CO-MORBIDITY OF AND TREATMENT FOR IRRITABLE BOWEL SYNDROME, DEPRESSION AND ANXIETY IN RESIDENTS OF RETIREMENT VILLAGES

By

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DECLARATION

I hereby declare that the work that is submitted here is the result of my own independent investigation. Where help was sought, it was acknowledged. I further declare that this work is submitted for the first time at this university/faculty towards an M. Med. Sc. Degree (Pharm.) and that it has never been submitted to any other university/faculty for the purpose of obtaining a degree.

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A TROMP Date

DEDICATION

Dedicated to my mother

“For teaching me that the road to success
is paved with obstacles.”

“Education is the most powerful weapon you can use to change the world”

Nelson Mandela

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ABSTRACT

KEY TERMS: Irritable bowel syndrome, depression, anxiety, elderly, antidepressants, anxiolytics, proton pump inhibitors, brain-gut axis, co-morbidity, pharmacotherapy.

Introduction:

Irritable bowel syndrome (IBS), depression and anxiety are very common and often co-occur. Data for depression prevalence in the elderly in South Africa is available, but there is no data on the prevalence of anxiety and IBS in this population. Further, the existing literature does not report on the influence of medication use on these conditions.

Aim and objectives:

The aim of this study was to determine the prevalence and co-morbidity of IBS, depression and anxiety in retirement village residents against the background of the pattern of medication use.

Specific objectives of the study were the assessment of current symptoms of IBS, depression and anxiety and the assessment of the use of antidepressants, anxiolytics and gastrointestinal (GI) medications that might influence the symptoms of IBS.

Methods:

Two hundred ambulant residents older than 50 years were recruited from 2 retirement villages in an urban setting in South Africa by means of convenience sampling. A cross-sectional observational study was performed with a questionnaire. The questionnaire consisted of the Manning criteria and the Hospital Anxiety and Depression Scale (HADS), supplemented by custom-designed questions to evaluate medication use.

Results:

The prevalence of IBS, depression and anxiety were found to be 4.5%, 3.0% and 4.5%, respectively. Sixty-nine participants (34.5%) reported antidepressant use. Selective serotonin re-uptake inhibitors (SSRIs) were used by 63.8% and tricyclic antidepressants (TCAs) by 33.3% of participants reporting antidepressant medication use, fluoxetine and amitriptyline being used in the majority of such cases. Forty-one participants (20.5%) reported the current use of benzodiazepines (BZDs). Proton pump inhibitors (PPIs) were used by 17.5%. The majority of participants using antidepressants, anxiolytics and PPIs were taking these for one year or longer.

Participants taking PPIs or antidepressants were more likely to experience symptoms of IBS than those who were not taking PPIs or antidepressants and these differences were statistically significant. BZDs did not have an influence on the presence of IBS symptoms. There was no association between constipation and use of the target medication groups.

Conclusion:

The lower than expected prevalence of IBS, depression and anxiety occurred against the background of a high level of prolonged antidepressant, anxiolytic and proton pump inhibitor use.

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LIST OF ACRONYMS

BGA: Brain-gut axis
CC: Chronic constipation
CNS: Central Nervous System
CYP: Cytochrome P450
DSM5: The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
FDA: United States Food and Drug Administration
GABA: Gamma-aminobutyric acid
GF: Germ - free
GI: Gastrointestinal
GORD: Gastro-oesophageal reflux disease
HA: Hyperammonemia
HADS: Hospital Anxiety and Depression Scale
IL-1β: Interleukin-1 beta
IL-10: Interleukin 10
IBS-C: Irritable bowel syndrome associated with constipation
IBS-D: Irritable bowel syndrome associated with diarrhoea
IBS: Irritable bowel syndrome
MDD: Major Depressive Disorder
NSAID: Nonsteroidal anti-inflammatory drug
NA: Noradrenaline
PPI: Proton pump inhibitors
PUD: Peptic ulcer disease
QoL: Quality of life
5HT: Serotonin, 5-Hydroxytryptamine
SERT -/-: Serotonin re-uptake transporter lacking
SIBO: Small intestinal bacterial overgrowth
SNRI: Serotonin noradrenaline re-uptake inhibitor
SASH: South African Stress and Health
SSRI: Selective serotonin re-uptake inhibitor
TCA: Tricyclic antidepressant

UFS: University of the Free State

USA: United States of America

WHO: World Health Organization

LIST OF TERMINOLOGY

1. Anti-nociceptive

Action against the capability of appreciation? or transmission of pain (Stedman's Medical Dictionary 27th Ed).

2. Anxiety

Anxiety is a feeling of fear, unease, and worry. The source of these symptoms is not always known (PubMed Health Glossary a, n.d.).

3. Autoimmune

Cells and/or antibodies arising from and directed against the individual's own tissues, as in autoimmune disease (Stedman's Medical Dictionary 27th Ed).

4. Depression

A temporary mental state or chronic mental disorder characterized by feelings of sadness, loneliness, despair, low self-esteem and self-reproach, accompanying signs include psychomotor retardation or less frequently agitation, withdrawal from social contact and vegetative states, such as loss of appetite and insomnia (PubMed Health Glossary b, n.d.).

5. Dysbiosis

Dysbiosis (also called dysbacteriosis) refers to microbial imbalance on or inside the body, most commonly involving the digestive tract or skin (Farlex. a: Online).

6. Elderly

A person that is at least 50 years of age (WHO: online).

7. Functional disorder

A physical disorder in which the symptoms have no known or detectable organic basis, but are believed to be the result of psychological factors, such as emotional conflicts or stress (Dictionary.com Online).

8. Brain-gut axis

The brain-gut axis refers to the biochemical signalling taking place between the gastrointestinal tract and the nervous system, often involving intestinal microbiota (Kennedy *et al.* 2014).

9. Hyperalgesia

An increased sensitivity to pain, which may be caused by damage to nociceptors or peripheral nerves. Temporary increased sensitivity to pain also occurs as part of sickness behaviour, the evolved response to infection (Wikipedia a: Online).

10. Inflammatory bowel disease

A group of chronic intestinal diseases characterized by inflammation of the large or small intestine. The most common types are ulcerative colitis and Crohn's disease (MedicineNet.com. d: Online).

11. Major depressive episode

A state of depression with all the classic symptoms (anhedonia and lethargy, sleep disturbance, despondency and morbid thoughts, feelings of worthlessness and sometimes attempted suicide), but with no known organic dysfunction (Farlex.b: Online).

12. MiRNA

Small non-coding RNA molecule found in plants, animals, and some viruses. miRNA is responsible for RNA silencing and post-transcriptional synchronization of gene expression (Wikipedia b: Online).

13. MiRNome

The full spectrum of miRNAs expressed in a specific genome (Wikipedia b: Online).

14. Neuronal plasticity

Ability of neurons and neural elements to adapt in response to intrinsic and extrinsic signals (Wainwright & Galea 2013).

15. Paracrine

Relating to a kind of hormone function in which the effects of the hormone are restricted to the local environment (Stedman's Medical Dictionary 27th Ed).

16. Pharmacoepidemiology

The study of the distribution and determinants of drug-related events in populations and its application to efficacious drug treatment (Farlex. c: Online).

17. Postprandial

During or relating to the period after mealtime (MedicineNet.com. b: Online).

18. Quality of life

The general well-being of individuals and societies (Wikipedia. c: Online).

19. Somatic

Relating to the body, especially as distinct from the mind (MedicineNet.com. c: Online).

20. Somatization

A tendency to experience and communicate psychological distress in the form of somatic symptoms and to seek medical help for them (Wikipedia. d: Online).

21. Viscera

Referring to the internal organs in the main cavities of the body, especially those in the abdomen, e.g. the intestines (MedicineNet.com. a: Online).

22. Xenobiotic

Foreign chemical substance found in an organism that is not normally naturally produced by or expected to be present in it. It can also cover substances which are present in much higher concentrations than normal (Farlex. d: Online).

CHAPTER 1

GENERAL PERSPECTIVE AND ORIENTATION

1.1 INTRODUCTION

Irritable bowel syndrome (IBS) is an extremely common condition, yet without a clear pathophysiology, it is regarded as a "functional disease" (Longstreth & Burchette 2003). The lack of proof for a biological reason for its existence contributes to lack of understanding of the problems experienced by patients suffering from IBS and even stigmatization. Although the disease does not result in increased mortality, it leads to significant impairment of quality of life (QoL) if frequent and severe symptoms occur (Camilleri as cited in Mach 2004; Ehrenpreis 2005). Remarkable evidence suggests that significant psychological distress, depression and anxiety occur with higher frequency in patient populations (Tang *et al.* 2012; Mykletun *et al.* 2010; Tosic-Golubovic *et al.* 2010), as well as in the general public with IBS symptoms, regardless of whether these individuals seek professional help for their symptoms or not. Likewise, pharmacotherapy for these conditions show a considerable overlap, with antidepressants being used in the treatment of both anxiety and IBS, for instance (Sainsbury & Ford 2011; Lacy *et al.* 2009). A new paradigm is now emerging that aims to explain these commonalities on the grounds of a common aetiology; namely the dysregulation of communication between the gut and the brain (Fichna & Storr 2012).

This study aims to add to the understanding of the problem of co-morbidity of IBS, depression and anxiety and the influence of medication use on this phenomenon in elderly individuals.

1.2 BACKGROUND

IBS was reported to equally affect people on different continents and of different races (Mach 2004) and has a significant impact on quality of life (QOL) (Wang *et al.* 2012; Singh *et al.* 2012; Cho *et al.* 2011; Culpepper & Connor 2004).

1.2.1 Prevalence of irritable bowel syndrome

Estimated to occur in 10-15% of the general population, the global prevalence of IBS was reported as being 11.0% (Canavan *et al*. 2014). Singh *et al.* (2012) found a large proportion (80%) of patients with IBS at a tertiary level institution to have associated psychiatric co-morbidity and 85.9% of IBS patients had somatic co-morbidities or overlapping functional gastrointestinal (GI) diseases.

Women overall have a greater prevalence of IBS symptoms than men and are also more likely to suffer from IBS associated with constipation (IBS-C). Men, on the other hand, more often present with IBS associated with diarrhoea (IBS-D) (Adeyemo *et al*. 2010).

While IBS is common among young and middle-aged patients alike, Ehrenpreis (2005) pointed out that between 10% and 20% of patients over the age of 60 have symptoms consistent with an IBS diagnosis, and yet, only 10% are diagnosed (Friedel *et al*. as cited in Ehrenpreis 2005). Besides underdiagnosis, the implications of IBS in the elderly differ from that in other age groups: the higher risk for cancer necessitates more thorough investigation and polypharmacy and its related risks increase due to higher co-morbidity (Ehrenpreis 2005).

1.2.2 Co-morbidity of irritable bowel syndrome, depression and anxiety

Butt *et al.* (2012) found that the association between depression and anxiety and IBS was stronger than the association of IBS with other chronic diseases, including migraine and hypertension. They proposed that early screening for depression and anxiety in IBS patients might be useful for effective management of IBS.

A study by Farzaneh *et al.* (2013) revealed that almost half of the 153 treatment-seeking IBS patients included in their study also presented with anxiety and/or depression.

Anxiety disorders are a significant factor in the lives of elderly persons. Beekman *et al.* (1998) found a prevalence of anxiety disorders as high as 10% in a study among elderly persons in the Netherlands. Generalized anxiety disorder has also been found to have a significant negative impact on QoL in the elderly. . Itis often associated with co-morbid depression, which in older South Africans is seen as a health concern calling for appropriate interventions to reduce the occurrence of these conditions (Peltzer & Phaswana-Mafuya 2013).

The links between depression, anxiety and IBS extend further to include aetiological factors. For instance, stress was found to be a major contributing factor in the development of IBS (Naeem *et al.* 2012). Modabbernia *et al*. (2012) also found that psychological factors seem to modulate symptom severity in IBS patients. Likewise, life-time history of a broad range of major life traumas, beyond those experienced in early childhood or that are abusive in nature, were associated with increased IBS risk in women veterans (White *et al.* 2010).

Explanations for the co-occurrence of these conditions are characterized by vagueness. Mykletun *et al.* (2010) interpret the significant association of IBS

with anxiety and mood disorders as suggestive that IBS is a disorder with a "psychosomatic" component. An emerging paradigm, however, now establishes IBS, anxiety and depression as connected by a common pathophysiological denominator, namely the dysregulation of the communication between the gut and the brain.

1.2.3 Irritable bowel syndrome and medication

The choice of therapy in IBS is currently directed by the predominance of diarrhoea or constipation. It is, however, acknowledged that this approach is not optimal and Trinkley and Nahata (2011) proposed that a more targeted treatment approach directed by the individual patient's primary symptom(s), rather than global IBS symptoms, might be desirable.

The potential overlap in aetiology of IBS, depression and anxiety also has implications for potential overlap in the effect of medications for IBS, depression and anxiety. Culpepper and Connor (2004) proposed that effective management of anxiety symptoms in IBS patients would increase their QOL. The use of antidepressants also influence symptoms of IBS and are indeed used in the treatment of IBS (Sainsbury & Ford 2011; Lacy *et al.* 2009).

Psychotropic drug use is, however, a concern amongst the elderly (Giron *et al.* 2001). Pharmacokinetic and pharmacodynamics changes that occur with ageing result in altered drug responses in this population. At the same time, elderly patients are excluded from clinical trials, both because of age and co-morbidity. There is therefore often insufficient evidence regarding the relative risks and benefits of therapeutic agents in this population (Zhan *et al.* 2001).

In summary then, there is a high prevalence of anxiety-depressive disorders in IBS patients and patients with anxiety and depression are more likely to experience IBS (Butt *et al.* 2012). On the other hand, the symptoms of IBS are

influenced by the use of antidepressants (Sainsbury & Ford 2011; Lacy *et al.* 2009) and anxiolytics (Naeem *et al*. 2012).

1.3 RATIONALE FOR THE STUDY

IBS, depression and anxiety as individual conditions are common in elderly individuals (Stewart *et al*. 2014; Friedel *et al*. as cited in Ehrenpreis 2005; Forlani *et al.* 2014). These conditions show a significant overlap in occurrence. It is therefore reasonable to expect that co-morbidity involving these conditions will be high in elderly populations and that pharmacotherapy for these conditions will contribute significantly to the total medication use in these populations. Elderly populations also use more medications, which may influence the expression of IBS, depression and anxiety.

1.4 PROBLEM STATEMENT

The gap in the knowledge is that there is no data on the prevalence of IBS and its co-occurrence with depression and anxiety and the treatment thereof in the elderly in South Africa.

1.5 AIM OF THE STUDY

The aim of the study is to determine the prevalence and co-morbidity of IBS, depression and anxiety in retirement village residents and the influence of treatment for these conditions.

1.6 RESEARCH QUESTIONS

What is the prevalence of IBS, depression and anxiety in a population of retirement village residents based on the presence of current symptoms?
What is the prevalence of the use of antidepressants, anxiolytics and medications that may influence the symptoms of IBS in the same population?
To what extent does the medication use influence the manifestation of symptoms?

Specific objectives were as follows:

- Assessment of current depression and anxiety symptoms in subjects by the Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith 1983).

- Assessment of current IBS symptoms by the Manning diagnostic criteria for IBS.

- Assessment of the use of prescribed and over-the-counter antidepressants, anxiolytics and GI medications.

- Seeking associations between a diagnosis of IBS (or individual symptoms associated with IBS) and the use of specific classes of medication.

- Stratification of prevalence of IBS, depression and anxiety by gender.

1.7 SIGNIFICANCE OF THE STUDY

This study seeks to contribute to the understanding of the overlap between IBS, anxiety and depression and the interaction between these conditions and medication use.

1.8 SCOPE OF THE STUDY

The general purpose of the study was to determine the prevalence of IBS, depression and anxiety and medications used for these conditions in a population of retirement village residents.

