Research Review
PRODUCT REVIEW

Imodium® (loperamide)

About the Reviewers

Andi Shirtcliffe

Andi Shirtcliffe is a director of Integrated Pharmacy Care Ltd, a Company that provides pharmacist consulting services. Her current clinical work is as an advisory pharmacist in psychogeriatrics. Andi is actively involved in intern pharmacist assessment and pharmacist competence standard setting. She is deputy chair of the New Zealand College of Pharmacists, and a member of the Pharmacy Council of New Zealand's Pre-registration Assessment Board. Andi also belongs to the Podiatrists Board's Prescriber Review Committee and is an honorary lecturer at the Auckland University's School of Pharmacy.

Dr John Wyeth

Dr Wyeth MBChB, MD, FRACP, FRCP (London) is a Gastroenterologist in both Public and Private Practice in Wellington. He is the Clinical Leader in Gastroenterology and GI Endoscopy Services at Capital and Coast Health DHB and is the current President of the New Zealand Society of Gastroenterology. His teaching commitments include appointments as a Clinical Senior Lecturer for the Wellington School of Medicine and a Senior Lecturer for the School of Dietetics. After completing his specialist training he undertook a Doctoral thesis on dietary fibre in the large bowel. Current research and clinical interests include nutrition and functional foods, irritable bowel syndrome, inflammatory bowel disease and motility conditions of the gut.

About Research Review

Research Review is an independent medical publishing organisation producing electronic publications in a wide variety of specialist areas. Product Reviews feature independent short summaries of major research affecting an individual medicine or technique. They include a background to the particular condition, a summary of the medicine and selected studies by a key NZ specialist with a comment on the relevance to NZ practice. Research Review publications are intended for New Zealand medical professionals.

This review discusses the evidence in support of the use of Imodium® (loperamide), an established and effective treatment for acute diarrhoea.

Incidence and prevalence of diarrhoea in New Zealand

Infectious diarrhoea is the most common type of diarrhoea worldwide and the leading cause of childhood death in developing countries. While very few people in New Zealand die of diarrhoeal illnesses, the disease burden is substantial.

The New Zealand Food Safety Authority recently estimated that as many as 6.5 million cases of diarrhoea and vomiting occur in New Zealand every year and that about 5.2 million working days are lost each year (by both the sufferers and their carers) due to acute gastrointestinal illness (AGI).[1] The estimated number of cases (any diarrhoea or vomiting of infectious cause) in 2006 was 1.11 per person per year.[2] According to findings published in 2010 from a large, community-based study investigating AGI in New Zealand, the prevalence is highest in children aged <5 years and lowest in those aged >64 years.[3] That same study reported a mean duration of illness of 2.5 days, with the most common symptoms being diarrhoea (82.5%), stomach cramps (75.7%), nausea (56.9%) and vomiting (49.0%). Every year, episodes of AGI in New Zealand result in nearly 1 million visits to the general medical practitioner and dispensing of over 300,000 courses of antibiotics.[3]

Treatment and management options

Notably, opinions differ as to what constitutes an episode of diarrhoea; the choice of definition has a major impact upon reported incidence rates.[4,5] The Bristol Stool Scale is an easy way to define diarrhoea, and serves as a recognised, general measurement used by the health care profession to evaluate the consistency or form of stools.[6] Bowel movements are classified into 7 distinct categories; the form of the stool correlates directly with the amount of time it has spent in the colon (the diarrhoeal type of stool has spent the least time in the colon). Diarrhoea is most inclusively defined as an abnormal increase in stool weight and/or frequency of unusually liquid bowel movements, varying in intensity from `mild' to `severe' (see text box).[7]

Definition of diarrhoea[7]

Severe diarrhoea (of any duration) is defined as diarrhoea with one or more of the following:

- fever >38.5°C
- bloody stools
- profound systemic illness/toxicity
- haemodynamic instability
- >6 diarrhoeal episodes per day for >5 days

Mild to moderate diarrhoea is defined as:

- any diarrhoea not meeting the severe category.

Best practice for diarrhoea treatment

- Act early
- Be proactive – recommend loperamide
- Know when to advise people to seek medical advice

- Self-medication with loperamide in otherwise healthy adults is safe
  - Loperamide has no risk of dependency behaviour and very low risk of toxicity (no overdose risk), with a side effects profile not different from placebo
  - Loperamide does not cross the blood-brain barrier
  - Avoid using loperamide in diarrhoea with bleeding
- Treatment of acute diarrhoeal episodes relieves discomfort and social dysfunction; there is no evidence that it prolongs the illness
  - Loperamide is a better choice than Lomotil®/Diastop®
  - Compared with loperamide alone, a combination of simethicone and loperamide (Imodium Advanced®) has a faster speed of action onset and reduces gas-related abdominal discomfort
- Loperamide is the drug of choice for a variety of diarrhoeal syndromes, including acute, nonspecific (infectious) diarrhoea, travellers' diarrhoea, chemotherapy-related and protease inhibitor-associated diarrhoea
  - Loperamide reduces intestinal secretions and reduces intestinal motility (dual action)
  - Loperamide has the additional benefit of increasing anal sphincter tone
- Oral rehydration treatment (e.g. glucose and electrolyte solutions) does not relieve diarrhoea or shorten its duration

Importantly, a recently published comprehensive analysis of the available literature has highlighted measurement issues in randomised clinical trials (RCTs) of paediatric acute diarrhoeal diseases.[8] Even methodologically sound clinical trials have used heterogeneous definitions of diarrhoea and primary outcomes, they have employed instruments that lack validity and reliability, and they focus on indices that may not be important to participants. Standard definitions and valid, reliable outcomes are therefore needed for defining and measuring acute diarrhoeal diseases in children; the same observations have been made of RCTs in adult populations.[9]

Diarrhoeal episodes are usually brief and self-limiting, but associated with discomfort, disability and social embarrassment, and with faecal incontinence (real or threatened) typically requiring urgent treatment.

