatment of Opioid-Induced Constipation in Patients with Chronic Noncancer Pain. Pain Med. 18, 2350–2360 (2017).

58. Hale, M., Wild, J., Reddy, J., Yamada, T. & Arjona Ferreira, J. C. Naldemedine versus placebo for opioid-induced constipation (COMPOSE-1 and COMPOSE-2): two multicentre, phase 3, double-blind, randomised, parallel-group trials. lancet. Gastroenterol. Hepatol. 2, 555–564 (2017).

59. Poulsen, J. L., Brock, C., Olesen, A. E., Nilsson, M. & Drewes, A. M. Clinical potential of naloxegol in the management of opioid-induced bowel dysfunction. Clinical and Experimental Gastroenterology 7, 345–358 (2014).

60. Webster, L. et al. A phase 2, double-blind, randomized, placebo-controlled, dose-escalation study to evaluate the efficacy, safety, and tolerability of naloxegol in patients with opioid-induced constipation. Pain 154, 1542–1550 (2013).

61. Chey, W. D. et al. Naloxegol for Opioid-Induced Constipation in Patients with Noncancer Pain. PRA Interna- tional Salt Lake City (L.W.); AstraZeneca Pharm. N Engl J Med 370, 2387–96 (2014).

62. Tack, J., Lappalainen, J., Diva, U., Tummala, R. & Sostek, M. Efficacy and safety of naloxegol in patients with opioid-induced constipation and laxative-inadequate response. United Eur. Gastroenterol. J. 3, 471–480 (2015).

63. Eldon, M. A. et al. Safety, tolerability, and pharmacokinetics of multiple ascending doses of naloxegol. Clin. Pharmacol. Drug Dev. 4, 442–448 (2015).

64. Webster, L. et al. Randomised clinical trial: The long-term safety and tolerability of naloxegol in patients with pain and opioid-induced constipation. Aliment. Pharmacol. Ther. 40, 771–779 (2014).

65. Bui, K., She, F. & Sostek, M. The effects of renal impairment on the pharmacokinetics, safety, and tolerability of naloxegol. J. Clin. Pharmacol. 54, 1375–1382 (2014).

66. Bui, K., She, F. & Sostek, M. The effects of mild or moderate hepatic impairment on the pharmacokinetics, safety, and tolerability of naloxegol. J. Clin. Pharmacol. 54, 1368–1374 (2014).

67. Gottfridsson, C., Carlson, G., Lappalainen, J. & Sostek, M. Evaluation of the Effect of Naloxegol on Cardiac Repolarization_ A Randomized, Placebo- and Positive-Controlled Crossover Thorough QT/QTc Study in Healthy Volunteers. Clin. Ther. 35, 1876–1883 (2013).

68. Bui, K., Zhou, D., Sostek, M., She, F. & Al-Huniti, N. Effects of CYP3A Modulators on the Pharmacokinetics of Naloxegol. J. Clin. Pharmacol. 56, 1019–1027 (2016).

69. Bui, K. et al. The effect of quinidine, a strong P-glycoprotein inhibitor, on the pharmacokinetics and central nervous system distribution of naloxegol. J. Clin. Pharmacol. 56, 497–505 (2016).

70. Halawi, H. et al. Effects of naloxegol on whole gut transit in opioid-naïve healthy subjects receiving codeine: A randomized, controlled trial. Neurogastroenterol. Motil. e13298 (2018).

71. Lawson, R., King, F., Marsh, K., Altincatal, A. & Cimen, A. Impact of Treatment with Naloxegol for Opioid-Induced Constipation on Patients' Health State Utility. Adv. Ther. 33, 1331–1346 (2016).

72. Gaertner J, Siemens W, Camilleri M, Davies A, Drossman DA, Webster LR, B. G. Definitions and outcome measures of clinical trials regarding opioid-induced constipation: a systematic review. J Clin Gastroenterol. 49, 9–15 (2015).

73. Chaussade, S. et al. Determination of total and segmental colonic transit time in constipated patients. Dig. Dis. Sci. 34, 1168–1172 (1989).

74. Cowlam, S. et al. Blinded comparison of faecal loading on plain radiography versus radio-opaque marker transit studies in the assessment of constipation. Clin. Radiol. 63, 1326–1331 (2008).

75. Knudsen, K. et al. Gastrointestinal Transit Time in Parkinson's Disease Using a Magnetic Tracking System. J. Parkinsons. Dis. 7, 471–479 (2017).