An investigation into the prevalence of IBS, depression and anxiety and the overlap in the occurrence of these conditions was performed. Medication use was also recorded, focusing specifically on the use of GI medication, antidepressants and anxiolytics. The literature that investigates the possibility of an overlap in the origin of IBS and depression and anxiety was explored and evidence was gained through the analysis of current symptoms as well as medication use patterns to provide a bilateral perspective on this phenomenon.

Volunteers were recruited from 2 retirement villages in an urban area in central South Africa, with a total number of residents of 442. The study was executed in 2013, during the months of September, October and November.

The results should be seen in the context of the study population of relatively affluent residents of retirement villages in previously exclusively white residential areas. The relative affluence was deduced from the level of medical scheme cover (92%) that was significantly higher than the average for the South African population (18.4%) (Statistics South Africa 2013). The results therefore cannot be generalized to the South African population as a whole, as the prevalence of IBS could be very different in a different

socio-economic group and/or cultural group. It may, however, serve as a reference point for similar studies in elderly populations.

Only residents that gave informed consent participated, therefore some participants were excluded based on whether they 'felt like it" or not. One of the symptoms related to the diagnosis for depression in this study is the loss of enjoyment of activities that were enjoyed before. It was also assumed that participants would be honest and open about their medication use.

The questionnaire did not provide a means of evaluating dosages of medication use.

The definitive diagnosis of IBS occurs after exclusion of organic disease. As the researcher did not perform special investigations on participants, the diagnosis of IBS by means of the Manning criteria should be regarded with caution. One participant that was diagnosed with IBS reported blood mixed with stools and three of the participants diagnosed with IBS reported weight loss. These symptoms may indicate the presence of organic disease. The Manning criteria also do not include constipation as part of the diagnostic criteria for IBS.

Medication for IBS and GI medication are generally overlapping significantly and therefore the total use of GI medication use was recorded rather than medication used exclusively for IBS.

1.9 RESEARCH APPROACH AND METHODOLOGY

The study was designed as a cross sectional observational study with analytical elements.

A questionnaire was developed that consists of 2 standardized self-reporting questionnaires expanded with custom designed questions (Appendix A).
The prevalence of IBS, depression and anxiety were assessed by making use of the HADS and Manning diagnostic criteria, while medication use patterns were assessed by making use of a list of medications with related questions developed by the researcher.

The questionnaire was designed with sections on demographic information, medical history, depression, anxiety, GI symptoms and medication use. The questionnaire was tested by performing a pilot study.

Data capturing was performed by the Information Technology Centre and data analysis was performed with the assistance of the Department of Biostatistics, University of the Free State.

1.10 IMPLEMENTATION OF FINDINGS

The study highlights the issues of polypharmacy and appropriate prescribing in the elderly. Publication of the findings and recommendations will be of interest for medical practitioners in family practice, Internal medicine, Gastroenterology, Psychiatry and Geriatrics.

Recommendations are made for prescribing medication for IBS, depression and anxiety in the elderly and areas that need further investigation are identified.

1.11 ARRANGEMENT OF THE DISSERTATION

The present chapter introduces the background and rationale of the study, based on an emerging paradigm for the pathophysiology of IBS, depression and anxiety.

The broad goal and objectives of the study are outlined as well as a research approach and methodology.

In the next two chapters the literature that was studied, is described.

Chapter 2 deals with the epidemiology and pathophysiology of IBS, depression and anxiety, the concept of the brain-gut axis, dysregulation of the brain-gut axis and the role of disruption of the microbiota and the association of stress with increased intestinal permeability, visceral sensitivity and modified GI motility and inflammation.

In chapter 3 therapeutic strategies for the treatment of IBS and prescribing of medication in the elderly are discussed. The opening of the chapter covers the development of the broad pharmacological approach to IBS, followed by specific treatment options currently available and concluding with specific treatment related issues regarding IBS in the elderly.

Chapter 4 describes the methodology that was followed in this study, sketching the study environment and differentiating the study population as well as outlining the development of the questionnaire and the process of data collection.

The results of the study and statistical analysis are reported in chapter 5.

Chapter 6 comprises a discussion of the results, its limitations and implications and recommendations that emanate from the results.

1.12 CONCLUSION

Chapter 1 dealt with the background and the rationale for the study. Recent discoveries that expanded the understanding of the aetiology and pathophysiology of IBS and created an awareness of a potential common origin with depression and anxiety provide the background for the study. The background to the research question includes the unexplained co-existence of IBS, depression and anxiety and the treatment of these conditions in the elderly. The study observes medication use patterns and the prevalence of individual symptoms of IBS, depression and anxiety in elderly individuals to gain a bilateral perspective on the co-morbidity of and treatment for IBS, depression and anxiety in the elderly population. The researcher's concern is an expected higher prevalence of IBS, depression and anxiety in the elderly, contributing to polypharmacy in this group.

Bearing these perspectives in mind, the epidemiology, aetiology and pathophysiology of IBS, depression and anxiety will be described in chapter 2.

CHAPTER 2

THE EPIDEMIOLOGY AND PATHOPHYSIOLOGY OF IRRITABLE BOWEL SYNDROME, DEPRESSION AND ANXIETY

The epidemiology and pathophysiology of IBS need to be understood in order to develop better interventions. A closer look at the tendency for co-occurrence of IBS and depression and/ or anxiety has already yielded some evidence in support of a common aetiology for these conditions.

In this chapter we describe the clinical manifestations of IBS, depression and anxiety and explain how the current understanding of these conditions developed with particular emphasis on shared aspects of their respective pathophysiology and epidemiology.

2.1 IRRITABLE BOWEL SYNDROME

IBS is still described as a "functional disorder" characterized by altered bowel habits and abdominal pain in patients presenting with GI symptoms in the absence of organic pathology (Burbige 2010).

2.1.1 Diagnostic criteria for irritable bowel syndrome

The diagnosis of IBS in clinical settings is challenging because of the overlap of IBS symptoms with those of organic diseases, such as celiac disease, inflammatory bowel disease and bile acid diarrhoea (Jones *et al.* 2014). The diagnosis is therefore always subject to the exclusion of these organic conditions. Several sets of diagnostic criteria were developed for the diagnosis of IBS, based on symptoms experienced.

2.1.1.1 *The Rome criteria*

The Rome criteria for diagnosing functional GI diseases was developed in 1990 and since 2000 the Rome II criteria took the lead in clinical practice and research. Since then, an enhanced version of the Rome criteria has been developed as the Rome III criteria and discussions for the development of Rome IV have commenced (Jung 2011).

For a diagnosis of IBS according to the Rome III criteria, an uncomfortable sensation of the abdomen, not described as pain or abdominal pain, should be present in association with two or more of the following for at least 3 days per month in the last 3 months: symptom change for the better with defecation; onset associated with a change in frequency of stools; or change in appearance of stool. These criteria should have been fulfilled for the preceding 3 months and symptom onset should have been at least 6 months before diagnosis. The criteria can only be used for the diagnosis of IBS in the absence of inflammatory, metabolic, anatomic or neoplastic activity.

2.1.1.2 *The Manning criteria*

The Manning criteria are the most validated tool for the diagnosis of IBS. Talley *et al*. (1990) found the sensitivity of the Manning criteria to be 65% and specificity 86% for the diagnosis of IBS. The Manning criteria were also found to be the most reliable when compared with other diagnostic algorithms of its time, such as the Rome I, the Rome II and the Kruis criteria (Manning *et al*. 1978). The criteria are ideal for use in a research setting with low technology input as it clusters symptoms that are considerably more associated with IBS than with organic disease, i.e. abdominal bloating; abdominal pain reduced by defecation; and more frequent and looser stools at onset the onset of pain (Manning *et al.* 1978). The diagnosis can therefore be made with reasonable accuracy with a self-administered questionnaire, consisting of six questions. Besides the symptoms already mentioned, the patient also indicates the

presence or absence of mucus in the stool and incomplete defecation. The main shortcoming of the Manning criteria is that it does not provide means of discerning IBS associated with diarrhoea (IBS-D) from IBS associated with constipation (IBS-C) (Dang *et al*. 2012).

Despite the existence of various sets of diagnostic criteria, IBS remains under-diagnosed. Olafsdottir *et al*. (2012) found that physicians only diagnose about half of IBS patients. Few physicians in their study made use of IBS criteria and awareness of diagnostic criteria for IBS varied between specialists in gastroenterology and general practitioners. Patients were likewise not well-informed about their condition.

2.1.2 Future prospects for diagnosis

The ideal diagnostic test for IBS will include a combination of gene expression and serological markers with psychological measures and will be able to differentiate IBS-C from IBS-D (Jones *et al*. 2014). Jones *et al.* (2014) identified 34 biomarkers for the diagnosis of IBS that may be used in future.

2.1.3 Types of irritable bowel syndrome

Two kinds of IBS can be distinguished: (1) IBS mainly confined to GI symptoms with absence of or few other physical complaints or psycho-behaviour present and (2) IBS symptoms as part of a broader spectrum of multiple physical symptoms in combination with depression and anxiety; and effects on cognition and behaviour (Hausteiner-Wiehle *et al*. 2014).

Systematic investigation of underlying anxiety and depression and other associated factors is therefore relevant to determine appropriate treatment. An integrative, multidisciplinary biopsychosocial intervention might be appropriate for more extensive cases.

2.1.4 Prevalence of irritable bowel syndrome

The prevalence of IBS reported in literature fluctuates largely as the diagnostic criteria used to define the condition differ. The use of different criteria makes it difficult to compare the variation of prevalence of IBS in different geographical areas or cultures.

The prevalence of IBS as defined by the Manning criteria, for example, was found to be 11.5% in a Chinese community (Chang *et al*. 2010). A Nigerian population study found a prevalence of 33% by making use of the Rome II criteria (Ladep *et al.* 2007).

Nevertheless, the prevalence of IBS is said to be on the rise in developing countries (Gwee 2005). This finding might be of relevance to Africa, but due to the scarcity of such studies in Africa, no data in support of this could be found.

Women are more susceptible to IBS (Mulak *et al*. 2014). This can be explained by evidence that androgens play a protective role against the development of visceral hyperalgesia in IBS through modulation of pain perception and anti-inflammatory action (Akiho *et al*. 2010).

2.1.5 Aetiology of irritable bowel syndrome

IBS is a multi-factorial disease, the development and expression of which is related to both genetic (Sato *et al.* 2012; Zhang *et al*. 2011) and environmental factors (Böhn *et al*. 2013; Hayes *et al*. 2014; Verdu 2011).
Zhang *et al.* (2011) showed that IBS patients with depression had a specific change in gene expression of tyrosine hydroxylase and Sato *et al.* (2012) found that genetic polymorphisms and haplotypes of corticotropin-releasing hormone receptor 1 could steer the development of IBS.

A non-genetic contribution is suggested by the increased risk for IBS among spouses of diagnosed patients (Waehrens *et al*. 2014). IBS sufferers believe that specific food can trigger IBS symptoms, specifically food that contains carbohydrates, fat, biogenic amines and histamine-releasing food items (Böhn *et al*. 2013; Hayes *et al*. 2014; Verdu 2011).

2.2 DEPRESSION AND ANXIETY

Depression and anxiety were found by the Global Burden of Disease study of 2010 to be the most important contributors to disability caused by mental disorders world-wide (Whiteford *et al.* 2013). This was true for all geographical regions of the world, but were especially prominent in countries where conflict prevailed. Depression also shows an increasing trend from previous cycles of the same study. It is currently identified as the 4th leading cause of disability globally and is estimate to be the second leading cause by 2020 (Kessler & Bromet 2013). Similar to IBS, there is no single accepted theory for the cause of depression and anxiety yet, but constant new discoveries add to a complex scenario on which future interventions will be modeled (Den Boer 2006; Messaoudi *et al*. 2011).

2.2.1 Clinical presentation

Clinical depression is a mood disorder in which feelings of sadness, loss, anger or frustration interfere with everyday life for a prolonged period of time (National Institute of Mental Health n.d. a). Generalized anxiety disorder (GAD) is a mental health condition in which a person is often worried or anxious about several things and finds it hard to control this (National Institute of Mental Health n.d. b). The two conditions often occur together. A study by Lamers *et al*. (2011) showed that of patients with a depressive disorder, 67% had a current and 75% had a lifetime co-morbid anxiety disorder and of patients with an anxiety disorder, 63% had a current and 81% had a lifetime depressive disorder.

The DSM5 criteria for Major Depressive Episode (MDE) (Bromet *et al.* 2011) requires the presence of 5 or more from a set of 9 criteria to be present during the same 2 weeks. One of the symptoms present must be a depressed mood or loss of interest or pleasure. These symptoms must cause significant distress or loss of function and not be the direct consequence of drug abuse or a medical condition.

Anxiety disorders refer to a whole range of diagnosis. In the context of the present study the terms anxiety and depression are used to refer to subjective experiences expressed and weighted by responses to the HADS questionnaire.

2.2.2 Prevalence of depression

Moussavi (in Kessler & Bromet 2013) summarized the prevalence of MDE in the WHO global survey across 60 countries. The average prevalence over a twelve month period was found to be 3.2% in participants in the absence of comorbid physical disease and 9.3% to 23% in individuals with chronic conditions.

2.2.2.1 *Depression in the elderly*

Major depression incidence in the population 70 years and older seem to not be higher than in younger population groups, yet major depression is listed among the 15 most problematic disorders in the elderly as found in the Global Burden of Disease study (Prince *et al.* 2015).

A British survey in South East London, investigating the prevalence of depression in the elderly mentally infirm care sector, revealed a prevalence of 22% (Stewart *et al*. 2014).

Yaka *et al*. (2014) found a high prevalence of depression of 18.5% in community dwelling elderly in an urban area of Izmir, Turkey. Depression in the elderly was found to be more common in females; people with low education; chronic diseases; low income; as well as increased independence.

2.2.2.2. *Depression in South Africa*

The national prevalence of depression in South Africa was shown to be lower than that of the United States of America, but higher than Nigeria's. A national representative home survey in 2002 to 2004 showed major depressive disorder (MDD) prevalence to be 4.9% during the 12 months prior to the interview (Tomlinson *et al*. 2009).

The SASH survey (Herman *et al.* 2009), a national survey that was conducted with 4351 participants in 2009, revealed a MDD prevalence of 4.9% in the general South African population.

Strydom *et al*. (2012) examined the prevalence of depression in grade 11 and 12 school learners in Bloemfontein in central South Africa. They found a prevalence of 5.3% with moderate to severe depression symptoms amongst the 515 learners that participated in the study.

A study by Peltzer and Phaswana-Mafuya (2013) on depression in the elderly in South Africa revealed a prevalence of 4% over the preceding 12 months. Similar to the current study, participants taking antidepressant therapy were not excluded from this study.

2.2.3 Prevalence of anxiety

A study review by Baxter *et al*. (2013) including 87 studies over 44 countries revealed the prevalence of anxiety disorders to vary from 0.9% to 28.3% in the year 2012 compared to the previous year's figures of 2.4% to 29.8%. The variation in the data can be explained by several factors including: gender; age; culture; conflict; economic pressure; and urbanization. The global prevalence of anxiety disorders was found to be 7.3%, ranging from 5.3% in African cultures to 10.4% in the European cultures.

2.2.3.1 *Anxiety in the elderly*

The global burden of disease found that both depression and anxiety tend to become less prevalent after middle-age (Whiteford *et al.* 2013). Nevertheless, anxiety disoirder have been found to significantly impair QoL in the elderly (Porensky *et al.* 2009). Lamers *et al.* (2011) concluded that the fact that depression commonly occurs in combination with anxiety necessitates care to be given in the treatment thereof in the elderly.

Forlani *et al*. (2014) conducted a survey involving 366 elderly participants without dementia in Faenza in Northern Italy. The study revealed a high prevalence of anxiety disorders in elderly people, especially those who were medically ill. Anxiety prevalence was found to be 21% and in their study the proportion of participants with anxiety, but not depression, was found to be 56.9%. Ageing females were more likely to develop anxiety than males

(Catuzzi & Beck 2014), possibly due to the anti-inflammatory properties of dihydrotestosterone (Vignozzi *et al*. 2012).