Acute uncomplicated diarrhoea is commonly treated by self-medication; sufferers will often seek and purchase medication without prescription for symptom relief.[9] Medication choice is usually based on the recommendation of health professionals, who are informed by guidelines issued by regulatory medical and pharmaceutical authorities. However, recommended regimens vary widely between `official' guidelines and much confusion exists amongst the many publications and Web sites offering advice on the management of acute diarrhoea, or advice to travellers.[9,10] A group of experts from different relevant disciplines reviewed the literature in 2001 to determine best practice.[9]

This research group reviewed the scientific basis for the widespread belief that diarrhoea represents a form of defence mechanism by enteric lavage, a belief that has led to a number of current guidelines stating that anti-diarrhoeal drugs that reduce stool output are harmful and may delay the excretion of pathogens. The research group argues that the evidence fails to support this defence hypothesis and that, furthermore, treatment of acute episodes relieves discomfort and social dysfunction; there is no evidence that it prolongs the illness. Self-medication in otherwise healthy adults is safe.

Oral rehydration solutions

The extrapolation to adults of the WHO guidelines for the treatment of acute diarrhoea in young children has reinforced the notion that replacement of fluid loss with oral rehydration solutions (ORS) are the only justifiable, and presumably adequate, therapy in adults.[11] These ORS (glucose/electrolyte mixtures) increase intestinal absorption of sodium and water.[11] They effectively combat dehydration and its serious consequences, and are the treatment of choice in infants and young children, the frail and very elderly.[11] The recently published NICE clinical guideline for the treatment of diarrhoea in children aged <5 years advises giving 50 mL/kg of ORS over 4 hours to replace the fluid deficit plus an additional volume of ORS to provide the maintenance fluids required for that 4-hour period of time.[12] Notably, ORS do not reduce the duration of diarrhoea, nor reduce the number of stools. They are of no benefit to the adult who can maintain sufficient fluid intake during the diarrhoea episode; ORS provide short-term relief only for those who are incapacitated.[13]

A variant of ORS, a reduced osmolarity solution, has proven superior over the standard ORS in the reduction of faecal volume and duration of diarrhoea, and consequently, is now the recommended WHO-ORS formulation for the treatment of acute non-cholera diarrhoea.[14] The addition of zinc supplementation is recommended by the WHO in the treatment of acute diarrhoeal illness.[14] Modifying ORS with amino acid supplementation (i.e. glycine, alanine, and glutamine) has been attempted, in the hopes of improving sodium and water absorption.[14] However, this has proven costly and does not decrease the duration of diarrhoea or volume of stools, so is not currently recommended for widespread use. Limited data are available on the use of ORS in the treatment of travellers' diarrhoea, acquired during the course of travel.

Probiotics

Probiotics are defined as living micro-organisms (bacterial strains and yeasts), which upon ingestion in certain numbers exert health benefits beyond inherent general nutrition and are therefore potentially useful in the treatment of diarrhoea.[15,16]

Different strains of probiotics include various *Lactobacillus*, *Bifidobacterium* and *Streptococcus* species and the yeast *Saccharomyces boulardii*. Scant evidence supports the notion that probiotics reduce pathogen colonisation in humans or that they confer protection against organisms such as *Vibrio cholerae* or *Escherichia coli*.[17-20] Various pharmacological effects that have been attributed to probiotics include increased disaccharidase activity, the production of antibacterial substances, competition for bacterial adhesion, stimulation of various immune defence mechanisms and, in the case of *Saccharomyces*, a protective effect and specific activities against various enteric pathogens.[15,16,21-23] Shortcomings associated with much of this evidence include the fact that it has been obtained from *in vitro* studies or from *in vivo* studies using germ-free, gnotobiotic or weaning animals (characterised by immature bacterial colonisation of the bowel and immune responses), following `pre-treatment' with high doses. The reported effects are species-specific, dose-dependent, and vary in the rapidity of onset and duration of efficacy.[24,25] Importantly, many factors may materially impact on the role of these agents in the clinical setting: the viability of any strain depends on the storage life of the probiotics as well as their resistance to gastric acid secretion.[15]

Controlled clinical trials support the use of some probiotics in infantile (rotaviral) diarrhoea.[21,22] However, very little if any evidence exists for benefits of currently recommended doses of probiotics in acute diarrhoea in the adult, whether travelling or at home, especially during the first 24 or 48 hours.[25-31] Dose-response studies and the selection of more effective probiotic strains may eventually lead to better treatment options.