76. Poulsen, J. L. et al. The impact of opioid treatment on regional gastrointestinal transit. J. Neurogastroenterol. Motil. 22, 282–291 (2016).

77. Nilsson, M. et al. Opioid-induced bowel dysfunction in healthy volunteers assessed with questionnaires and MRI. Eur. J. Gastroenterol. Hepatol. 28, 514–524 (2016).

78. Frank, L., Kleinman, L., Farup, C., Taylor, L. & Miner, P. Psychometric validation of a constipation symptom assessment questionnaire. Scand. J. Gastroenterol. 34, 870–7 (1999).

79. Lewis, S. J. & Heaton, K. W. Stool form scale as a useful guide to intestinal transit time. Scand. J. Gastroenterol. 32, 920–924 (1997).

80. Harris, M. L. et al. Neurophysiological evaluation of healthy human anorectal sensation. Am. J. Physiol. Gastrointest. Liver Physiol. 291, G950–G958 (2006).

81. Rao, S. S. C. et al. Minimum standards of anorectal manometry. Neurogastroenterol. Motil. 14, 553–9 (2002).

82. Alqudah, M. M., Gregersen, H., Drewes, A. M. & McMahon, B. P. Evaluation of anal sphincter resistance and distensibility in healthy controls using EndoFLIP ©. Neurogastroenterol. Motil. 24, e591-9 (2012).

83. Sandberg, T. H. et al. A novel semi-automatic segmentation method for volumetric assessment of the colon based on magnetic resonance imaging. Abdom. Imaging 40, 2232–2241 (2015).

84. Nilsson, M. et al. Quantification and variability in colonic volume with a novel magnetic resonance imaging method. Neurogastroenterol. Motil. 27, 1755–1763 (2015).

85. Haase, A. M. et al. Pilot study trialling a new ambulatory method for the clinical assessment of regional gastrointestinal transit using multiple electromagnetic capsules. Neurogastroenterol. Motil. 26, 1783–1791 (2014).

86. Hiroz, P., Schlageter, V., Givel, J. C. & Kucera, P. Colonic movements in healthy subjects as monitored by a magnet tracking system. Neurogastroenterol. Motil. 21, 1–10 (2009).

87. Fei, G. et al. Lubiprostone Reverses the Inhibitory Action of Morphine on Intestinal Secretion in Guinea Pig and Mouse. J. Pharmacol. Exp. Ther. 334, 333–340 (2010).

88. Drewes, A. M. et al. Gut pain and hyperalgesia induced by capsaicin: A human experimental model. Pain 104, 333–341 (2003).

89. Drewes, A. M. et al. Multimodal assessment of pain in the esophagus: a new experimental model. Am. J. Physiol. - Gastrointest. Liver Physiol. 283, G95–G103 (2002).

90. Barrow, L. et al. Quantitative, noninvasive assessment of antidiarrheal

actions of codeine using an experimental model of diarrhea in man. Dig. Dis. Sci. 38, 996–1003 (1993).

91. Wirtz, S., Neufert, C., Weigmann, B. & Neurath, M. F. Chemically induced mouse models of intestinal inflammation. Nat. Protoc. 2, 541–546 (2007).

92. Poulsen, J. L. et al. Colorectal Transit and Volume During Treatment With Prolonged-release Oxycodone/Naloxone Versus Oxycodone Plus Macrogol 3350. J. Neurogastroenterol. Motil. 24, 119–127 (2018).

93. Poulsen, J. L. et al. Prolonged-Release Oxycodone/Naloxone Improves Anal Sphincter Relaxation Compared to Oxycodone Plus Macrogol 3350. Dig. Dis. Sci. 62, 3156–3166 (2017).

94. Wong, B. S. et al. The effects of methylnaltrexone alone and in combination with acutely administered codeine on gastrointestinal and colonic transit in health. Aliment. Pharmacol. Ther. 32, 884–893 (2010).

95. Abrahamsson, H. Gastrointestinal motility disorders in patients with diabetes mellitus. J. Intern. Med. 237, 403–9 (1995).

96. Fasano, A., Visanji, N. P., Liu, L. W. C., Lang, A. E. & Pfeiffer, R. F. Gastrointestinal dysfunction in Parkinson's disease. Lancet Neurol. 14, 625–639 (2015).

97. Dhingra, L. et al. A qualitative study to explore psychological distress and illness burden associated with opioid-induced constipation in cancer patients with advanced disease. Palliat. Med. 27, 447–456 (2013).