2.2.3.2 *Anxiety in South Africa*

The prevalence of anxiety disorder in the general population of South Africa was found to be 8.1% by the SASH survey (Herman *et al.* 2009) conducted with 4351 participants in 2009 and 32.0% amongst 515 grade 11 and 12 school learners (Strydom *et al.* 2012).

There is a general lack of data on the prevalence of anxiety disorders amongst the elderly population of South Africa.

2.2.4 Aetiology of depression and anxiety

Aetiological insights for depression and anxiety are evolving, fed by a constant stream of laboratory based and diet-related discoveries in this field (Den Boer 2006).

None of the several therories of depression, including the monoamine hypothesis, alterations in neurotrophic factors, and the upregulation of adult hippocampal neurogenesis sufficiently explain the pathophysiology for depression completely (Wainwright & Galea 2013). Neuroplasticity theories postulate that vulnerable phenotypes exist that are neurobiologically predisposed to the development of depression and anxiety in adulthood. A combination of genetic disposition and early stress in critical phases of development occurring during a period of active neuronal plasticity appear to permanenty render central corticotropin-releasing factor (CRF) hyperactivity and enhanced stress reactivity in adulthood (Heim & Nemeroff 1999; Penza *et al*. 2003).

The monoamine theory has long been the cornerstone of understanding the origins of depression (Hall 1998). This theory, formulated by Schildkraut in 1965 (Den Boer 2006), states that depression is associated with the reduction of catecholamines, especially noradrenaline (NA) and serotonin (5HT). Although the monoamine theory has been suggested by Hinz *et al*. 2012 to be of historical importance only, it has been regarded for the past 50 years as specifically relevant, not only as the cornerstone for understanding depression, but also as the foundation for the development of new antidepressant agents (Hindmarch 2002).

According to novel discoveries, inflammation and neurodegeneration both seem to play a crucial role in the development of depression. Maes *et al*. (2009) demonstrated that increased neurodegeneration might at least in part be caused by inflammation as plasma levels of several cytokines are elevated during depressive episodes and return to normal levels after full recovery (Dahl *et al*. 2014).

A study by Tynan *et al*. reviewed by Walker (2013), found that selective serotonin re-uptake inhibitors (SSRIs) and serotonin–noradrenaline re-uptake inhibitors (SNRIs) have anti-inflammatory properties and dihydrotestosterone was found to exert an immune regulatory affect on human cells, inhibiting their potential to actively induce and/or modulate autoimmune and inflammatory responses (Vignozzi *et al*. 2012) and could possibly be a contributing factor to women being more susceptible to anxiety and depression than males.

Several discoveries shed light on the development of depression: segment variations in several genes involved in regulating dopamine neurotransmission (Pearson-Fuhrhop *et al.* 2014); and the discovery that short-term exposure to gluten specifically induces simultaneous (or acute) feelings of depression. Pearson-Fuhrhop *et al.* postulated that this effect could be brought about by an increase in cortisol secretion with negative affect (i.e. anxiety and depression). Their study however, found cortisol levels to remain similar across all dietary treatments. They also postulated that decreased serotonin (5-hydroxytryptamine; 5-HT) concentration in the brain could be the causative

mechanism. As a third possible explanation, they postulated the involvement of the so-called gluten 'exorphins'. These opioid peptides derived from partially digested food proteins such as gluten can alter intestinal function, cross the blood-brain barrier and interfere with emotional processes by altering other hormonal or neurotransmitter systems via the opioid receptors as well as endogenous opioid peptides in the CNS. A fourth possible explanation involves gluten-mediated changes in gut microbiota (Peters *et al*. 2014).

2.3 CO-MORBIDITY OF IRRITABLE BOWEL SYNDROME AND DEPRESSION AND ANXIETY

In this section available data on the possibility for a common origin of these diseases will be explored.

2.3.1 Prevalence of co-morbidity

A study by Farzaneh *et al.* (2013) revealed that almost half of the 153 treatment-seeking IBS patients included in their study also presented with anxiety and or depression. The higher levels of anxiety and depression in patients with IBS were also confirmed in a review by Fond *et al*. (2014) that included 10 studies with a total of 885 patients and 1384 healthy controls.

2.3.2 The overlapping roles of neurotransmittors

Alterations in noradrenergic systems are implicated in the pathophysiology of depression, anxiety and IBS. IBS patients with depression demonstrated a specific change in gene expression of tyrosine hydroxylase, which indicates that drugs strengthening noradrenergic function might be useful in the treatment of IBS patients with depressive disorder (Zhang *et al.* 2011).

Evidence also exists that serotonin (5HT) plays a role in both depression and IBS. As a poly-functional signalling molecule, 5HT acts as a neurotransmitter, paracrine factor, endocrine hormone, intestinal anti-inflammatory and growth factor (Gershon 2013). Patients with depression have abnormalities in brain 5HT mediated processes. 5HT pathways provide a noticeable innervation to emotional processing circuitry, including the amygdala and prefrontal cortex, demonstrated by brain-imaging investigations. Cowen (2008) reasoned that it is possible that impaired 5-HT innervation of this circuitry is associated with negative biases in the processing of emotional information. Patients with diarrhoea predominant IBS have significantly higher postprandial 5-HT concentrations and a longer duration of 5-HT peak than healthy volunteers (Bearcroft *et al.* 1998). Abnormal intestinal motility observed in serotonin re-uptake transporter (SERT) -/- mice suggests that a defect resulting in an excessive concentration of 5HT reaching enteric receptors might contribute to the pathogenesis of IBS (Chen *et al.* 2001). The 5HT receptors responsible for the enhancement of peristalsis include 5-HT_{1p} and 5-HT_4. Transmission of signals from the gut to the CNS are mediated by $5HT_3$ receptors. There also seem to be a strong association between impaired 5-HT1A receptor functioning and depression (Deakin 1998).

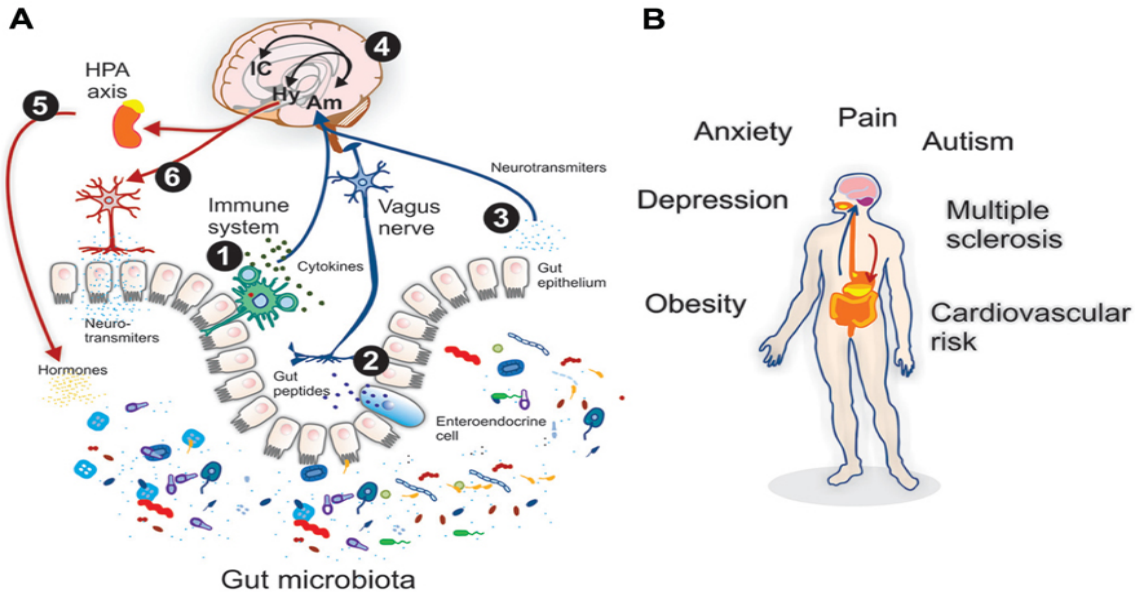
2.3.3 Towards an integrative model for irritable bowel syndrome

There is a growing understanding of the interrelatedness of IBS, depression and anxiety. This awareness has been voiced in various terms, including “biopsychosocial model” (Katsanos *et al.* 2012); “biobehavioural model” (Mayer *et al*. 2001). The underlying train of thought is that the multifactorial pathology for the disease seeks contribution of different fields of science and health care.

The bio-psychosocial model of IBS maintains that a wide range of environmental and psychosocial factors cause irregularity of the brain-gut axis (BGA), leading to the onset of IBS.

2.3.3.1 The concept of the brain-gut axis

The BGA describes the biochemical signalling between the GI tract and the nervous system, often related to changes in intestinal microbiota, which have been shown to play an important role in healthy brain function (Kennedy *et al.* 2014). Figure 1 shows the two way biochemical signalling between the GI tract and the CNS and how it influences various health risks.



(A) Microbiota–gut–brain (MGB) axis. Bidirectional communication between the gut microbiota and the central nervous system (CNS) by direct and indirect pathways; which involves endocrine, immune and neural pathways. On the afferent arm (blue arrows): (1) lymphocytes sense cytokines released (2) vagus nerve may be activated by gut peptides released (3) Neurotransmitters or its precursors produced as microbiota metabolites can have endocrine or paracrine effects in the gut epithelium. (4) Centrally, after brainstem relays discrete neural networks described as the amygdala and the insular cortex (IC) are main integrators of visceral inputs. Frequently hypothalamic (Hy) activation initiates the efferent arm (red arrows): (5) corticosteroids, release as results of the hypothalamic–pituitary–adrenal (HPA) axis activation, modulates gut microbiota composition. (6) Neuronal efferent activation may include the so called "anti-inflammatory cholinergic reflex" and/or sympathetic activation, both liberating classical neurotransmitters that may affect directly the gut microbiota composition.

(B) Health conditions affected by the MGB axis. Health conditions that may be affected by intestinal microbiota, including: visceral pain, autism spectrum disorders, obesity, cardiovascular risk, anxiety/depression and multiple sclerosis.

(*From:* Montiel-Castro *et al*. 2013)

Figure 1: The brain-gut axis

Regulation of the BGA includes afferent/efferent regulatory autonomic neural pathways, hormones and nutrients. The BGA is in control of physiological processes, such as satiety and food intake, regulation of glucose, fat and bone metabolism and hormone secretion (Romijn *et al*. 2008).

Significant evidence suggests the central involvement of the BGA in the progression of IBS and IBS-like symptoms (Fichna & Storr 2012; Mayer *et al.* 2014), specifically involving modifications in the bi-directional signalling between the enteric nervous system and the central nervous system. Several mechanisms may contribute to the disturbance and deterioration of the BGA, including altered stress response, corticotrophin-releasing factor release and processing, 5HT signalling and release, inflammatory insults and deranged conduction and processing of information (Coss-Adame & Rao 2014).

2.3.3 Irregularity of the brain-gut axis through the disruption of microbiota structure

Evidence of significant interaction between the gut microbiota and the CNS function of the host is constantly accumulating (Bravo *et al.* 2011; Mayer *et al.* 2014). The vagus nerve in particular is identified as a modulating communication factor between the bacteria in the gut and the brain.

The gut was found to play a crucial role in mood and behaviour, considering the gut's multi-component communication with the CNS (Farmer *et al.* 2014). A study by Cryan and O'Mahony (2011) suggested that there is an increasing need to understand the molecular, cellular and physiological basis of the impact of microbiota on brain function as it was discovered that the vagus nerve plays a crucial role in the transmission of immune information between the gut and the brain and also in homeostasis of the immune system.

A distinct disorder in the composition of the gut microbiota structure in animal models of depression and stress was discovered and has direct implications

for the development of psychobiotic-based therapeutic strategies for psychiatric disorders (Dinan & Cryan 2013).

2.3.3.2 Animal studies

Analysis of the fecal microbiota of humans and 59 other mammalian species has shown that the gut microbiota of humans living a modern lifestyle is typical of omnivorous primates (Ley *et al.* cited in Kosiewicz 2011).

Bailey *et al.* (2011) reported that microbiota are primarily and interactively involved in stressor-induced immune-enhancement in a mouse model. A study by Crumeyrolle-Arias *et al.* (2014) has shown that, in a stress-sensitive rat strain, absence of gut microbiota exacerbates the neuro-endocrine and behavioural response to acute stress and significantly modifies the dopaminergic turnover rate in cortical structures involved in the regulation of stress and anxiety.

Taken together, these studies suggest the existence of strong interrelationships between the intestinal microbiota and mediators of depression and anxiety. The therapeutic implications of these findings were also tested.

A study by Neufeld *et al*. (2011) showed reduced anxiety-like behaviour in germ free (GF) mice as well as in GF mice colonized with specific pathogen-free feces, thereby introducing normal gut microbiota.

Messaoudi *et al*. (2011) showed that consumption of probiotic formulas containing *L. helveticus* R0052 and *B. longum* R0175 in combination reduced anxiety-like behaviour in rats.

A study by Luo *et al*. (2014) on hyperammonia-mediated cognitive decline and anxiety-like behaviour in rats proved that the probiotic *L. helveticus* strain

NS8 could be considered a probiotic treatment for neurological disorders and suggested that the effect of probiotic treatment in improvement of behaviour may be attributed to its immune-modulatory properties that attenuates neuroinflammation and decreases 5-HT metabolism.

The role that environmental factors such as food items play in altering the microbiota structure was shown by feeding germ-free (GF) mice colonized with human fecal microbial communities a high-fat and sugar diet instead of a low-fat, plant polysaccharide-rich diet. Results clearly indicated an increase in *Firmicutes* and decrease in *Bacteroidetes* (Turnbaugh *et al*. as cited in Kosiewicz *et al.* 2011). Microbiota have been shown to contribute to proper development of the immune system by GF mice having poorly developed lymphoid tissues and spleens with few germinal centers and poorly formed T and B cell zones, hypoplastic Peyer's patches, lower numbers of lamina propria CD4+ cells and IgA-producing plasma cells (Macpherson & Harris as cited in Kosiewicz 2011).

Application of animal data to humans in depression and anxiety are however especially limited because of the involvement of emotional and subjective experiences that cannot be captured in animals.

2.3.3.3 Human studies

Kennedy *et al*. (2014) identified three key elements that play a role in IBS, namely stress; immune activation; and chronic pain. These elements exert bi-directional influence between the brain and the gut.

Human studies on microflora in humans suggests that gut microflora has a role to play in the pathophysiology of IBS, depression and anxiety via the enteric nervous system as well as centrally (Messaoudi *et al.* 2011; Nasser *et al.* 2014; Piche 2014; Gao 2013; Shin 2011; Kosiewicz *et al*. 2011; Konturek *et al*. 2011; Vanuytsel *et al*. 2014; Marshall *et al*. 2004; Crumeyrolle-Arias *et*

al. 2014; Foster & Neufeld 2013; Bailey *et al*. 2011; Hong & Ree 2014; O'Malley *et al.* 2011).

A review by Hong and Ree (2014) indicated that several recent studies have consistently found that intestinal dysbiosis is associated with IBS. Although further research is needed over the exact compositional alteration of the gut microbiota in IBS, clinical data support the idea of diverse and unstable bacterial communities in IBS (Kennedy 2014).

2.3.3.2.1 *Inflammation*

Nasser *et al.* (2014) studied human intestinal biopsies to better understand the pathogenesis of IBS. By using this method they could confirm that IBS patients had altered structural signalling pathways. A low grade of inflammation was also found. It seems possible that increased inflammatory signalling could be steered by alteration in micriobiota structure.