Adsorbents

Clinical evidence of adsorbents, including charcoal, pectins, tannin albuminate (plus ethacrine), clays (aluminium silicates and kaolin) or activated clays (attapulgite, diosmectite), provides scant proof of their efficacy in acute adult diarrhoea.[9]

Antimicrobial agents

The routine use of antimicrobials is not advised for non-travellers' diarrhoea, which may be a result of viruses or non-infectious agents, besides bacterial pathogens.[9] Travellers' diarrhoea, in contrast, is usually bacterial, and as travellers are vulnerable to strains of pathogens against which they have no acquired immunity, the resulting illness may be more severe and prolonged (see text box).[9] The non-specific nature of diarrhoeal symptoms make it difficult to target the treatment to a single pathogen and therefore a broad-spectrum antimicrobial is preferable.[9]

Conclusive evidence is lacking as to antimicrobials having the ability to prevent the complications of acute diarrhoea, such as dehydration, toxic dilatation, bacteremia or post-diarrhoea irritable bowel syndrome. Use of antimicrobials is limited by cost, the need for a prescription, drug-drug interactions, skin reactions or photosensitivity (especially for cotrimoxazole or nitrofuran derivatives), secondary diarrhoea/colitis, and increasing bacterial resistance.[25] Dosages must be modified for use in children, pregnant and nursing women, and the elderly.[9] Nevertheless, antimicrobials are commonly used for empirical treatment of secretory/invasive travellers' diarrhoea (quinolones first-line, cotrimoxazole second-line) and for secretory non-travellers' diarrhoea in cases where the pathogen is known.

Travellers' diarrhoea[32]

Travellers' diarrhoea (TD) is defined as ≥3 unformed stools in 24 hours accompanied by at least 1 of the following: fever, nausea, vomiting, cramps, tenesmus, or bloody stools (dysentery), in a traveller from a developed country visiting a less developed country. It is usually a benign self-limited illness lasting 3 to 5 days (mean 3.6 days).

Dietary restrictions

It is generally agreed that fluid intake must be maintained. WHO recommends the use of ORS; glucose-containing fluids and electrolyte-rich soups are usually sufficient for adults.[11] Early resumption of feeding and solid food intake reportedly speeds recovery in children, whereas it is unclear as to whether fasting or dieting is beneficial to the treatment of acute diarrhoea in adults, or that solid food hastens or retards recovery.[11]

Drugs modifying gut motility and/or secretion

Opioids proved to be effective antidiarrhoeal agents for more severe cases of diarrhoea during the 1800s.[33] However, they have central effects, are habit-forming, and need prescriptions in most countries. The use of antimotility agents in the US for the management of diarrhoea date back to diphenoxylate hydrochloride, with atropine being the first antimotility agent to be licensed in 1960. The atropine was combined with diphenoxylate to prevent overdose, as objectionable anticholinergic effects (elevated heart rate, urinary retention, flushing, vomiting) would be experienced before the occurrence of drug reactions from the diphenoxylate.[33]

Loperamide

Loperamide was synthesised in 1969 in an attempt to improve upon diphenoxylate as an antidiarrhoeal.[34] A major advantage of this peripherally-acting opiate is that it is considered to be free of abuse potential because of its low oral absorption and inability to cross the blood-brain barrier, resulting in minimal central nervous system effects.[33] It has multiple antisecretory actions and nonopioid effects in the human colon, and a prolonged duration of action over diphenoxylate.[35,36] Loperamide reduces the number of diarrhoeal stools passed by approximately 60%, while in healthy adults, a therapeutic 4 mg dose does not significantly slow orocaecal transit.[9,33] Higher or repeated doses, which increase drug concentration in the enterohepatic circulation, retard jejunal or orocaecal transit, but the therapeutic dosage normalises transit – particularly in the first 3 days – and is the drug of choice for a variety of diarrhoeal syndromes, including acute, nonspecific (infectious) diarrhoea; travellers' diarrhoea; and chemotherapy-related and protease inhibitor-associated diarrhoea.[9,37]

Simethicone, a chemically inert compound that is not absorbed from the gastrointestinal tract, is indicated for relief of gas-related abdominal discomfort. A combination of simethicone and loperamide effectively increases the speed of action onset and reduces gas-related abdominal discomfort;[38] the product is available in New Zealand as a pharmacy medicine under the name of Imodium Advanced®.

Dosing schedule:[39]

Acute diarrhoea:

- Adults and children >12 years: an initial dose of 2 loperamide 2 mg tablets followed by 1 tablet after every subsequent loose stool – usually only needed for 3 days
- If needed for longer duration or lack of effect – the user should seek medical attention
- Patients should be advised to discontinue loperamide if they develop constipation (or as soon as bowel movements return to normal)

Chronic diarrhoea:

- Adults and children >12 years: an initial dose of 2 loperamide 2 mg tablets daily; this initial dose should be adjusted until 1–2 solid stools a day are obtained, which is usually achieved with a maintenance dose of 1 – 6 tablets daily.
- Need to titrate dosing with effect
- Only risk is constipation – simply stop the medication
- No long-term side-effects

The maximum dose for acute and chronic diarrhoea is 8 tablets daily.