98. Drossman, D. A. The Role of Psychosocial Factors in Gastrointestinal Illness. Scand. J. Gastroenterol. 221, 1–4 (1996).

99. Bhatia, V. & Tandon, R. K. Stress and the gastrointestinal tract.: EBSCOhost. J. Gastroenterol. Hepatol. 20, 332–339 (2005).

100. Brune & Patrignani, P. New insights into the use of currently available non-steroidal anti-inflammatory drugs. J. Pain Res. 8, 105 (2015).

101. Goldstein, B. J. & Goodnick, P. J. Selective serotonin reuptake inhibitors in the treatment of affective disorders - III. Tolerability, safety and pharmacoeconomics. J. Psychopharmacol. 12, S55–S87 (1998).

102. Price, D. D. Psychological and neural mechanisms of the affective dimension of pain. Science 288, 1769–72 (2000).

103. Argoff, C. E. et al. Consensus Recommendations on Initiating Prescription Therapies for Opioid-Induced Constipation. Pain Medicine (United States) 16, 2324–2337 (2015).

104. Rentz, A. M., Yu, R., Müller-Lissner, S. & Leyendecker, P. Validation of the Bowel Function Index to detect clinically meaningful changes in opioid-

induced constipation. J. Med. Econ. 12, 371–383 (2009).

105. Olesen, A. E. & Drewes, A. M. Validated tools for evaluating opioid-induced bowel dysfunction. Adv. Ther. 28, 279–294 (2011).

106. Slappendel, R., Simpson, K., Dubois, D. & Keininger, D. L. Validation of the PAC-SYM questionnaire for opioid-induced constipation in patients with chronic low back pain. Eur. J. Pain 10, 209–209 (2006).

107. Knudsen, K., Krogh, K., Østergaard, K. & Borghammer, P. Constipation in parkinson's disease: Subjective symptoms, objective markers, and new perspectives. Mov. Disord. 32, 94–105 (2017).

108. Heaton, K. W. & O'Donnell, L. J. An office guide to whole-gut transit time. Patients' recollection of their stool form. J. Clin. Gastroenterol. 19, 28–30 (1994).

109. Halmos, E. P. et al. Inaccuracy of patient-reported descriptions of and satisfaction with bowel actions in irritable bowel syndrome. Neurogastroenterol. Motil. e13187 (2017).

110. Martelli, H. et al. Some parameters of large bowel motility in normal man. Gastroenterology 75, 612–8 (1978).

111. Heaton, K. W. et al. Defecation frequency and timing, and stool form in the general population: a prospective study. Gut 33, 818–824 (1992).

112. Webster, L. et al. A phase 2, double-blind, randomized, placebo-controlled, dose-escalation study to evaluate the efficacy, safety, and tolerability of naloxegol in patients with opioid-induced constipation. Pain 154, 1542–1550 (2013).

113. Mark, E. B. et al. Assessment of colorectal length using the electromagnetic capsule tracking system: a comparative validation study in healthy subjects. Color. Dis. 19, O350–O357 (2017).

114. Gregersen, T., Haase, A.-M., Schlageter, V., Gronbaek, H. & Krogh, K. Regional Gastrointestinal Transit Times in Patients With Carcinoid Diarrhea: Assessment With the Novel 3D-Transit System. J. Neurogastroenterol. Motil. 21, 423–32 (2015).

115. Haase, A. M. et al. Regional gastrointestinal transit times in severe ulcerative colitis. Neurogastroenterol. Motil. 28, 217–224 (2016).

116. Neumann, T. & Paaschen, H. Van. -Naloxol (NKTR-118) as an oral peripheral opioid antagonist in healthy male subjects: a double-blind, placebo-controlled, dose escalation crossover study. San Fr. CA (2007).

117. hiroz, p., schlageter, v., givel, j. -c. & kucera, p. Colonic movements in healthy subjects as monitored by a Magnet Tracking System.

Neurogastroenterol. Motil. 21, 838-e57 (2009).

118. Moylan, S. et al. Are abdominal x-rays a reliable way to assess for constipation? J. Urol. 184, 1692–1697 (2010).

119. Bendezú, R. A. et al. Intestinal gas content and distribution in health and in patients with functional gut symptoms. Neurogastroenterol. Motil. 27, 1249–1257 (2015).

120. Laghi, A. Computed tomography colonography in 2014: An update on technique and indications. World J. Gastroenterol. 20, 16858–16867 (2014).