Low-grade inflammation in the gut mucosa of IBS patients is associated with deranged intestinal barrier function (Piche 2014). The intestinal barrier consists of tight junction proteins that form a critical platform regulating epithelial barrier integrity and mucosal immune activation.
The association between the level of anxiety/depression and altered interleukin-1 beta (IL-1β) and interleukin 10 (IL-10) levels in IBS patients is significant, resulting in increased inflammatory cytokines, believed to aggravate IBS (Gao 2013).

2.3.3.2.2 *Immune function*

A study by Shin (2011) concluded that antibodies against gonadotropin-releasing hormone (GnRH) are commonly associated with IBS and not with

organic diseases and suggested that IBS might be of an autoimmune origin. GnRH was found to not only play a role in reproductive function, but also in the immune system (Min *et al.* 2009).

A review by Kosiewicz *et al.* (2011) confirmed the association of genetic and environmental factors that can influence the microbiota structure, which in turn leads to increase in inflammation; activates an immune response and ultimately leads to the development of auto-immune diseases.

2.3.3.2.3 *Stress*

Stress exposure is a primary risk factor in the pathogenesis of depression and anxiety as well as that of IBS. In the latter case, stress increases intestinal permeability and visceral sensitivity, modifies GI-motility, and results in extensive mast cell activation presenting with the release of many pro-inflammatory mediators (Konturek *et al*. 2011).

A study by Vanuytsel *et al.* (2014) suggested that acute psychological stress can increase small intestinal permeability in humans. IBS is also associated with increased intestinal permeabililty (Marshall *et al*. 2004).

Notable discoveries showed that stress has a significant influence on the composition of the gut microbiota. Bidirectional communication between the microbiome and the CNS affects immune responses and regulation of serotonergic and GABAergic signalling systems in the CNS (Crumeyrolle-Arias *et al*. 2014; Foster & Neufeld 2013; Bailey *et al*. 2011).

The close association between stress factors, such as corticotropin-releasing factor and pro-inflammatory cytokines seems promising for the development of new therapeutic strategies for IBS (O'Malley *et al*. 2011).

2.3.3 Other potential aetiologic factors

A review on the effects of glyphosate (N-phosphonomethyglycine) used in agriculture on the microbiota in humans revealed the toxic role that these herbicides play in the pathophysiology of modern diseases, including inflammatory bowel disease and depression. It was found that glyphosate acts synergistically with other xenobiotics by impairing detoxification processes. Samsel and Seneff (2013) concluded that glyphosate is the most non eco friendly chemical in our environment.

The important role of the close association of human microbiota to "our natural miRNome" was recently suggested. The human miRNome can be defined as the full spectrum of miRNAs (small non-coding RNA molecules involved in gene expression) expressed in a specific genome (Masotti 2012).

It was also discovered that ageing-associated oxidative stress may cause morphologic alterations of bacterial cells, thus affecting the optimum potential and virulence capacity of an anaerobic bacterium and finally the manner of interaction with the host (Patrignani *et al*. 2014).

2.3.4 Implications for therapy

The evolving neurobiological model of IBS implies that similar treatment approaches might be used to treat both GI symptoms and affective symptoms. Friedrich *et al.* (2010), however, concluded that the benefits of antidepressant therapy in patients with IBS are limited.

Friedrich *et al.* (2010) suggested that the benefits of antidepressant therapy for IBS and comorbid depression is still in controversy. In particular, SSRI efficacy in the treatment of IBS-C has not been clarified (Friedrich *et al.* 2010). A literature review by Pae *et al.* (2007) on SSRIs effectiveness in IBS showed that SSRIs may promote well-being and assist in improvement in the QOL in

patients with IBS. It appears that this improvement may be independent of the improvement in anxiety or mood symptoms, although more evidence is needed in this area.

Marks *et al*. (2008) did a prospective study on 72 IBS diagnosed patients, administered paroxetine at flexible dosing (12.5-50mg/day) or placebo for 12 weeks. The study was however, too small to clarify the utility of SSRIs in IBS.

Unlike the situation with SSRI's, there is considerable clinical evidence for the efficacy of tricyclic antidepressants (TCAs) in IBS-D (Schoenfeld 2005). Confirmed by a placebo-controlled trial, TCAs are more effective than placebo in relieving GI symptoms and associated symptoms in IBD-D; but not IBS-C. These results are explained as reflecting the constipating effect of TCAs due to its anticholinergic effects (Schoenfeld 2005).

TCAs are, however, considered second-line agents, because of poor tolerability and much higher toxicity in overdose compared to SSRIs (Friedrich *et al*. 2010).

2.4 CONCLUSION

A growing body of evidence suggests that a common origin of IBS and depression/anxiety exists. This emerging understanding necessitates a rethinking of therapeutic strategies. The recognition that IBS and depression/anxiety could be inflammatory diseases ushers in a wealth of new possibilities for treating and preventing these co-morbidities (Littrell 2012).

CHAPTER 3

THERAPEUTIC STRATEGIES FOR IRRITABLE BOWEL SYNDROME AND PRESCRIBING MEDICATION FOR THE ELDERLY

In this chapter the general approach to current medical treatment of IBS is presented, followed by individual profiles of current IBS regimens. The chapter concludes with a contextualization of the treatment of IBS, depression and anxiety for actual prescribing of medication for the elderly.

3.1 PHARMACOLOGICAL APPROACH TO IRRITABLE BOWEL SYNDROME

Mertz (2003) recommended that the treatment of IBS should be based on whether constipation, diarrhoea or pain is the most dominant feature as well as the severity of symptoms. Pharmacotherapy, according to Mertz, is thus indicated for symptom relief in moderate cases, using antispasmodics, laxatives and low dose TCAs. In severe cases, the management shifts to 5HT agonists and antagonists together with psychotherapy, TCAs and sedatives.

By 2013, though, there was a growing understanding that the pathophysiology of IBS encompasses multiple factors, including events located in the brain-gut axis and neuro-immune connections (De Ponti 2013). De Ponti suggested that the target for intervention should be a complete pathophysiological system instead of only a specific receptor. The different pathophysiological target systems suggested are: secretion; motility; visceral sensitivity; neuro-immune interactions; inflammation; and the brain-gut axis.

De Ponti described the ideal drug for IBS treatment (De Ponti 2013) as a drug with continuous duration of action, good oral bio-availability and a half-life that allows once-daily dosing. The drug should also be free of serious adverse

risks and to minimize the risks of drug-drug, drug-food and drug-herbal interactions, cytochrome P450 substrates should be avoided.

3.2 CURRENT TREATMENT OPTIONS

The relationship between pathophysiology and treatment is a two-way process. While the understanding of the disease process is vital for developing treatment strategies, the response of a particular condition to various treatments may open new insights into the pathophysiology.

3.2.1 Drugs affecting motility and secretion

In the following paragraphs, drugs affecting motility and secretion will be discussed, including anticholinergic drugs, drugs acting on 5HT receptors and others.

3.2.1.1 *Anticholinergic drugs*

In a review study by Trinkley and Nahata (2011), dicyclomine has been found to improve overall IBS symptoms and abdominal pain. Anticholinergic drug use is, however, not recommended for the elderly (as they are at greater risk to develop confusion, dry mouth, constipation and other anticholinergic effects) as a result of reduced clearance (Nobili *et al*. 2011).

3.2.1.2 *Drugs acting on serotonin receptors*

Tegaserod (a 5HT4 agonist) was previously approved by the FDA for the treatment of IBS, but was removed from the market in 2007 due to its cardiovascular side effects. Effective therapy is necessary, but must be safe, given the low mortality of IBS (Wood 2012).

Prucalopride is a highly selective 5-HT4 agonist used for the treatment of IBS. The drug stimulates colon movement (Quigley 2012; De Ponti 2013) and is effective for chronic constipation (CC) (Corsetti & Tack 2014). It has a good safety profile, reported in extensive clinical and cardiovascular trials to date. Its efficacy and safety has also been proven in elderly patients with cardiovascular co-morbidity (Camilleri *et al.* 2009). Prucalopride is currently not registered in South Africa.

Ramosetron (5µg oral, once daily for 12 weeks) improved stool consistency in males with IBS-D, compared to placebo (Fukudo *et al.* 2014). Ramosetron is a selective 5-HT3 receptor antagonist in the afferent vagal nerve-endings in the GI mucosa and decreases motility. Ramosetron is currently not registered in South Africa.

3.2.1.3 *Other drugs affecting motility and secretion*

Linaclotide is effective in the treatment of both CC and IBS-C, however, should rather be avoided in the elderly (Corsetti & Tack 2014). This drug was classified as a guanylate cyclase-C agonist. It elevates cyclic guanosine monophosphate (cGMP) that causes increased production of intestinal chloride and bicarbonate. These changes stimulate peristalsis and shorten transit time. The drug is poorly absorbed and is generally without serious adverse effects. Application in vulnerable populations, such as the elderly should, however, be carefully considered as complications, such as diarrhoea and cardiovascular disease may have serious outcomes. Linaclotide is approved by both the European Medicines Agency (EMA) and the American

Food and Drug Administration (FDA) for IBS. Linaclotide has not yet been approved in South Africa.

Lubiprostone is a bicyclic fatty acid extracted from prostaglandin E1. It specifically activates chloride channel protein 2 (CIC-2) channels that occur on the apical aspect of GI epithelial cells. The drug increases the production of chloride-rich intestinal fluid resulting in enhanced peristalsis. Several clinical trials suggested that lubiprostone is generally safe and well-tolerated when used for up to a year in IBS-C patients (Mozaffari *et al*. 2014; Chey *et al*. 2012). Safety in the elderly still needs clarification. Lubiprostone is EMA and FDA approved for IBS, but not yet approved in South Africa.

3.2.2 Antidepressants

Antidepressants are effective in treating symptoms of IBS (Sainsbury & Ford 2011; Lacy *et al.* 2009). This probably occurs as a result of their antinociceptive properties, although additional effects on GI transit may also be advantageous. Whether any benefit is gained via the treatment of co-existent depression, remains unclear.

3.2.2.1 *Tricyclic antidepressants*

TCAs act on the central nervous system by inhibiting the re-uptake of both 5HT and NA. These drugs have strong anticholinergic effects that contribute largely to their side effect profiles. It also, however, underlies their usefulness in IBS, assisting in the relief of diarrhoea. Like other anticholinergic drugs, these drugs are, however, not recommended for use in the elderly, due to an increased risk for cardiotoxicity, delirium, acute glaucoma and urinary retention in this segment of the population (Nobili *et al*. 2011).

While a study by Sainsbury *et al*. (2011) could not show a correlation between an improvement in depression scores and improvement in IBS symptoms in patients on antidepressants, one should consider that the doses employed for the treatment of IBS are generally much lower than doses for treatment of depression. Nagari and Thomas (2014) recommended a starting amitriptylline dose of 10 mg daily with incremental increase over weeks to the maximum tolerated dose, no higher than 30 mg for the treatment of IBS. In contrast, the standard dosing regimen for amitriptylline for the treatment of depression is 75-100 mg per day (Arroll *et al.* 2005).

Thoua *et al*. (2009) demonstrated that amitriptyline reduces stress-induced electrical hypersensitivity, independent of autonomic tone. The authors proposed their method as a possible study model for further investigation of drug efficacy in IBS.

3.2.2.2 *Selective serotonin re-uptake inhibitors*

Controversy still exists regarding the benefit of SSRIs in the treatment of IBS symptoms (Friedrich *et al.* 2010). Fluoxetine is not only an antidepressant, but is also effectively used in the treatment of other mental disorders, such as *bulimia nervosa*, *anorexia nervosa*, certain anxiety disorders and obsessive-compulsive disorder (Perez-Caballero *et al.* 2014).

In accordance with the monoamine theory, fluoxetine exerts its therapeutic effect in depression by increasing the concentration of 5HT in the neuronal synaptic cleft through the inhibition of the re-uptake of 5HT. New neuro-imaging and neurochemical research, however, shows that fluoxetine also stimulates neurogenesis in cortical GABAergic interneurons and may thus aid in the recovery from the loss of neurons caused by depression (Ohira *et al*. 2013). This evidence supports the notion that depression is a degenerative process and may lead to the development of new antidepressants with new

mechanisms of action, improved efficacy and safety. Fluoxetine use for IBS, however, needs further evaluation (Ghaedi 2013).

Paroxetine was recommended as a key drug in the early treatment of IBS-D (Kato & Misawa 2005) and was found to be very effective in reducing abdominal pain and associated symptoms of IBS (Masand *et al*. 2002).

3.2.3 Drugs affecting the gut microbiota

One of the most exciting new developments in the treatment of IBS between 2005 and 2014 is the growing awareness of the role of the intestinal microbiota. This opened up the possibility of using probiotics and non-systemic antibiotics in IBS treatment (Cash 2014).

Many IBS patients present with a modified intestinal microbiota structure and some respond positively to treatments aimed at re-establishing a healthy microbiota (König & Brummer 2014).

Kosiewicz *et al.* (2011) proposed that certain commensal bacteria that display protective effects with regard to inflammation or auto-immune diseases can be used to prevent or treat such conditions. *Bifidobacterium, Bacteroides, Clostridium* and *Lactobacillus species* are suggested.

Probiotics have also been shown to have beneficial effects on neuro-inflammation and decreased 5HT metabolism as previously discussed in chapter 2 (Luo *et al*. 2014). This finding supports a potential role for probiotics in the treatment of CNS conditions.

More research is needed on the immune modulatory effects of probiotics and how it influences behaviour before this can be applied. Yet, probiotics may have a role to play in enhancing the action of psychotropic drugs. Bravo *et al.* (2011) provided further evidence in support of this idea when they proved that

Lactobacillus rhamnosus (*JB-1)* can alter GABAB1b mRNA expression in the brain with increases in cortical regions (cingulate and prelimbic) and associated reductions in expression in the hippocampus, amygdala, and *locus coeruleus*. Their study also showed that *L. rhamnosus* (*JB-1*) reduced GABAAα2 mRNA expression in the prefrontal cortex and amygdala, but increased GABAAα2 in the hippocampus. Their study concluded that *L. rhamnosus* (*JB-1*) reduced stress-induced corticosterone and anxiety- and depression-related behaviour.
This may, for instance, be exploited in using lower doses of psychotropic drugs, combined with probiotics without compromising efficacy, yet gaining in safety and reduced side effects.

Unresolved issues regarding the use of probiotics include the identification of the most effective strains. Currently, increasing evidence points to *Bifidobacterium infantis* 35624 being the strain of choice for IBS. *Bifidobacterium infantis* 35624 is particularly effective in decreasing GI inflammation. Only two randomized controlled trials however have confirmed its efficacy and safety in the treatment of IBS (Brenner & Chey 2009) so far.

A task team of the American College of Gastroenterology could not find proof of the efficacy of *Lactobacillus* either on its own or in probiotic combinations. More positive results were found for *Bifidobacterium* (Aragon *et al*. 2010). Many of the studies reviewed were, however, small in size, of short duration and had considerable shortcomings.

There are many issues regarding probiotics that still need to be settled in well designed clinical trials. These include: therapy duration; whether therapy should be administered as maintenance therapy or only during acute exacerbations; which IBS symptoms require treatment as well as cost-effectiveness.

Of particular concern is the issue of quality control of these products (Elliot & Teversham 2004). Recent legislative changes brought probiotics under the

control of the Medicines Control Council (Doms 2014) by categorizing them as category A drugs. Formulations containing concentrations of live probiotic species beyond a specified threshold concentration and marketed with specific therapeutic claims are now classified as schedule 1 medication and formulations containing concentrations below the threshold concentration and marketed with only general health claims, as schedule 0 (The Medicines and Related Substances Control Act No. 90 of 1997, as amended 2014: s22A(2)). Both these schedules can be acquired without a prescription. The major change is therefor in the level of control over manufacturing standards.