The following persons should seek medical advice:

- Frail or elderly (>75 years)
- Persons with concurrent significant systemic illnesses, or with recurrent diarrhoea due to chronic bowel disease
- Children (<12 years)
- No improvement in 48 hours
- Symptoms exacerbate/overall condition worsens
- Warning signs or symptoms develop
  Fever, blood in stools, drowsiness, unable to continue adequate fluid intake/persistent vomiting

Good tolerability

The side effect profile of loperamide is not statistically significantly different from placebo. Loperamide is generally well tolerated at recommended nonprescription doses, with the most common side effects related to the impact on bowel motility (abdominal pain, distention, bloating, nausea, vomiting, and constipation).[36,37] Constipation is rare in cases of acute diarrhoea. Loperamide is not recommended for use in children younger than 2 years, as this age group is susceptible to adverse central and peripheral (ileus) side effects, thought to be due to immature hepatic function and blood-brain barrier, or inadvertent overdose.[9] However, loperamide has a very low risk of toxicity and an established safety profile in adults and in pregnancy.[9,40]

The following consumer warnings are provided on loperamide packaging:

- Should you have a fever or notice blood in your stools consult your healthcare professional
- Do not use in pregnancy or lactation
- Do not give to children under 12 years of age
- If diarrhoea persists beyond 48 hours see your doctor

Treatment options (J Wyeth 2010, pers. comm., 29 August)

Antidiarrhoeals e.g. loperamide, diphenoxylate	Reduces diarrhoea Good data for reduced number of days with diarrhoea
Oral rehydration treatment e.g. glucose and electrolyte solutions	Does not relieve diarrhoea or shorten its duration The young, frail and elderly should take ORS and seek medical advice
Probiotics e.g. lactobacilli yoghurts	Some evidence of benefit Don't specifically treat the symptoms
Antimicrobials	Not appropriate for self-medication, except for travellers based on medical advice
Fluid intake	No effect on diarrhoea Maintain adequate fluid intake as guided by thirst
Food intake	No effect on recovery time Avoid fatty, heavy, spicy or stimulant foods

Clinical efficacy of loperamide in the treatment of acute diarrhoea

A multicentre double-blind study in acute diarrhoea comparing loperamide (R 18553) with two common antidiarrhoeal agents and a placebo[41]

Summary: This 24-hour comparative study determined that **loperamide has a significantly faster onset of action and is more effective and better tolerated** in the symptomatic control of acute diarrhoea than diphenoxylate, clioquinol/phanquone or placebo.

A total of 213 patients aged 9–82 years with acute diarrhoea were randomly assigned to treatment with capsules containing either loperamide 2 mg (n=56), diphenoxylate 2.5 mg (n=48), clioquinol 200 mg plus phanquone 20 mg (n=50), or placebo (n=59). Each participant was administered two capsules, in the presence of the investigator. The primary study outcome, the median time to first unformed stool after 1 dose, was significantly prolonged for the patients who received loperamide (24 h) than for those who received diphenoxylate (2 h), clioquinol/phanquone (3 h), or placebo (2 h) ($p<0.05$ for loperamide compared with each group). Unpleasant gastrointestinal phenomena occurred most frequently in patients given placebo; loperamide recipients did not report any non-gastrointestinal adverse experiences (see Table 1).

Comment: (AS) With acute diarrhoea this is the sort of study you want to see reported. Really what people want to know in this situation is; will this make a difference for me...today. Can I make it to that function and still function? With a global increase in strain on the health budget, we should all be looking to promote self-care and consumer responsibility for our own health where safe and possible. This provides evidence of efficacy and confidence that patients can self-manage this common condition safely with minimal side effects.

(JW) As well as confirming efficacy and safety of loperamide, this trial highlights that a single dose of loperamide is effective in reducing symptoms of diarrhoea in a rapid timeframe. This is important for sufferers of acute diarrhoea. It is also reassuring for those people who either don't wish to take lots of medication or have concerns about long-term use of medication.

Table 1. Adverse experiences reported during the 24-hour trial

	Number of patients reporting stated type of adverse experiences							
	Gastrointestinal				Other			
	abdominal cramps	nausea	anorexia	vomiting	tiredness	dizziness	headache	Total
L	4	0	0	1	0	0	0	5
D	7	2	0	0	0	0	1	10
C/P	2	1	0	0	0	1	0	4
P	7	2	2	1	1	0	0	13
Total	20	5	2	2	1	1	1	32

L = loperamide group; D = diphenoxylate group; C/P = clioquinol/phanquone group; P = placebo group.

Loperamide-simethicone vs loperamide alone, simethicone alone, and placebo in the treatment of acute diarrhea with gas-related abdominal discomfort. A randomized controlled trial[38]

Summary: A loperamide/simethicone combination chewable product provided faster and more complete relief of acute nonspecific diarrhoea and associated gas-related abdominal discomfort than either of its components or placebo. The combination was also well tolerated.

This trial included 493 adults aged 18–63 years with acute diarrhoeal illness symptoms lasting <48 hours before study entry and moderate-to-severe gas-related abdominal discomfort, who presented at a primary care, ambulatory clinic in Acapulco, Mexico. Each patient was randomly assigned to receive 2 chewable tablets containing loperamide 2 mg plus simethicone 125 mg (n=124), loperamide 2 mg (n=123), simethicone 125 mg (n=123), or placebo (n=123). This was followed by 1 tablet after each unformed stool, up to 4 tablets in any 24-hour period.