121. Pritchard, S. E. et al. Fasting and postprandial volumes of the undisturbed colon: Normal values and changes in diarrhea-predominant irritable bowel syndrome measured using serial MRI. Neurogastroenterol. Motil. 26, 124–130 (2014).

122. Chaddock, G. et al. Novel MRI tests of orocecal transit time and whole gut transit time: Studies in normal subjects. Neurogastroenterol. Motil. 26, 205–214 (2014).

123. Marciani, L. et al. Postprandial Changes in Small Bowel Water Content in Healthy Subjects and Patients With Irritable Bowel Syndrome. Gastroenterology 138, 469–477.e1 (2010).

124. Lam, C. et al. Distinct Abnormalities of Small Bowel and Regional Colonic Volumes in Subtypes of Irritable Bowel Syndrome Revealed by MRI. Am. J. Gastroenterol. 112, 1–10 (2016).

125. Bendezú, R. A. et al. Colonic content: effect of diet, meals, and defecation. Neurogastroenterol. Motil. 29, (2017).

126. Li, X. H. et al. Abdominal MRI at 3.0 T: LAVA-flex compared with conventional fat suppression T1-weighted images. J. Magn. Reson. Imaging 40, 58–66 (2014).

127. Beddy, P. et al. T1-weighted fat-suppressed imaging of the pelvis with a dual-echo Dixon technique: initial clinical experience. Radiology 258, 583–589 (2011).

128. Placidi, E. et al. The effects of loperamide, or loperamide plus simethicone, on the distribution of gut water as assessed by MRI in a mannitol model of secretory diarrhoea. Aliment. Pharmacol. Ther. 36, 64–73 (2012).

129. Andresen, V. & Layer, P. Medical Therapy of Constipation : Current Standards and Beyond. 123–127 (2018).

130. Carrington, E. V et al. Advances in the evaluation of anorectal function. Nat. Publ. Gr. 15, 309–323 (2018).

131. Mion, F., Garros, A., Subtil, F., Damon, H. & Roman, S. Anal sphincter

function as assessed by 3D high definition anorectal manometry. Clin. Res. Hepatol. Gastroenterol. 10–13 (2018).

132. Chowdhury, A. R. & Lorber, S. H. Effects of glucagon and secretin on food- or morphine-induced motor activity of the distal colon, rectum, and anal sphincter. Am. J. Dig. Dis. 22, 775–780 (1977).

133. Read, M., Read, N. W., Barber, D. C. & Duthie, H. L. Effects of loperamide on anal sphincter function in patients complaining of chronic diarrhea with fecal incontinence and urgency. Dig. Dis. Sci. 27, 807–14 (1982).

134. Wilder-Smith, C. H. & Bettiga, A. The analgesic tramadol has minimal effect on gastrointestinal motor function. Br. J. Clin. Pharmacol. 43, 71–75 (1997).

135. Göke, M., Ewe, K. & Donner, K. Influence of loperamide and loperamide oxide on the anal sphincter. Dis. colon (1992).

136. Sternini, C., Patierno, S., Selmer, I.-S. & Kirchgessner, A. The opioid system in the gastrointestinal tract. Neurogastroenterol. Motil. 16, 3–16 (2004).

137. Rattan, S. The internal anal sphincter: Regulation of smooth muscle tone and relaxation. Neurogastroenterol. Motil. 17, 50–59 (2005).

138. Cheeney, G., Nguyen, M., Valestin, J. & Rao, S. S. C. Topographic and manometric characterization of the recto-anal inhibitory reflex. Neurogastroenterol. Motil. 24, (2012).

139. Dinning, P. G., Carrington, E. V. & Scott, S. M. Colonic and anorectal motility testing in the high-resolution era. Current Opinion in Gastroenterology 32, (2016).

140. Gourcerol, G. et al. Do endoflip assessments of anal sphincter distensibility provide more information on patients with fecal incontinence than high-resolution anal manometry? Neurogastroenterol. Motil. 28, 399–409 (2016).

141. Sørensen, G. et al. Distensibility of the anal canal in patients with idiopathic fecal incontinence: A study with the Functional Lumen Imaging Probe. Neurogastroenterol. Motil. 26, 255–263 (2014).

142. Fynne, L. et al. Distensibility of the anal canal in patients with systemic sclerosis: A study with the functional lumen imaging probe. Color. Dis. 15, (2013).

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