3.2.4 Antimicrobials

The antimicrobial rifaximin also has the potential to improve IBS symptoms (Cash 2014). Apart from its antibiotic effects, rifaximin increases the expression of the pregnane X receptor (PXR). This nuclear receptor regulates an important defence mechanism through increasing detoxification and clearance of toxins as well as enhancing intestinal barrier function (Mencarelli *et al*. 2010). The increased expression of PXR could benefit the treatment of IBS as low-grade inflammation in the gut mucosa in IBS is associated with deranged intestinal barrier function. (See chapter 2 on the effect of stress on small intestinal permeability in humans.)

Rifaximin is approved by the FDA for the treatment of IBS. Safety and tolerability during and after treatment was found comparable to placebo. Safety in the elderly has, however, not been confirmed (Schoenfeld *et al.* 2014). Rifaximin is not available in South Africa.

3.2.5 Anxiolytics

As stress is contributing largely to the development of IBS (Naeem *et al*. 2012), it is expected that anxiolytics could assist in the treatment and/or prevention of the disease.

The use of benzodiazepines (BZDs) in particular is, however, problematic in elderly patients (Brekke *et al*. 2008). Long-term use of BZDs in the elderly is associated with serious complications, such as decreased mobility and impaired execution of daily routines, such as bathing, dressing, toilet routine, eating and transportation. BZDs may also increase nociception. BZD drugs, especially short acting ones, increase the risk for fractures in elderly people (Petrov *et al*. 2014).

3.2.6 Other options

Hajhashemi *et al.* (2004) investigated the composition and anti-inflammatory properties of cumin extract, a herbal preparation used in traditional Iranian medicine. Analysis of the oil by gas chromatography mass spectrometry resulted in the identification of 20 compounds, the major ingredients being para-cymene and thymoquinone. Anti-inflammatory activity was confirmed in both a rat and a mouse model of inflammation.

Subsequently, 57 patients diagnosed with IBS (according to the ROME II diagnostic criteria) participated in a prospective trial (Agah *et al*. 2013). A questionnaire was used to record changes in GI symptoms 2 and 4 weeks after first cumin drop administration and 2 and 4 weeks after treatment discontinuation. The authors concluded that cumin can be effective in improving all IBS symptoms. Lack of a placebo control group in this study however weakens the evidence.

No other studies have yet been done to support the efficacy of cumin in the treatment of IBS. Considering its low cost and easy availability, cumin may have considerable economic benefits as treatment for IBS in developing countries.

3.2.7 Effectiveness of drug therapy for IBS

A study by Shah and Pimental (2014) evaluated the net value of drugs for treatment of IBS and found that most IBS treatments have a simultaneous opposing adverse effect on IBS that exceed the benefits. Lubiprostone caused diarrhoea in excess of placebo in 3.9% and linaclotide in 15.3% of cases. For IBS-D, alosetron and TCAs caused constipation among a respective group of 16.9% and 13.0%. Only rifaximin did not cause the adverse event oppossing the underlying motility complaint and the drug seems to have only benefits, no disadvantages.

3.3 CHALLENGES IN PRESCRIBING FOR IRRITABLE BOWEL SYNDROME IN THE ELDERLY

In the final part of this chapter, prescribing in the elderly will be discussed with particular emphasis on the challenges involved in the selection of medication for IBS.

3.3.1 Ageing population

From a global perspective, the section of the population above the age of 60 is expected to double from almost 11% in 2011 to 22% in 2050, an absolute increase from 800 million to 2 billion individuals (Bloom *et al.* 2011).

The ageing population is viewed as proof of successful implementation of public health policies and socio-economic development and is most likely the result of substantial advances in preventive medicine, medical and pharmacological research. This phenomenon, however, requires society to adapt, in order to accommodate declining functional capacity, specific social needs and increased security and health care requirements of the elderly.

3.3.2 Multiple diseases and polypharmacy in the elderly

Mental and physical diseases are the leading causes for the very old to lose their independent living (WHO n.d. b). The growing elderly population thus will force health care practitioners of the future to expand their focus on medical care, considering age-related changes, co-morbidities, polypharmacy, psychological and socio-economic factors, as well as the personal preferences of their clientele.

Polypharmacy is a concern amongst the elderly. Various studies found a considerable negative impact on the health of elderly persons as a result of a number of medications, to the extent that this needs to be further researched. Physicians need to evaluate each medication on every patient visit (Hajjar *et al*. 2007).

A change in approach is not only important to provide individualized elderly care, but also because of financial imperatives. The cost of polypharmacy and hospitalization for adverse effects could be decreased by a rational approach to the medical treatment of the elderly. Appropriate prescribing might improve QoL in various ways (Olsson *et al.* 2011), such as improved cognitive and behavioural function in dementia patients when anticholinergic or antispasmodic drugs are avoided in the treatment of IBS (McLeod *et al.* 1997).

3.3.3 Main age-related changes in organ systems particularly associated with prescribing medication for irritable bowel syndrome

The pharmacokinetics and pharmacodynamics of drugs change with ageing. Lack of compliance further increases the complexity of prescribing for the elderly (Nobili *et al*. 2011).

3.3.3.1 *Pharmacokinetic changes*

The ageing process is accompanied by major shifts in the relative contribution of body water, lean muscle mass and fat to the body composition. These changes have profound effects on drug distribution. In general, the elderly display reduced volume of distribution for water-soluble drugs, e.g. bentyl dicyclomine and increased volume of distribution of lipid-soluble drugs, e.g. BZDs (Mangoni & Jackson 2004). The altered body composition causes higher blood levels at normal doses for water-soluble drugs and prolonged duration of action of lipid-soluble drugs. Both water and lipid-soluble drugs may therefore require dose reduction or longer dose intervals.

Age-related GI function changes include reduced secretion of gastric acid and pepsin, resulting in reduced absorption of certain drugs, while GI motility and digestion remain relatively unchanged (Blechman *et al*.; Webster *et al.*; Husebye *et al*. as cited in Mangoni & Jackson 2004).

3.3.3.2 *Pharmacodynamic changes*

Elderly patients are more sensitive to the effects of CNS drugs (Feinberg, 1993). This is due to a general morphological regression in neurological structure and central vasculature. These changes lead to an over-expression of the effects of CNS drugs, including decreased mobility and the

experiencing of delirium. As previously referred to, anticholinergic drugs are known to bear a higher risk for causing confusion, delirium and postural hypotension in the elderly.

3.3.3.3 *Compliance*

Reduced adherence to drug therapies have also been associated with the elderly population (Gellad *et al*. 2011), because of more practical difficulties, such as impaired memory and being properly informed about their medication.

3.3.4 Psychotropic medication use in the elderly

Despite warnings from health associations worldwide about the risks of prescribing psychotropic drugs in the elderly, the use of these drugs remains high in the elderly, especially in the case of nursing home residents. Alessi-Severini *et al.* (2013) showed BZD use to be above 10% in both community and personal care homes. Possible reasons for the high use of psychotropic drugs in the elderly is the high prevalence of depression and anxiety that was found in elderly residents (see 2.2.2.1). Contributing factors may be decreased function, social isolation and adjustments necessary for the elderly to adapt to their social surroundings.

3.3.5 Antidepressants and benzodiazepines

A study done by Frank (2014) in a Canadian province suggested that the effectiveness of pharmacological treatment of depression is not substantially affected by age. SSRIs and other newer antidepressants including serotonin noradrenaline re-uptake inhibitors (SNRIs) are generally safe. The fact that these drugs are safe in cardiovascular conditions and has less anticholinergic

action than TCAs are particularly relevant to their use in elderly patients (Wiese 2011).

As previously referred to by Feinberg (1993), elderly people have an increased sensitivity to BZDs and the use thereof may lead to CNS effects ranging from subtle changes in mental state to over-sedation and delirium. The impairment of motor coordination causes an increased risk for falls and subsequent fractures.

3.3.6 Inappropriate prescribing for elderly patients

A study by Brekke *et al.* (2008) assessed prescription data for elderly patients (older than 70 years) for 12 months, retrieved from the Norwegian Prescription Database (n=85,836). Results showed that 18.4% of the patients received one or more inappropriate prescription items from their general practitioner during the one year period, measured in relation to 13 prescription standard indicators (defined items used to measure the quality of prescriptions). Long-acting BZDs (4.6%) were the most frequent inappropriate item on prescriptions. They also found that elderly patients often received prescriptions for drugs that were contra-indicated in their age group; or the incorrect dosage for their age, all of which can contribute largely to polypharmacy (Brekke *et al*. 2008).

Chetty and Gray (2004) performed a cross-sectional survey of chronic prescriptions issued to patients aged 65 years and older in a provincial government pharmacy providing services to PHC clinics and retirement villages in Durban, South Africa. 6410 prescriptions were reviewed and they found that 30% of this elderly population received at least one inappropriate medication as defined by the Beers criteria.

3.3.7 Exclusion from clinical research

The elderly are currently largely excluded from clinical trials, despite their obvious higher need for medication use. The European Forum for Good Clinical Practice Geriatric Medicines Working Party of 2013 stated that due to the change in demographics of the global population, pharmaceutical companies have a responsibility to provide sufficient evidence on the use of their products in patients above 65 years of age (Alvino 2014). Asahina *et al.* (2014) recommended that the inclusion of this population group should become a regulatory recommendation and an essential prerequisite for

regulatory affairs. Such harsh requirements may, however, have a detrimental effect on drug development as a whole.

3.4 CONCLUSION

Prescribing for elderly individuals is complex due to altered body composition, decreasing organ function and age-related pharmacodynamic changes. Increasing co-morbidities lead to more drugs being used, thus leading to the problem of polypharmacy in this age group (Brekke *et al*. 2008). As evidence for a common or at least overlapping origin for IBS, depression and anxiety emerges, a single treatment that addresses a common target may be a reality in future.

While it is clear that TCAs benefit those suffering from IBS, paroxetine will theoretically be a better option in the elderly, providing treatment that combines the safety of an SSRI and the efficacy of a TCA due to its strong anticholinergic properties.

In the next chapter we will describe the methodology used in this study.

CHAPTER 4

METHODOLOGY

4.1 INTRODUCTION

The study investigated the co-existence of IBS, depression and anxiety in a population of elderly residents of two retirement villages in Bloemfontein, the capital of the Free State province, South Africa. Drug use for GI conditions, depression and anxiety were recorded.

4.2 RESEARCH DESIGN

A cross sectional observational study design was employed.

4.3 PARTICIPANTS

All subjects were residents of two retirement villages in Bloemfontein, Free State province, South Africa. All participants were ambulant and able to give voluntary consent.

4.3.1 Selection of participants

4.3.1.1 Inclusion criteria

Residents at Striata and Ons Tuiste retirement villages above the age of 50, who were able to give informed consent and give answers to the specific questions asked by the researcher, were included in the research. Potential

participants were not excluded on the grounds of being on medication or not being on medication.

4.3.1.2 Exclusion criteria

Participants were excluded from the study according to the following criteria:

- Participants who used a wheelchair or who were confined to a bed for prolonged periods of time;
- Admission to the frail care unit;
- Positive history of colon cancer;
- Positive history of cancer of any other part of the GI system;
- Small or large bowel resection;
- Stomach resection;
- Resection of any other part of the GI system (excluding appendectomy); and
- Residents under the age of 50 years or above the age of 90.

4.3.2 Sample size

For a confidence level of 95% and a margin error of 5%, the calculated sample size was 200 for an estimated 20% prevalence of IBS. The total number of residents in Striata, excluding the frail care unit, was 253. The total number of residents in Ons Tuiste was 189. One hundred and seventy one residents from Striata and 29 residents from Ons Tuiste were recruited.

4.3.3 Sampling method

A list of names of all the residents was obtained from the managers of the two institutions and participants were selected on the basis of convenience sampling. The researcher went from door to door to recruit potential participants. A screening section (section A of the questionnaire) containing the exclusion criteria was first handed out. Willing residents were requested to continue with the completion of the questionnaire only if all inclusion and exclusion criteria were met.

4.4 MEASUREMENT

A questionnaire was used to record participants' medication use as well as current symptoms of IBS, other GI symptoms, depression and anxiety (Appendix A)

4.4.1 Questionnaire

The questionnaire was designed with sections on demographic information, medical history, depression, anxiety and GI symptoms and medication as well as supplement use. The section on GI symptoms incorporated the Manning criteria (Manning *et al*. 1978) as a diagnostic tool for IBS as well as the HADS (Zigmond & Snaith 1983) for the diagnosis of anxiety/depression.

4.4.1.1 *Measurement of gastrointestinal symptoms*

The definitive point for the diagnosis of IBS in this study, was the presence of abdominal distension; reduced pain by defecation; and frequent and/or looser stools at the onset of pain, as these four symptoms were found to be considerably more associated with IBS than organic disease. When mucus

and incomplete defecation are present as well, the patient is most likely to have IBS rather than an organic disease (Manning *et al*. 1978).

4.4.1.2 *Measurement of depression and anxiety*

Depression and anxiety symptoms were measured by means of a validated screening instrument, the HADS (Zigmond & Snaith 1983). Cut-off points for the diagnosis of depression and anxiety were put into place according to the instruction of the original authors. For the depression subscale a score of 7 or less indicates the absence of depression, scores of 8 to 10 indicate doubtful cases and scores of 11 or more indicate definite cases. For the anxiety subscale the same score ranges applied. Zigmond and Snaith (1983) recommended that the HADS should be supplemented by a brief interview in the case of the elderly. In this study, interviews were not deemed practical, due to time constraints and it was also regarded as outside the scope and aim of the study.

4.4.1.3 *Measurement of medication*

The questionnaire included lists of the most frequently used antidepressants, GI medications and anxiolytics compiled by the researcher, based on her experience in various pharmacies in South Africa over a period of 6 years in practice as a pharmacist. A list of supplements was also compiled that were suggested to assist in the management of depression and anxiety or insomnia. Participants were asked to indicate current use and duration of use. An additional subsection was added to the medication history section of the questionnaire to provide for medication that was not listed.

4.4.2 Validity and reliability of data

The questionnaire was tested by performing a pilot study. Six participants were selected from another retirement village for the pilot study. Apart from the institution where they were recruited, they were selected according to the criteria for the actual research population. The pilot study was done to assess the amount of time needed for filling in the questionnaire and clarity and comprehension of questions asked. The filling in of the questionnaire took approximately 30 minutes, at most one hour.

In order to prevent bias, the researcher read the questions and answers to choose from to the participant in a monotone voice. Questions and options were repeated on request of participants. The researcher verified the reported medication use by checking participants' medication boxes (at Striata) or medication charts (at Ons Tuiste).

4.5 ETHICAL ASPECTS

4.5.1 Informed consent

Informed consent was obtained from all individual participants according to the requirements of the Ethics Committee of the UFS Faculty of Health Sciences (Appendix B).

4.5.2 Permission

Permission was obtained from the management of the respective institutions (Appendix C).

Permission was obtained from GL-Assessment to use the HADS for diagnosis of depression and anxiety (appendix D) (Zigmond & Snaith 1983).

No permission is required to make use of the Manning criteria diagnostic algorithm for this study (Manning *et al*. 1978).

Both instruments were translated into Afrikaans to facilitate comprehension of questions by Afrikaans speaking participants.

4.5.3 Confidentiality

Questionnaires were marked by codes to protect the identity of the individual participants. Biases were minimized by anonymous participation.

4.6 PROTOCOL TRANSGRESSIONS AND ADAPTATIONS

The age restriction for participating in this study was initially set at 85 years. This limitation was changed as it was found that many potential participants above 85 fitted the rest of the criteria. Fifteen participants eventually fell into the group of 85+.

At Ons Tuiste the participants' prescriptions were checked instead of the medication boxes as medication was handed out by a professional nurse.

4.7 DATA ANALYSIS

All information gathered was coded on the questionnaire (Appendix A). Data typists of the UFS Information Technology Centre captured the data.

Results were summarized by frequencies and percentages (categorical variables) and mean, standard deviations or percentiles (numerical variables), summary of raw data (appendix E). Associations between categorical

variables were assessed using Chi-Square or Fisher's exact tests (in the case of small cell sizes). A p-value of <0.05 was considered statistically significant. SAS version 9.4 was used for all statistical processing. The results are reported in the next chapter.