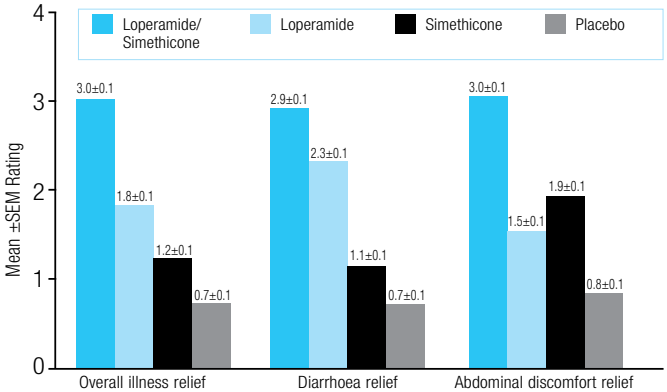
Patients in the combination loperamide/simethicone treatment group reported significantly ($p<0.001$) faster relief for the primary diarrhoeal outcome of median time to last unformed stool compared with patients who received loperamide alone, simethicone alone, or placebo (9.7 hours vs 23.4 hours, 32.5 hours and 39.0 hours, respectively).

Patients who received the combination loperamide/simethicone treatment also reported significantly ($p<0.001$) faster relief for gas-related symptom relief efficacy and time to complete relief of gas-related abdominal discomfort (gas pain, cramps, gas pressure, and bloating), than patients given either loperamide alone, simethicone alone, or placebo.

The combination product achieved a significantly higher end-of-study patient-assessed rating than either ingredient alone or placebo ($p<0.001$ for loperamide/simethicone in comparison with each of the other treatment groups) (see Figure 1).

Comment: (JW) Patients with acute diarrhoeal illnesses generally have other symptoms than simply diarrhoea. Abdominal cramps and gas distension are often quite troubling. This study demonstrates the efficacy of loperamide and also loperamide/simethicone combination tablets for these associated symptoms of an acute diarrhoeal illness. Other studies have confirmed the efficacy of loperamide in managing diarrhoea, continence and borborygmi (wind pain) in patient groups with irritable bowel syndrome and long-term symptoms.

Figure 1. Mean patient-assessed end-of-study effectiveness evaluation (on a 4-point scale where 0=poor and 4=excellent)



Randomized, double-blind, placebo-controlled clinical trial of loperamide plus simethicone versus loperamide alone and simethicone alone in the treatment of acute diarrhea with gas-related abdominal discomfort[42]

Summary: The conclusions of the above trial are strengthened by the clinical findings from this one, in which a **loperamide/simethicone combination product was well tolerated and more efficacious than loperamide alone**, simethicone alone, or placebo for acute nonspecific diarrhoea and gas-related abdominal discomfort. As with the trial by Kaplan and colleagues, loperamide/simethicone was better than loperamide alone or placebo in reducing the number of stools within the initial 12 hours of the study, the time period in which an antidiarrhoeal drug would be expected to be effective; symptomatic improvement that generally occurs thereafter blurs any apparent differences between active treatment and placebo.

This multicentre, double-blind, 48-hour study randomly assigned patients to receive 2 tablets, each containing either loperamide 2 mg plus simethicone 125 mg (n=121), loperamide 2 mg (n=120), simethicone 125 mg (n=123), or placebo (n=121), followed by 1 tablet after each unformed stool, up to 4 tablets in any 24-hour period. In recognition of the differing opinions as to what constitutes an episode of diarrhoea,[4,5] this study employed two different protocol-specified definitions (stricter definition vs alternate definition) of the time to last unformed stool. The stricter definition considered an unformed stool after a 24-hour period of formed stools or no stools to be a continuance of the original episode; if no unformed stools were observed, then time to last unformed stool was 0. The alternate definition considered an unformed stool after a 24-hour period of formed stools or no stools to be a new episode.

Data are reported from an intent-to-treat analysis (n=453). **Patients in the loperamide/simethicone group reported significantly faster relief** for the primary outcome measure of median time to last unformed stool, based on the stricter definition, compared with patients in the sirnethicone alone (8.7 hours vs 27.0 hours; p=0.0001) or placebo (8.7 hours vs 30.5 hours; p=0.0001) groups; the difference between loperamide/simethicone and loperamide alone, however, was not statistically significant (8.7 hours vs 12.5 hours; p=0.0709). In addition, according to the stricter definition, a greater percentage of patients in the loperamide/sirnethicone group (13%) had time to last unformed stool of 0 compared with patients in the loperamide alone (11%), simethicone alone (8%), or placebo groups (3%).

Based on the alternate definition, the time to last unformed stool was significantly shorter in the loperamide/simethicone group (7.6 hours) compared with the loperamide alone (11.5 hours; p=0.0232), simethicone alone (26.0 hours p=0.0001), or placebo (29.4 hours; p=0.0001) groups. Patients in the loperamide/simethicone, loperamide alone, and simethicone alone groups had reductions of 74%, 61%, and 12%, respectively, in the median time to last unformed stool compared with patients assigned to placebo. Using the alternate definition, a greater percentage of patients in the loperamide/simethicone group (14%) had time to last unformed stool of 0 compared with patients in the loperamide alone (12%), simethicone alone (8%), or placebo groups (3%).

Patient satisfaction, as measured by end-of-study patient-assessed outcome measures, was significantly in favour of the combination product over either ingredient alone or placebo (see Table 2).