CHAPTER 5

RESULTS

5.1 GENERAL DESCRIPTION OF POPULATION

The study population consisted of 200 participants recruited from two retirement villages in Bloemfontein, South Africa. One hundred and seventy one residents from Striata and 29 residents from Ons Tuiste were recruited. Fifty (25%) were male and 150 (75%) were female. One hundred and eighty four (92%) belonged to a medical scheme and 16 (8%) had no medical scheme cover.

Seven participants of Ons Tuiste (24.1%) did not belong to a medical scheme in comparison to 9 participants (5.3%) of Striata. Based on this observation, there is a difference in socio-economic circumstances of the two settings. The participants could however be seen as belonging to the same broad socio-economic group, i.e being able to afford residential care and both groups had easy access to medical care.

The level of independence in the two groups differed based on observations by the researcher including the level of to medication control. Ons Tuiste participants were accommodated in private rooms in a communal setting and were dependent on nursing personnel for medication administration, while Striata residents had separate houses and took responsibility for their own medication administration. This was however not seen as factors that would impact on the accuracy of the measurements.

The two groups were comparable with regard to age and sex distribution (mean age for Ons Tuiste: 76 years; range 52-85 years; mean age for Striata: 77 years; range 59-90 years).

Figure 1 shows the overall age distribution of the study population.

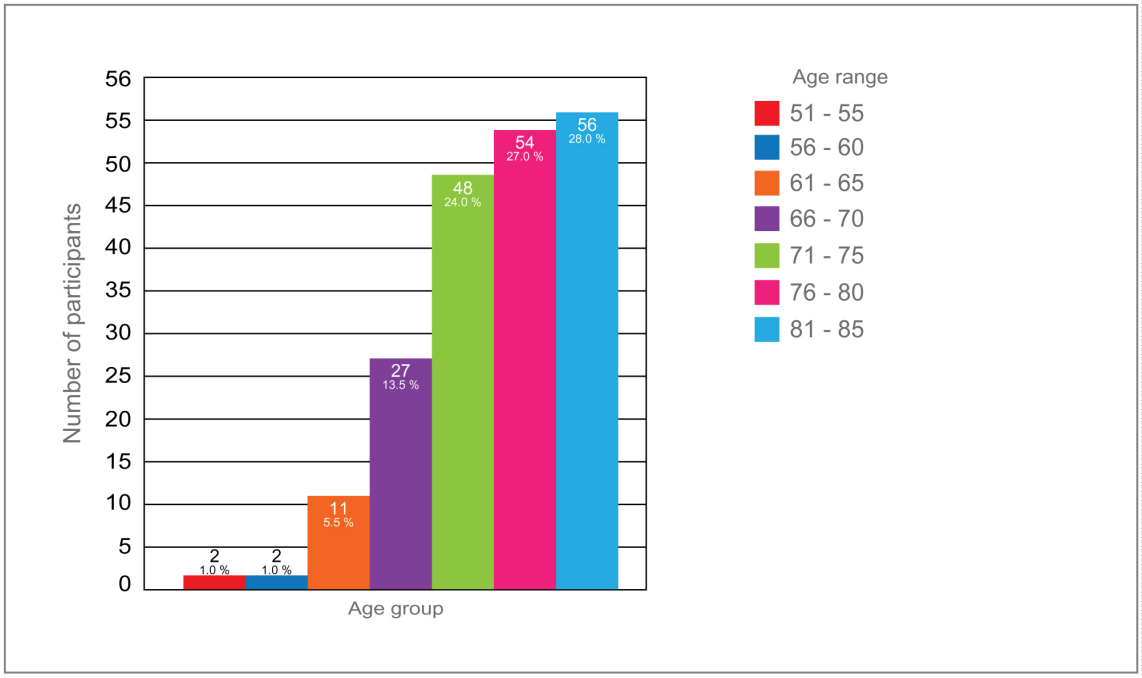


Figure 1: Age distribution of participants (n=200)

The majority of the study population were above the age of 70 years. The median age for the total population was 77 years (range: 52-90).

5.2 PREVALENCE OF IRRITABLE BOWEL SYNDROME, DEPRESSION AND ANXIETY

Table 1 shows the prevalence of symptoms for the diagnosis of IBS according to the Manning criteria and other GI symptoms, listed in descending frequency for all participants and stratified by gender.

Table 1: Current symptoms for the diagnosis of irritable bowel syndrome according to the Manning criteria and other gastrointestinal symptoms by gender

Symptom	Females (n=150) Number (%)	Males (n=50) Number (%)	Total (n=200) Number (%)
Manning Criteria			
A visible bloated belly	55 (36.7%)	12 (24.0%)	67 (33.5%)
Feeling of incomplete emptying	33 (22.0%)	6 (12.0%)	39 (19.5%)
Abdominal pain relieved by passing stools	20 (13.3%)	5 (10.0%)	25 (12.5%)
More frequent stools with onset of pain	14 (9.3%)	4 (8.0%)	18 (9.0%)
Looser stools with onset of pain	11 (7.3%)	3 (6.0%)	14 (7.0%)
Phlegm in stool	3 (2.0%)	4 (8.0%)	7 (3.5%)
IBS	6 (4.0%)	3 (6%)	9 (4.5%)
Other gastrointestinal symptoms			
Constipation	62 (41.3%)	15 (30.0%)	77 (38.5%)
Stools floated on water	8 (5.35%)	1 (2.0%)	9 (4.5%)
Blood mixed with stools	2 (1.3%)	3 (6.0%)	5 (2.5%)

IBS=Irritable bowel syndrome

A visible bloated belly was the most commonly experienced symptom in the current study population, occurring in a third of all the participants. A visible bloated belly and a feeling of incomplete emptying occurred more frequently in females.

Nine participants (4.5%) showed a positive diagnosis for IBS according to the questions listed in the Manning criteria. Four (2%) had IBS alone and five (2.5%) had IBS in association with constipation. IBS in association with constipation was therefore more common than IBS in the absence of constipation, but the numbers are very small.

More than a third of the participants reported chronic constipation with a slightly higher prevalence in females than in males. With regard to bowel habits, 69 (34.5%) of all the participants, had only constipation, six (3.0%) had only diarrhoea and 8 (4.0%) were experiencing alternating episodes of diarrhoea and constipation. The majority of cases with reported constipation therefore did not report alternating episodes of diarrhoea.

Table 2 shows the distribution according to a total score for depression and anxiety according to the HADS.

Table 2: Distribution of total depression and anxiety scores per category by gender

Score	Females (n=150) Number (%)	Males (n=49) Number (%)	Total (n=199*) Number (%)
HADS Depression			
0-7 (non-cases)	141 (94.0%)	46 (93.9%)	187 (94.0%)
8-10 (doubtful cases)	5 (3.3%)	1 (2.0%)	6 (3.0%)
≥ 11 (definite cases)	4 (2.7%)	2 (4.1%)	6 (3.0%)
HADS Anxiety			
0-7 (non-cases)	129 (86.0%)	46 (93.9%)	175 (88.0%)
8-10 (doubtful cases)	14 (9.3%)	1 (2.0%)	15 (7.5%)
≥ 11 (definite cases)	7 (4.7%)	2 (4.1%)	9 (4.5%)

HADS=Hospital Anxiety and Depression Scale
**One male participant did not complete the HADS*

By far the majority of the participants tested negative for depression and anxiety. The prevalence of depression in males was higher than that in females although the female group showed more doubtful cases. The numbers here are, however, small and the difference between the genders was therefore not significant (Fisher's exact test, p=0.86). Anxiety affected more individuals in the study population than depression. Similar to the prevalence for depression, anxiety also showed the trend of a higher prevalence in females.

Figure 2 shows the overlap in the occurrence of IBS, depression and anxiety based on the presence of symptoms measured by the Manning criteria and relevant HADS, respectively.

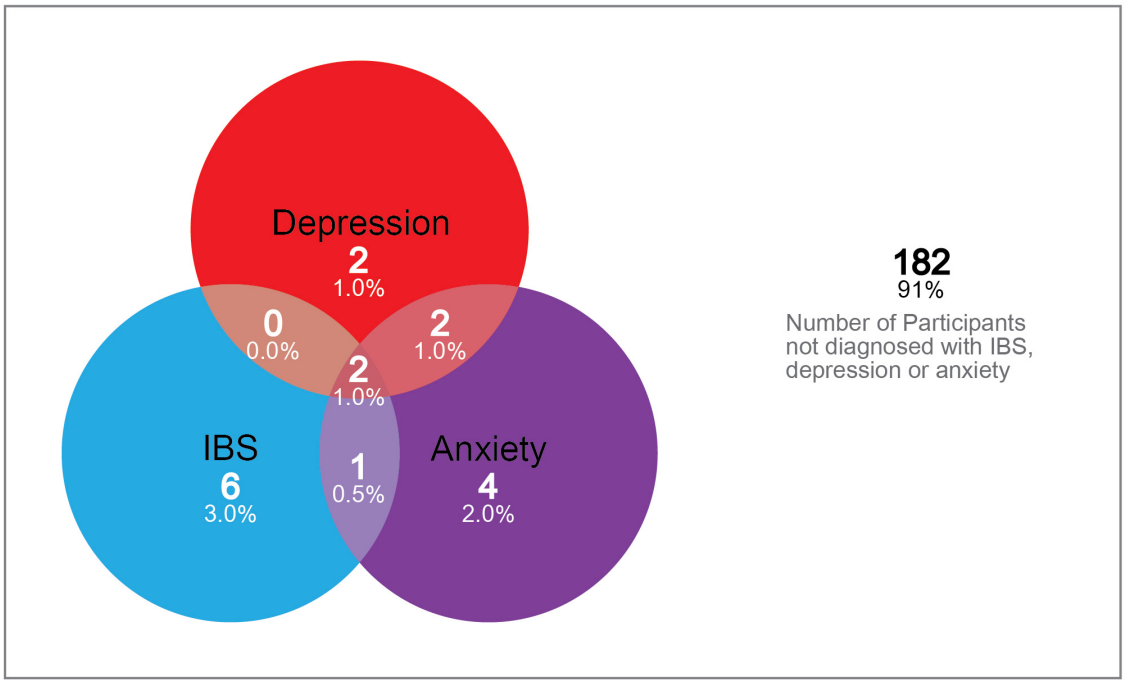


Figure 2: Co-occurrence of irritable bowel syndrome, depression and anxiety symptoms
IBS= Irritable bowel syndrome
**One male participant did not complete the HADS (n=199)*

More than half of the anxiety cases co-occurred with the other two conditions. Two thirds of the depression cases co-occurred with the other two conditions. More cases complying with enough of the Manning criteria to fulfill the diagnosis of IBS presented in isolation. IBS was only associated with depression when anxiety was also present. The numbers here are however very small and should be interpreted with caution.

Table 3 represents a summary of the positive responses to individual items pertaining to current depression symptoms according to the HADS.

Table 3: Depression symptoms currently experienced scored according to the Hospital Anxiety and Depression Scale (n=199*)

Score item	0 Number (%)	1 Number (%)	2 Number (%)	3 Number (%)
1. I don't enjoy still the things I used to enjoy	123 (61.8%)	52 (26.1%)	19 (9.6%)	5 (2.5%)
2. I can not laugh and see the funny side of things	181 (91.0%)	13 (6.5%)	3 (1.5%)	2 (1.0%)
3. I do not feel cheerful	148 (74.4%)	40 (20.1%)	6 (3.0%)	5 (2.5%)
4. I feel as if I have slowed down	28 (14.1%)	85 (42.7%)	44 (22.1%)	42 (21.1%)
5. I have lost interest in my appearance	159 (79.9%)	33 (16.6%)	4 (2.0%)	3 (1.5%)
6. I do not look forward to things with enjoyment	133 (66.8%)	49 (24.6%)	13 (6.5%)	4 (2.0%)
7. I can not enjoy a good book or radio or TV programmes	176 (88.4%)	18 (9.1%)	1 (0.5%)	4 (2.0%)

**One male participant did not complete the HADS*
0-3 scores represented the degree to which the participant experienced the specific feeling during the week before the participant had filled in the questionnaire. An answer of "0" represented the absence of the specific depressed feeling whereas a score of "3" represented the highest presence of the specific depressed feeling in the case of a specific participant.

The highest scores were seen in the case of item 4. In comparison, the other items scored considerably lower.

Table 4 shows a summary of the responses to individual items pertaining to anxiety symptoms at that time according to the HADS.

Table 4: Anxiety symptoms experienced at the time scored according to the Hospital Anxiety and Depression Scale (n=199*)

Score item	0 Number (%)	1 Number (%)	2 Number (%)	3 Number (%)
1. I feel tense or wound up	123 (61.8%)	61 (30.7%)	6 (3.0%)	9 (4.5%)
2. I sort of get a frightened feeling as if something awful is about to happen	155 (77.9%)	21 (10.6%)	15 (7.5%)	8 (4.0%)
3. Worrying thoughts go through my mind	126 (63.3%)	57 (28.6%)	5 (2.5%)	11 (5.5%)
4. I can not sit peacefully and feel relaxed	155 (77.9%)	24 (12.0%)	13 (6.5%)	7 (3.5%)
5. I get a sort of frightened feeling like "butterflies" in the stomach	155 (77.9%)	36 (18.1%)	6 (3.0%)	2 (1.0%)
6. I feel restless as if I have to be on the move	116 (58.1%)	36 (18.1%)	19 (9.6%)	28 (14.1%)
7. I get sudden feelings of panic	146 (73.4%)	42 (21.1%)	6 (3.0%)	5 (2.5%)

**One male participant did not complete the HADS*
0-3 scores represented the degree to which the participant experienced the specific feeling during the week that had passed before filling in the questionnaire. An answer of "0" represented the absence of the specific anxiety feeling whereas a score of "3" represented the highest presence of the specific anxiety feeling in the case of a specific participant.

The highest scores were recorded for item 6, indicating some degree of restlessness being present in a total of more than 40% of the population. This result is supported by the scores for item 4. A considerable portion showed a low level of tension (item 1) and worry (item 3).

5.3 MEDICATION USE

Figure 3 presents an overview of the reported medication use of the study population.

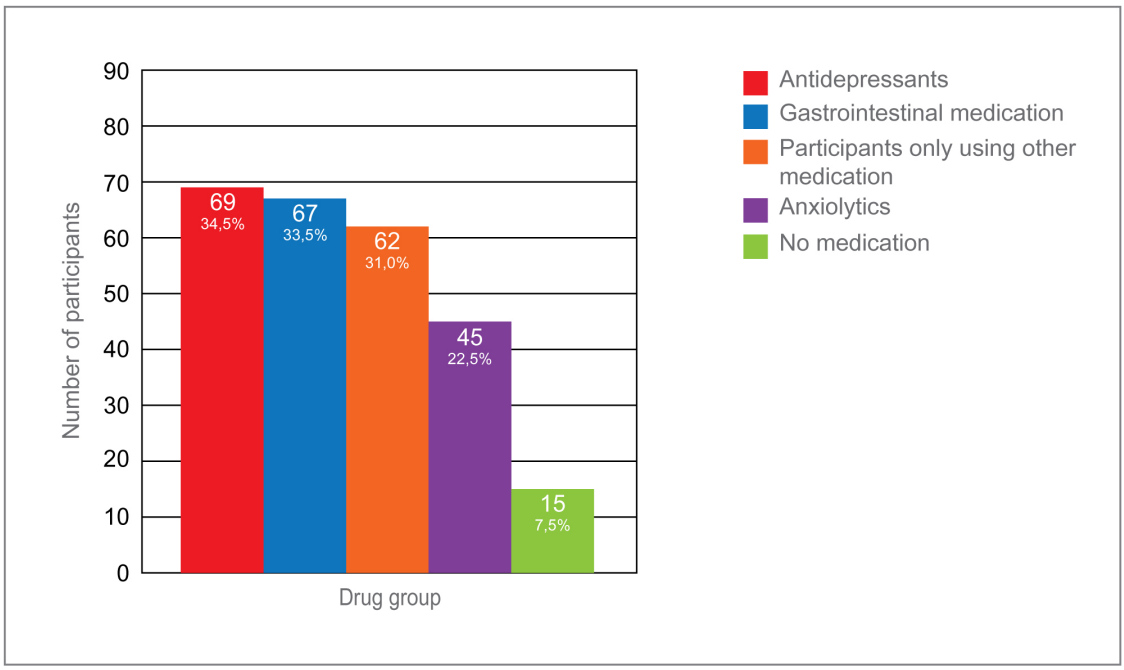


Figure 3: Overview of chronic medication use

According to figure 3, antidepressants were prescribed most often of the medication groups investigated followed by GI medication. A relatively small percentage of the population does not use medication (7.5%). Together with the 31% who use medication from other drug groups only, it means that more than 60% of participants were using one or more drugs from the three target groups of medication.