Table 2. End-of-study effectiveness

	Loperamide/ Simethicone	Loperamide alone	Simethicone alone	Placebo
Overall illness relief	2.8	2.4 p≤0.0052	2.1 p=0.0001	1.8 p=0.0001
Diarrhoea relief	2.8	2.4 p≤0.0052	2.0 p=0.0001	1.7 p=0.0001
Abdominal discomfort relief	2.8	2.1 p≤0.0052	2.2 p=0.0001	2.0 p=0.0001

Values represent least squares means (SEM)
p-values are versus loperamide/simethicone

Comment: (AS) In regard to both of these trials, it's all very well to measure outcomes such as (just for example) 'time till first bowel motion post-dose'; however, what patients want to know is both 'when will I *be* well' and 'when will I *feel* well?' These GI issues significantly contribute to the morbidity associated with acute diarrhoea and 'relieving morbidity' is ultimately where our treatment focus should be with a self-limiting condition.

(JW) In the second study, utilising a very similar protocol, different definitions of successful treatment for diarrhoea were employed. In analysing efficacy in acute diarrhoea, there is considerable variation in an untreated population, making assessment of efficacy over 24 hours difficult. Using stricter definitions of a successful response to treatment, the second study still revealed loperamide and loperamide/simethicone to have an advantage.

Prospective, controlled, multicentre study of loperamide in pregnancy[40]

Summary: This first prospective controlled study of loperamide in pregnancy of 105 cases, with 89 exposures in the first trimester, suggests that this drug does not increase the baseline risk of major malformations.

This study followed women counselled by five teratogen information centres on the safety and risk of loperamide in pregnancy; after delivery and compared with a similar group of women marched for age, smoking, alcohol and other exposures. Fifty-eight cases were from Toronto, Ontario; 25 from Rome, Italy; 16 from Jerusalem, Israel; four from Milan, Italy; and two from Helsinki, Finland. Indications for use were short-term, for an acute case of diarrhoea, or chronic, for bowel disease such as Crohn's disease or irritable bowel syndrome. The doses varied greatly, from 4 to 6 mg in total, to 2 to 6 mg per day throughout the pregnancy. Of all 105 cases, 89 of the women were exposed to loperamide in the first trimester of pregnancy. Between-group comparisons revealed no statistically significant differences in any of the end points that were analysed, including rates of major and minor malformations, spontaneous and therapeutic abortions, premature births, and mean birth weights (see Table 3). However, of women who took loperamide throughout their pregnancy, 21 of 105 had babies who were 200 g smaller than babies in the control group. There were no statistical differences in the preterm delivery rates between the acute users and chronic users – four of 74 (5%) and two of 21(9%) babies, respectively, were born before 36 weeks' gestation.

Table 3. Outcomes of loperamide use during pregnancy

Outcome	Cases (n=105)	Controls (n=105)	p-value
Live births	95	94	0.5
Spontaneous abortions	6	9	0.59
Therapeutic abortions	4	2	0.68
Major malformations	0	1	0.49
Minor malformations	3	3	0.62
Birth weight (g) (mean ± SD)	3368 ± 533	3407 ± 470	0.68

Comment: (AS) I didn't see anything here that would change my generic advice on the use of medicines in pregnancy. Ultimately, in pregnancy, the advice has to be that if a medicine is not needed then it shouldn't be taken. Acute, noninfectious, self-limiting diarrhoea is likely to resolve spontaneously without the use of pharmacological intervention. If it doesn't, this patient group should be seeking further medical direction. However, it is good to know that when the prescriber is required to assess the risk/benefit, there is a bit of information to guide the decision.

(JW) Diarrhoea in pregnancy can have significant consequences for both the mother and the baby. These consequences will depend on the stage of pregnancy when the illness occurs and the underlying cause. For acute, infectious diarrhoea, dehydration is the main concern and efforts to prevent dehydration should be the main focus. For those patients with chronic diseases such as inflammatory bowel disease or irritable bowel syndrome, the diarrhoea needs to be controlled. The principle of management should remain as treating the cause of the diarrhoea. However, this study has given reassurance with respect to using loperamide in pregnancy. A large number of patients with inflammatory bowel disease and irritable bowel syndrome are troubled by diarrhoea even when other aspects of their disease are adequately controlled.

Treatment of traveler's diarrhea with sulfamethoxazole and trimethoprim and loperamide[43]

Summary: Combination therapy with sulfamethoxazole plus trimethoprim and loperamide was superior to loperamide alone and superior to sulfamethoxazole/trimethoprim, when all were given for 3 days for travellers' diarrhoea. The combination product also appeared to be superior to sulfamethoxazole/trimethoprim given as a single large dose.

The study enrolled 227 US adults with acute diarrhoea in Mexico and randomly allocated them to receive, in addition to ad libitum fluid replacement, a single dose of sulfamethoxazole plus trimethoprim (1600 mg/320 mg; n=44) or 3 days of therapy with loperamide alone (4-mg loading dose, then 2 mg orally after each loose stool – with a daily dosage not to exceed 16 mg; n=46), sulfamethoxazole/trimethoprim (800 mg/160 mg orally twice daily; n=45), or the combination of both (n=47), or placebo (n=45).