Figure 4 shows the distribution of medication use for the three target groups of medication, indicating both single use and co-prescription of GI medication, antidepressants and anxiolytics.

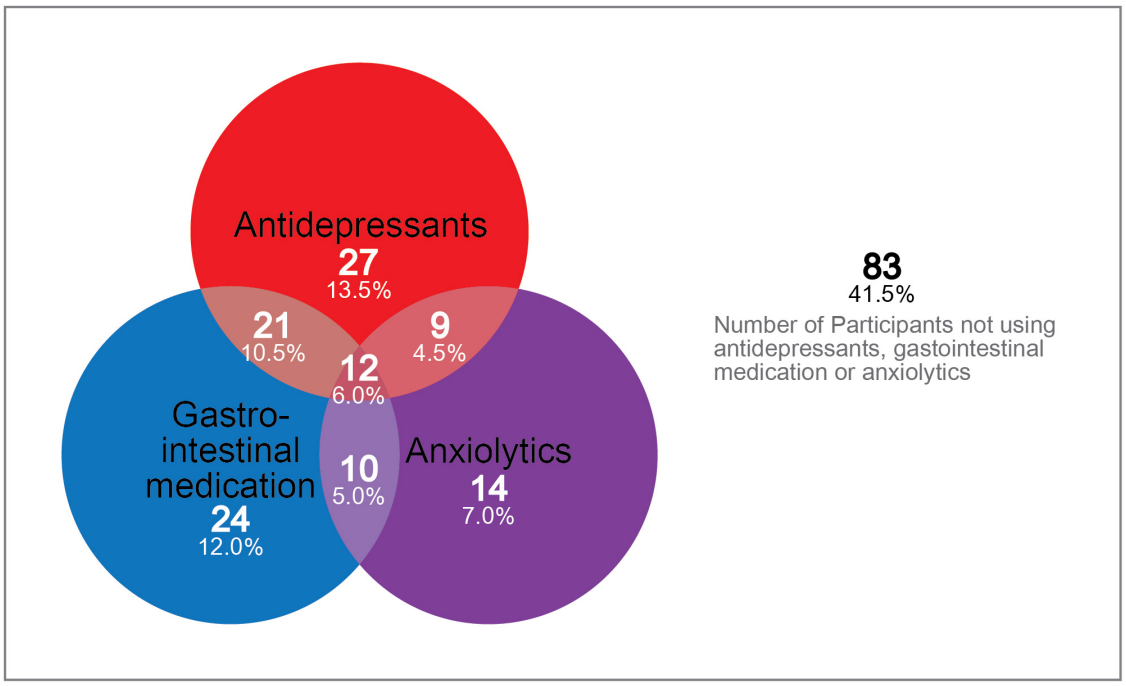


Figure 4: Co-prescription of gastrointestinal medication, antidepressants and anxiolytics

More than half the participants on antidepressants, anxiolytics or GI medication, also used medication from at least one of the other two groups.

Table 5 shows the frequency of GI medication, antidepressants and anxiolytics used by gender.

Table 5: Frequency of gastrointestinal medication, antidepressant and anxiolytic use by gender

Medication use	Females (n=150) Number (%)	Males (n=50) Number (%)	Total (n=200) Number (%)
Gastrointestinal medications			
PPIs	29 (19.3%)	6 (12.0%)	35 (17.5%)
Laxatives	13 (8.7%)	5 (10.0%)	18 (9.0%)
Other	20 (13.3%)	2 (4.0%)	22 (11.0%)
Anticholinergics	10 (6.7%)	1 (2.0%)	14 (7.0%)
Antidiarrhoeal medication	3 (2.0%)	0 (0.0%)	3 (1.5%)
Probiotics	5 (2.5%)	0 (0.0%)	5 (2.5%)
Antidepressants			
SSRIs	40 (26.7%)	4 (8.0%)	44 (22.0%)
TCAs	19 (12.7%)	4 (8.0%)	23 (11.5%)
Other	5 (3.3%)	2 (4.0%)	7 (3.5%)
Anxiolytics			
Benzodiazepines	35 (23.3%)	6 (12.0%)	41 (20.5%)
Other	2 (1.3%)	0 (0.0%)	2 (1.0%)

PPIs=Proton Pump Inhibitors; SSRIs=Selective Serotonin Re-uptake Inhibitors; TCAs=Tricyclic Antidepressants

Note that some participants used more than one type of GI medication, antidepressant and/or anxiolytic.

Anti-acid secretory drugs were used by 17.5% of participants. The most popular antidepressant group was the SSRIs comprising nearly 60% of all antidepressant prescriptions, followed by TCAs. Fluoxetine was the most commonly prescribed drug in the former group comprising almost half of the SSRI prescriptions. Virtually all anxiolytics reported were BZDs. Females were considerably more likely to use antidepressants (Chi^2 test, p=0.01) and anxiolytics (Chi^2 test, p=0.04) than men.

Supplements that are specifically indicated to assist in depression and anxiety treatment were taken in small percentages and a wide variety had been used with omega 3 supplement use the highest (22.5%), followed by magnesium (14.5%).

Table 6 shows the range and extent to which GI medication was used in the treatment of symptoms of IBS as well as other GI symptoms.

Table 6: Gastrointestinal medication use (n=200)

Group	Sub group	Number(%)
Antispasmodics	Anticholinergics	11 (5.5%)
Propulsives		3 (1.5%)
Antidiarrhoeal	Loperamide	3 (1.5%)
Probiotics		5 (2.5%)
Laxatives	Stimulant	5 (2.5%)
	Bulk-forming	2 (1.0%)
	Osmotic	11 (5.5%)
	Herbal preparations	6 (3.0%)
Anti-acid secretory drugs	Proton pump inhibitors	35 (17.5%)
	H2 receptor antagonists	2 (1.0%)
Other drugs for PUD[1] and/or GORD[2]	Alginic acid	6 (3.0%)
	Sucralfate	2 (1.0%)
Other		3 (1.5%)

PUD=Peptic ulcer disease; GORD=gastro-oesophageal reflux disease

PPIs were by far the most commonly used GI medication, followed by laxatives.

5.4 CONCURRENT SYMPTOMS AND MEDICATION USE

Table 7 shows the frequency of individual GI symptoms in participants with and without antidepressant use.

Table 7: Gastrointestinal symptoms and antidepressant use (n=200)

	On anti-depressants (n=69) Number (%)	Not on anti-depressants (n=131) Number (%)	p Value Chi^2
***A visible bloated belly**	34 (49.3%)	33 (25.2%)	0.0009
***Abdominal pain relieved by passing stools**	16 (23.2%)	9 (6.9%)	0.0009
***More frequent stools with onset of pain**	11 (15.9%)	8 (6.1%)	0.0397
***Looser stools with onset of pain**	9 (13.0%)	5 (3.8%)	0.0204 **
***Feeling of incomplete emptying**	20 (29.0%)	19 (14.5%)	0.0232
***Phlegm in stool**	4 (5.8%)	3 (2.3%)	0.2367 **
Constipation	26 (37.7%)	51 (38.9%)	0.8798
IBS according to Manning criteria	5 (7.2%)	4 (3.1%)	0.2798 **

**Symptoms that are listed in the Manning criteria **Fisher's exact test IBS = Irritable bowel syndrome*

Participants on antidepressants were significantly more likely to have individual symptoms associated with IBS than those not on antidepressants (Chi^2 and Fisher's exact test, p values ranged from 0.0009 to 0.0232). This may indicate that antidepressants in this population is not effective in the treatment of IBS, or that it worsen any presenting IBS symptom. Further research is needed to clarify this association. The exception was "phlegm in stool", which was not significantly higher in the antidepressant group (Fisher's exact test, p=0.2367). The prevalence of IBS according to the Manning criteria was not found significantly different between the group of participants that were using antidepressants and those that were not (Fisher's exact test, p=0.2798), but the numbers here are very small.

Table 8 shows PPI use and individual symptoms of IBS as well as the diagnosis of IBS

Table 8: Proton pump inhibitor use and individual symptoms of irritable bowel syndrome, constipation and a diagnosis of irritable bowel syndrome (n=200)

	On PPI (n=35) Number (%)	Not on PPI (n=165) Number (%)	p value Chi^2
***Visible bloated belly**	21 (60.0%)	46 (27.9%)	0.0003
***Abdominal pain relieved by passing stools**	9 (25.7%)	16 (9.7%)	0.0201**
***More frequent stools with onset of pain**	10 (28.6%)	9 (5.5%)	0.0002**
***Looser stools with onset of pain**	9 (25.7%)	5 (3.0%)	<0.0001**
***Feeling of incomplete emptying**	12 (34.3%)	27 (16.4%)	0.0151
***Phlegm in stool**	2 (5.7%)	5 (3.0%)	0.3540
Constipation	16 (45.7%)	61 (37.0%)	0.5597
IBS according to Manning criteria	7 (20.0%)	2 (1.2%)	0.0001**

*PPI = Proton pump inhibitor; IBS = Irritable bowel syndrome; * individual items listed as per Manning criteria*

***Fisher's exact test*

Five of the six items in the Manning criteria for IBS were found significantly higher in the group that were using PPIs (Chi^2 and Fisher's exact test, p values ranges from <0.0001 to 0.0201). The exception was phlegm in stool (Chi^2 test, p=0.3540). The occurrence of constipation between the two groups were also not significantly different (Chi^2 test, p=0.5597). More than half of the participants on PPIs experienced a visible bloated belly at the time of the study and this was significantly more than in participants not on PPIs (Chi^2 test, p=0.0003). Participants that used PPIs were also more likely to be diagnosed with IBS than participants not taking PPIs (Fisher's exact test, p=0.0001).

Table 9 shows the duration of use of PPIs in participants who reported the symptom of a visible bloated belly at the time of the study. These findings are based on reports by study participants and not on prescriptions or observational reports.

Table 9: Reported duration of proton pump inhibitor use in participants with a visible bloated belly(n=21)

Duration of proton pump inhibitor use	A visible bloated belly symptom (n=21) Number (%)
15 days to 6 months	2 (9.5%)
6 months to 1 year	3 (14.3%)
Longer than a year	16 (76.2%)

Three quarters of the participants on PPIs with a visible bloated belly had been using the PPI for longer than a year.

Table 10 shows SSRI use and individual IBS symptoms, constipation and a diagnosis of IBS at the time of the study.

Table 10: Selective serotonin re-uptake inhibitor use and individual irritable bowel syndrome symptoms, constipation and a diagnosis of irritable bowel syndrome

	On SSRI (n=41) Number (%)	Not on SSRI (n=159) Number (%)	p value Chi^2
***A visible bloated belly**	20 (48,8%)	47 (29.6%)	0.0201
***Abdominal pain relieved by passing stools**	13 (31.7%)	12 (7.5%)	<0.0001
***More frequent stools with onset of pain**	7 (17.1%)	12 (7.5%)	0.0757
***Looser stools with onset of pain**	7 (17.1%)	7 (4.4%)	0.0104
***Feeling of incomplete emptying**	12 (29.3%)	27 (17.0%)	0.0766
***Phlegm in stool**	4 (9.8%)	3 (1.9%)	0.0336 **
Constipation	17 (41.5%)	60 (37.7%)	0.6619
IBS according to Manning criteria	5 (12.2%)	4 (2.5%)	0.0191**

*SSRI=Selective Serotonin Re-uptake Inhibitor; IBS=Irritable bowel syndrome; * individual items listed as per Manning criteria. **Fisher's exact test*

Participants on SSRIs were significantly more likely to suffer from a visible bloated belly (Chi^2 test, p=0.0201), abdominal pain relieved by passing stools (Chi^2 test, p<0.0001), looser stools with onset of pain (Chi^2 test, 0.0104), phlegm in stool (Fisher's exact test, 0.0336) than those not on SSRIs. Almost

half of the participants on SSRIs were experiencing visible bloated bellies. Although the frequency of reported constipation was high in the group on SSRIs, it did not differ substantially from those not on SSRIs. The prevalence of IBS was higher in the group of participants that were using SSRIs. This may indicate that the type of SSRI taken by this population may worsen IBS symptoms, but the numbers here were very small.

Table 11 shows the frequency of individual symptoms of IBS, constipation and a diagnosis of IBS in participants on TCA therapy and those not using TCAs at the time of the study.

Table 11: Tricyclic antidepressant use and individual symptoms of irritable bowel syndrome, constipation and a diagnosis of irritable bowel syndrome (n=200)

	On TCA (n=24) Number (%)	Not on TCA (n=176) Number (%)	p value Chi^2
***A visible bloated belly**	12 (50.0%)	55 (31.3%)	0.0679
***Abdominal pain relieved by passing stools**	3 (12.5%)	22 (12.5%)	1.0000**
***More frequent stools with onset of pain**	3 (12.5%)	16 (9.1%)	0.7077**
***Looser stools with onset of pain**	4 (16.7)	10 (5.7%)	0.0701**
***Feeling of incomplete emptying**	8 (33.3%)	31 (17.6%)	0.0956**
***Phlegm in stool**	1 (4.2%)	6 (3.4%)	0.5973*|*
Constipation	5 (20.8%)	72 (40.9%)	0.0580
IBS according to Manning criteria	1 (4.2%)	8 (4.5%)	1.0000**

*TCA=Tricyclic Antidepressant; IBS=Irritable bowel syndrome; *individual items listed as per Manning criteria*

***Fisher's exact test*

Half of the participants on TCAs were experiencing a visible bloated belly and about a quarter of the participants on TCAs experienced constipation. The prevalence of IBS diagnosis in the group on TCAs, however, did not differ significantly from the group not on TCAs (Fisher's exact test, p=1.0000). Neither were there significant differences in the occurrence of individual IBS symptoms or constipation between the two groups (Chi^2 and Fisher's exact test, p values ranges from 0.0580 and 1.0000).

Table 12 gives a closer look at the duration of self reported antidepressant and/or anxiolytic therapy.

Table 12: Duration of self-reported antidepressant and anxiolytic use

	Duration	Number (%)
Antidepressants (n=73)	Less than 1 year	10 (13.7%)
	1 year and longer	63 (86.3%)
Anxiolytics (n=44)	Less than 1 year	11 (25.0%)
	1 year and longer	33 (75.0%)

This measurement was not based on written data. The majority of the participants on antidepressant therapy were already on antidepressants for longer than a year. The same applied to those on anxiolytics. Please note that the figures for this table were based on the self reported use and not the verified use of medication as reflected in other tables and figures.

Table 13 shows the frequency of use of various types of antidepressants and anxiolytics.