Subjects treated with the combination had the shortest average duration of diarrhoea compared with the placebo group (1 hour vs 59 hours), took the least amount of loperamide after the loading dose (3.8 mg), and had the shortest duration of diarrhoea associated with faecal leukocytes or blood-tinged stools (4.5 hours). A single dose of sulfamethoxazole/trimethoprim was also efficacious (28 vs 59 hours), but loperamide alone was significantly effective only when treatment failures were treated with antibiotics (33 vs 58 hours).

Comment: (AS) Ultimately what the travelling patient is interested in is 'how long will this last?' So when antibiotics are warranted, the combination is obviously the way to go with this patient group. There are significant morbidity and 'loss of enjoyment of life' issues with travellers' diarrhoea. Not to mention the fact that, so often when travelling, the timetable is not 100% under your control. Loperamide is a serious contender for the tourist medical kit, to enable travellers to keep to timetables and continue to enjoy their adventures.

(JW) Travellers' diarrhoea is usually of short duration but can lead to significant interruption to travel plans and inconvenience for the sufferer. Usually, a specific aetiologic agent is not identified. There is good evidence that antibiotics will shorten the duration of the acute illness when used appropriately and there are a number of antibiotics recommended in this situation. Some of the commonly used antibiotics and antibiotic combinations for travellers' diarrhoea are not available in NZ. From this study, the addition of loperamide to the empiric treatment plan has been shown to give further benefit.

CONCLUSION

(AS) Historically we have given advice to acute diarrhoea sufferers that has had a significant negative impact on their quality of life and ability to continue with day-to-day activities. Potentially, this advice has increased the holistic burden of this common and essentially self-limiting condition and should be revised. A busy worker's ability to continue at work is significantly compromised in the absence of symptom treatment. Parents with small children already cope with significant time away from work associated with childhood infectious diseases – additional days off for their own issues (as any parent knows) significantly adds to the household day-to-day stress. Elderly populations, especially those with reduced mobility, could benefit significantly from this shift in counselling advice. Pharmacists are well placed to be providing good, sound, evidence-based advice on the treatment of this common, self-limiting condition and can contribute significantly to reducing the total burden of acute diarrhoea in primary care.

(JW) Loperamide has been shown to be an effective and safe drug for the management of diarrhoea. It is indicated for use in a range of conditions including acute infectious diarrhoea, travellers' diarrhoea, inflammatory bowel disease and irritable bowel syndrome. Caution over its use is limited to the one scenario of acute diarrhoea with bleeding. Many people rely on loperamide to maintain a normal lifestyle without reliance on finding a toilet at short notice.

References

1. New Zealand Food Safety Authority. Acute Gastrointestinal Illnesses cost five million work days. Available from: http://www.nzfsa.govt.nz/publications/media-releases/2007/acute-gastro-media-release.htm
2. Lake R et al. Acute gastrointestinal illness (AGI) study: Final study report. ESR Client Report FW0753. 2007. Wellington: ESR. http://www.nzfsa.govt.nz/science/research-projects/gastrointestinal-report/Final_Report.pdf
3. Adlam SB et al. Acute gastrointestinal illness in New Zealand: a community study. Epidemiology and Infection. 2010 (in press) doi:10.1017/S0950268810000932.
4. Morris SS et al. Diarrhoea – defining the episode. Int J Epidemiol. 1994;23(3):617-23.
5. Baqui AH et al. Methodological issues in diarrhoeal diseases epidemiology: definition of diarrhoeal episodes. Int J Epidemiol. 1991;20(4):1057-63.
6. Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. Scand J Gastroenterol. 1997;32(9):920-4.
7. Guidelines & Protocols Advisory Committee, British Columbia Medical Association and British Columbia Ministry of Health, March 2009. Infectious Diarrhea – Guideline for ordering stool specimens.
8. Johnston BC et al. Measurement issues in trials of pediatric acute diarrheal diseases: a systematic review. Pediatrics. 2010;126(1):e222-e231.
9. Wingate D et al. Guidelines for adults on self-medication for the treatment of acute diarrhoea. Aliment Pharmacol Ther. 2001;15(6):773-82.
10. McIntosh IB et al. Health professionals' attitudes toward acute diarrhea management. J Travel Med. 2001;8(2):60-5.
11. WHO Diarrhoeal Disease Control Programme. Drugs in the management of acute diarrhoea in infants and young children. Report WHO/CDD/CMT/86.1. 1986.
12. Khanna R et al. Diarrhoea and vomiting caused by gastroenteritis in children under 5 years: summary of NICE guidance. BMJ. 2009;338:b1350.
13. Caeiro JP et al. Oral rehydration therapy plus loperamide versus loperamide alone in the treatment of traveller's diarrhoea. Clin Infect Dis 1999;28(6):1286-9.
14. Atia AN, Buchman AL. Oral rehydration solutions in non-cholera diarrhea: a review. Am J Gastroenterol. 2009;104(10):2596-604.
15. Lewis SJ, Freedman AR. Review article: the use of biotherapeutic agents in the prevention and treatment of gastrointestinal disease. Aliment Pharmacol Ther. 1998;12(9):807-22.
16. Macfarlane GT, Cummings JH. Probiotics and prebiotics: can regulating activities of intestinal bacteria benefit health? Br Med J. 1999;318(7189):999-1003.
17. Camarri E et al. A double-blind comparison of two different treatments for acute enteritis in adults. Chemotherapy. 1981;27(6):466-70.
18. Tojo M et al. The effects of Bifidobacterium breve administration on campylobacter enteritis. Acta Paediatr Jpn. 1987;29(1):160-7.
19. Mitra AK, Rabbani GH. A double-blind, controlled trial of Bioflorin (*Streptococcus faecium* SF68) in adults with acute diarrhea due to *Vibrio cholerae* and enterotoxigenic *Escherichia coli*. Gastroenterology. 1990;99(4):1149-52.
20. Clements ML et al. *Lactobacillus* prophylaxis for diarrhoea due to enterotoxigenic *Escherichia coli*. Antimicrob Agents Chemother. 1981;20(1):104-8.
21. Buts J-P. Mechanisms of action of biotherapeutic agents. In: Elmer GW McFarland L Surawic C, eds. Biotherapeutic Agents and Infectious Diseases. Totowa, NJ: Humana Press Inc, 1997:27-46.
22. Vandenplas Y. Bacteria and yeast in the treatment of acute and chronic infections. Part I. Clin Microbiol Inf. 1999;5(6):299-307.
23. Vandenplas Y. Bacteria and yeast in the treatment of acute and chronic infections. Part II. Clin Microbiol Inf. 1999;5(6):389-95.
24. Czerucka D et al. *Saccharomyces boulardii* inhibits secretagogue-mediated adenosine 3',5'-cyclic monophosphate induction in intestinal cells. Gastroenterology. 1994;106(1):65-72.
25. Shornikova AV et al. Bacteriotherapy with *Lactobacillus reuteri* in rotavirus gastroenteritis. Pediatr Infect Dis J. 1997;16(12):1103-7.
26. Steffen R et al. Efficacy and side-effects of six agents in the self-treatment of travellers' diarrhoea. Travel Med Int. 1988;6:153-7.
27. Scarpignato C, Rampal P. Prevention and treatment of traveler's diarrhea: a clinical approach. Chemotherapy. 1995;41 Suppl 1:48-81.
28. Kollaritsch HH et al. Prevention of traveller's diarrhoea. Comparison of different non-antibiotic preparations. Travel Med Int. 1989:9-17.
29. Buydens P, Debeuckelaere S. Efficacy of SF 68 in the treatment of acute diarrhoea. A placebo-controlled trial. Scand J Gastroenterol. 1996;31(9):887-91.
30. Höchter W et al. *Saccharomyces boulardii* in acute adult diarrhoea. Munch Med Wochenschr. 1990;132:188-92.
31. Wunderlich PF et al. Double-blind report on the efficacy of lactic acid-producing *Enterococcus* SF68 in the prevention of antibiotic-associated diarrhoea and in the treatment of acute diarrhoea. J Int Med Res. 1989;17(4):333-8.
32. de Bruyn G. Diarrhoea in adults (acute). BMJ evidence centre. Clinical evidence summary. http://bestpractice.bmj.com.ezproxy.auckland.ac.nz/best-practice/monograph/601.html
33. McMahan ZH, DuPont HL. Review article: the history of acute infectious diarrhoea management – from poorly focused empiricism to fluid therapy and modern pharmacotherapy. Aliment Pharmacol Ther. 2007;25(7):759-69.
34. Schiller LR. Review article: anti-diarrhoeal pharmacology and therapeutics. Aliment Pharmacol Ther. 1995;9(2):87-106.
35. Burleigh DE. Loperamide but not morphine has anti-secretory effects in human colon, in vitro. Eur J Pharmacol. 1991;202(2):277-80.
36. Baker DE. Loperamide: a pharmacological review. Rev Gastroenterol Disord. 2007;7 Suppl 3:S11-8.
37. Hanauer SB. The role of loperamide in gastrointestinal disorders. Rev Gastroenterol Disord. 2008;8(1):15-20.
38. Kaplan MA et al. Loperamide-simethicone vs loperamide alone, simethicone alone, and placebo in the treatment of acute diarrhea with gas-related abdominal discomfort. A randomized controlled trial. Arch Fam Med. 1999;8(3):243-8.
39. Medsafe. New Zealand Medicines and Medical Devices Safety Authority. Loperamide Data Sheet. http://www.medsafe.govt.nz/profs/datasheet/n/nodiatab.htm
40. Einarson A et al. Prospective, controlled, multicentre study of loperamide in pregnancy. Can J Gastroenterol. 2000;14(3):185-7.
41. Amery W et al. A multicentre double-blind study in acute diarrhoea comparing loperamide (R 18553) with two common antidiarrhoeal agents and a placebo. Curr Ther Res Clin Exp. 1975;17(3):263-70.
42. Hanauer SB et al. Randomized, double-blind, placebo-controlled clinical trial of loperamide plus simethicone versus loperamide alone and simethicone alone in the treatment of acute diarrhea with gas-related abdominal discomfort. Curr Med Res Opin. 2007;23(5):1033-43.
43. Ericsson CD et al. Treatment of traveler's diarrhea with sulfamethoxazole and trimethoprim and loperamide. JAMA. 1990;263(2):257-61.

This publication has been created with an educational grant from Johnson & Johnson (New Zealand) Limited. The content is entirely independent and based on published studies and the author's opinions. It may not reflect the views of Johnson & Johnson. Please consult the full Data Sheet at www.medsafe.govt.nz before prescribing. Treatment decisions based on these data are the full responsibility of the prescribing physician.