Table 13: Types of antidepressants and anxiolytics used (n=200)

Drug group or name	Females (n=150) Number (%)	Males (n=50) Number (%)	Total Number(%)
Antidepressants			
Fluoxetine	15 (10.0%)	1 (2.0%)	16 (8.0%)
Other SSRIs	24 (16.0%)	3 (6.0%)	27 (12.5%)
Amitriptyline	17 (11.3%)	4 (8.0%)	21 (10.5%)
Other TCAs	2 (1.3%)	1 (2.0%)	3 (1.5%)
Other antidepressants	5 (3.3%)	2 (4.0%)	9 (4.5%)
Anxiolytics			
Benzodiazepines	35 (23.3%)	6 (12.0%)	41 (20.5%)
Other	2 (1.3%)	0 (0.0%)	2 (1%)

SSRI=Selective Serotonin Re-uptake Inhibitors, TCA=Tricyclic Antidepressant

SSRIs were the most commonly prescribed group of antidepressants in the study population, comprising nearly 60% of antidepressant prescriptions. Fluoxetine was the most commonly prescribed drug in this group. TCAs were

used in more than 30% of participants on antidepressants, amitriptyline being used in the majority of such cases. Note that some participants used more than one type of antidepressant and/or anxiolytic.

Table 14 shows BZD use and individual symptoms of IBS, constipation and a diagnosis of IBS at the time of the study.

Table 14: Benzodiazepine use and individual symptoms of irritable bowel syndrome, constipation and a diagnosis of irritable bowel syndrome

	On BDZ (n=41) Number (%)	Not on BDZ (n=159) Number (%)	p value Chi^2
*** A visible bloated belly**	18 (43.9%)	49 (30.8%)	0.1135
***Abdominal pain relieved by passing stools**	7 (17.1%)	18 (11.3%)	0.3207
***More frequent stools with onset of pain**	3 (7.3%)	16 (10.1%)	0.7694 **
***Looser stools with onset of pain**	2 (4.9%)	12 (7.5%)	0.7391 **
***Feeling of incomplete emptying**	16 (39.0%)	23 (14.5%)	0.0004
***Phlegm in stool**	1 (2.4%)	6 (3.8)	1.0000**
Constipation	17 (41.5%)	60 (37.7%)	0.6619
IBS according to Manning criteria	1 (2.4%)	8 (5.0%)	0.6890**

*BDZ = benzodiazepine; IBS = Irritable bowel syndrome; * individual items listed as per Manning criteria*

*** Fisher's exact test*

Almost half of the participants on BDZs were experiencing a visible bloated belly, but the difference between those on BZDs and those not on BZDs was not significant (Chi^2 test, p=0.1135). Constipation prevalence was almost the same in both groups. A diagnosis of IBS was double in the group that was not using BZDs, but with small numbers involved, the p values here were not significant. The difference in the prevalence of individual items of IBS according to the Manning criteria was not significant in the two groups (Chi^2 and Fisher's exact test), p values ranges from 0.1135 to 1.0000) with the item "feeling of incomplete emptying" as the exception (Chi^2 test, p=0.0004).

Table 15 shows the symptoms of IBS, depression and anxiety in participants on GI, antidepressant and anxiolytics treatment.

Table 15: Medication use in participants with symptoms of irritable bowel syndrome, depression and anxiety

Medication used	IBS (n=9) Number (%)	Depression (n=6) Number (%)	Anxiety (n=9) Number (%)
Gastrointestinal medication			
Probiotics	0 (0.0%)	0 (0.0%)	1 (11.1%)
Antidiarrhoeals	0 (0.0%)	0 (0.0%)	1 (11.1%)
Laxatives	1 (11.1%)	0 (0.0%)	1 (11.1%)
Anti acid secretory	7 (77.8%)	4 (66.7%)	5 (55.6%)
No gastrointestinal medication	1 (11.1%)	2 (33.3%)	1 (11.1%)
Total	**9 (100.0%)**	**6 (100.0%)**	**9 (100.0%)**
Antidepressants			
Fluoxetine	2 (22.2%)	0 (0.0%)	1 (11.1%)
Other SSRI	3 (33.3%)	3 (50.0%)	3 (33.3%)
Amitriptyline	1 (11.1%)	1 (16.7%)	1 (11.1%)
Other TCA	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	0 (0.0%)	0 (0.0%)	0 (0.0%)
No antidepressant	3 (33.3%)	2 (33.3%)	4 (44.4%)
Total	**9 (100.0%)**	**6 (100.0%)**	**9 (100.0%)**
Anxiolytics			
Benzodiazepine	1 (11.1%)	3 (50.0%)	2 (22.2%)
None	8 (88.9%)	3 (50.0%)	7 (77.8%)
Total	**9 (100.0%)**	**6 (100.0%)**	**9 (100.0%)**

SSRI=Selective Serotonin Re-uptake Inhibitor; TCA=Tricyclic Antidepressant; IBS=Irritable bowel syndrome;

The majority of the participants with a positive diagnosis of IBS was on antidepressants and was most likely to use an SSRI. Anti acid secretory drugs were prescribed in the majority of participants with symptoms of all three conditions at the time of the study, while the use of other GI medications was negligible. Only one participant with IBS was not on medication, two participants with symptoms of depression were not on treatment, while the majority of participants with anxiety were on antidepressants and not on anxiolytics. Three of the individuals with depression were receiving BZDs. Half of the individuals diagnosed with depression were receiving BZDs.

Table 16 shows the reported perceived effectiveness of medication.

Table 16: Reported perceived effectiveness of medication

	No response Number (%)	Partial response Number (%)	Satisfactory response Number (%)
Gastrointestinal medication (n=59)	9 (15.5%)	6 (10.2%)	44 (74.6%)
Antidepressants (n=64)	4 (6.3%)	8 (12.5%)	52 (81.3%)
Anxiolytics (n=35)	1 (2.8%)	6 (17.1%)	28 (80.0%)

GI medication was the greatest concern with regards to effectiveness with fewer reports of satisfactory responses.

Table 17 shows the participants' responses with regard to their compliance with prescriptions.

Table 17: Self-reported compliance with prescription

	Compliant Number (%)	Non-compliant Number (%)
Gastrointestinal medication (n=59)	42 (71.2%)	17 (28.8%)
Antidepressants(n=64)	60 (93.8%)	4 (6.2%)
Anxiolytics(n=45)	25 (55.6%)	20 (44.4%)

Compliance with antidepressant prescriptions were the highest. The lowest compliance rates were seen with anxiolytics. "When necessary" dosing was not taken into account, which might have been common with anxiolytics.

5.5 SUMMARY OF KEY RESULTS

- The prevalence of IBS (see Table 1), depression and anxiety (see Table 2) were found to be 4.5%, 3.0% and 4.5% respectively.

- PPIs were the most commonly prescribed GI medication (see Table 6). Nearly half of the participants on GI medication were using PPIs.

- SSRIs were the most commonly prescribed group of antidepressants, comprising nearly 60% (see Table 5) of antidepressant prescriptions. Fluoxetine was the most commonly prescribed drug in this group (see Table 13).

- TCAs were used in more than 30% of the participants on antidepressants; amitriptyline being used in the majority of such cases.

- Almost all anxiolytic use recorded were BZDs (91.1%) (see Table 5)

- Individual items listed on the Manning criteria were more common in individuals on antidepressants than those not on antidepressants (p values ranging from 0.0009 to 0.0232 for 5 of the 6 items) (see Table 7).

- A visible bloated belly was particularly reported by significantly more participants on antidepressants (p=0.0009) (see Table 7) and those on PPIs (p=0.0003) (see Table 8), than by participants not using these medications.

- The majority of participants on antidepressants (86.3%), anxiolytics (75.0%) and PPIs (76.2%) were taking these for one year or longer (see Table 12 and 9).

5.6 CONCLUSION

The study did not confirm a high prevalence of current IBS, depression or anxiety of co-occurrence of the different diagnosis in this highly medicated population. Of concern, however, is the high use of antidepressants over extended periods of time. PPIs were likewise very commonly used and associated in this population with a high prevalence of bloatedness and other individual symptoms of IBS.

Results of the study will be discussed and practical recommendations will be proposed in Chapter 6.

CHAPTER 6

DISCUSSION AND RECOMMENDATIONS

This chapter commences with a discussion of the major results of the study, followed by the limitations. The chapter concludes with recommendations for practice and future research.

6.1 DISCUSSION OF KEY RESULTS

The results of this study showed a relatively low prevalence of IBS, depression and anxiety, but in more than half of the cases diagnosed with each of these conditions, comorbidity of at least one of the other conditions occurred. At the same time the results revealed high levels of medication use in the study population, especially with regard to antidepressants, anxiolytics and PPIs. The study also revealed significant differences with regard to the occurrence of individual items listed in the Manning criteria in groups on antidepressants and PPIs and those not using these medications.

6.1.1 Prevalence of irritable bowel syndrome, depression, anxiety and co-morbidity

The prevalence of IBS and anxiety in this study was lower than the global prevalence (Canavan *et al.* 2014), whereas the prevalence of depression was found to be similar to the results of a study in the general South African population (Herman *et al*. 2009).

6.1.1.1 Prevalence of irritable bowel syndrome

Canavan *et al.* (2014) concluded that IBS represents a considerable health care burden, irrespective of setting or geography, affecting around 11% of the population globally. The results of this study showed a lower than expected prevalence of IBS (see Table 1) of 4.5%. This is much lower than the 11.5% reported by Chang *et al*. (2010) in a Chinese community and the 33% reported by Ladep *et al.* (2007) in Nigerian outpatients. The higher prevalence of IBS found in these studies could be explained by a difference in the measuring instrument employed, which emphasizes the need for uniformity in measuring instruments. However, none of the studies mentioned reported on the existing medication use of their respective populations. The most likely explanation for the lower prevalence in the current study is the high prevalence of antidepressant, anxiolytic and GI medication use in the study population.

It is also plausible that the low prevalence of IBS found in this study may reflect the relative advantaged socio-economic circumstances of the participants. In support of this argument, Qumseya *et al.* (2014) reported a prevalence of IBS of 30% (28-33%) in a study population of 1352 Palestinians of 50 years and older. This particular study found a higher prevalence of IBS in refugee camps (34%) and in villages (34%) compared to urban centres (27%) ($p<0.05$).

6.1.1.2 Prevalence of depression

The prevalence of depression based on measurement of current symptoms in our population by the HADS was found to be 3% (see Table 2). This prevalence is comparable to the finding of Peltzer and Phaswana-Mafuja (2013) who reported a prevalence of depression in the elderly population of South Africa of 4%. Peltzer and Phaswana-Mafuya (2013) conducted a national population-based cross-sectional study in 2008 with 3,840 participants aged 50 years and above using the International Classification of Disease, 10th revision, Diagnostic Criteria for Research (ICD-10-DCR). Besides including a similar age group, this survey included participants on medication as was done in the current study. Their results also showed that self-reported depression symptoms in the 12 months prior to the survey, were associated with functional disability, lack of QOL and chronic conditions including angina, asthma, arthritis and nocturnal sleeping problems.

In the current study, the highest scores on the HADS for depression were seen with the item "I feel as if I have slowed down" (see Table 3). One might argue that this particular item is natural to the ageing process and might actually contribute to an "over-diagnosis" of depression.

6.1.1.3 Prevalence of anxiety

The current study found a prevalence of anxiety of 4.5% in the study population (see Table 2). The South African survey by Peltzer and Phaswana-Mafuya (2013) did not include anxiety prevalence in the elderly. Due to lack of data on the prevalence of anxiety in the elderly populations of South Africa, it is not possible to make direct comparisons. The prevalence of anxiety in the current study was, however, lower than the global prevalence of anxiety in the general population (7.3%) reported by Baxter *et al.* (2013) and also lower than the prevalence of anxiety in the general South African population (8.1%) reported by Herman *et al.* (2009). Forlani *et al*. (2014)

reported a much higher prevalence of anxiety in an elderly population in Northern Italy (21%). In their study, 366 adults older than 74 years, were evaluated by means of the Cambridge Mental Disorders of the Elderly Examination-Revised version (CAMDEX-R) test. The higher age group of their study population and the fact that a different measuring instrument was used, could be possible explanations for the much higher prevalence of anxiety found in the Italian study (see paragraph 2.3.4).

The highest scores for anxiety were seen for the item "I feel restless as if I have to be on the move" (see Table 4). This restlessness may indicate the presence of anxiety, but can also be interpreted as akathisia, a known side effect of many psychotropic drugs, including fluoxetine (Leo 1996). Modulation of striatal dopamine by SSRIs form a basis for this side effect, especially in the elderly (Baldessarini & Marsh 1990).

The most probable reason for the low prevalence of IBS, depression and anxiety in our study population was the high percentage of participants on GI medication (33.5%), antidepressants (34.5%) and anxiolytics (22.5%) (See Figure 3). Based on the analysis of symptoms in the presence or absence of target medication use, the symptoms measured might also reflect the result of medication use, rather than the primary diagnosis.

6.1.1.4 Prevalence of individual gastrointestinal symptoms of irritable bowel syndrome and constipation

Although the prevalence of IBS diagnosis was low, the prevalence of individual symptoms included in the diagnosis of IBS according to the Manning criteria were much higher (see Table 1) with the prevalence of these symptoms ranging from 3.5% to 33.5%. The prevalence of constipation was also high in this study population (38.5%).

6.1.1.4.1 Visible bloated belly

"Visible bloated belly" was found to be the most common individual symptom listed on the Manning criteria among the study population and occurred in 67 (33.5%) of the participants (see Table 2).

This symptom was slightly more common in female patients in this study compared to males, but the difference was not significant (p=0.1003). This is similar to the reports of a review study by Chang and Heitkemper (2002) that suggested females to be more sensitive for IBS than males. reported that the variation in sex hormones in women may aggrevate IBS in women during periods of lower estrogen and progesterone levels whereas men do not experience increased IBS symptoms during certain periods such as during menses in women. A review study by Sullivan (2012) found that in surveys of healthy individuals and populations, 10–30% experienced bloating often, or for extended periods of time.

6.1.1.4.2 High prevalence of constipation

The current study shows a prevalence of chronic constipation of 38.5% in the study population (see Table 2). Chronic constipation is not listed in the Manning criteria, but is a prominent feature of and distinguishing factor between the different types of IBS (Morley 2007). It is, however, also a common condition among elderly persons and the prevalence found in the current study is in line with the prevalence of constipation found by Talley *et al.* (1996) of 40.1% in an elderly population. Self-reported constipation was also found to be 30.7% in the age group 51 to 65 years in a population survey in Spain by Garrigues *et al.* 2004). The latter also found that the prevalence of constipation in the elderly did not differ significantly from that found in age groups 18 to 30 years and 31 to 50 years (29.2% in both). The high prevalence of constipation in participants in this study can not be due to the

use of TCAs as the prevalence of constipation was found to be lower in participants on TCAs (See Table 11).

6.1.1.5 The prevalence of individual symptoms included in the diagnosis of irritable bowel syndrome and constipation in participants on various types of medication

Five of the 6 symptoms listed as Manning criteria occurred significantly more in participants on antidepressants than in those not taking antidepressants (see Table 7). The symptoms that were found to be significantly higher in participants that were on antidepressant therapy include: a visible bloated belly (p=0.0009), abdominal pain relieved by passing stools (p=0.0009), more frequent stools with onset of pain (p=0.0397), looser stools with onset of pain (p=0.0204) and feeling of incomplete emptying (p=0.0232). These differences occurred irrespective of the group of antidepressants used (see Table 7). These differences might indicate that symptoms of IBS occur with the diagnosis of depression; or reflect a secondary effect of the medication itself. The fact that symptoms occurred irrespective of being on an antidepressant, could be indicative of a lack of efficacy of the prescribed antidepressants in this population.

The high overall prevalence of a visible bloated belly in the current study might be due to the high use of PPIs (see Table 3) (17.5%) as this symptom occurred in 60% (see Table 8) of participants on PPIs compared to 27.9% (see Table 8) of participants not on PPIs. This difference was statistically significant (p=0.0003). In 76.2% (see Table 9) of the participants that were using PPIs and were reporting a visible bloated belly, the duration of use of PPIs was reported as being longer than a year.

A possible explanation for this finding can be found in a study by Reddymasu *et al.* (2010). These authors found that a high percentage (36.0%) of IBS patients who had bloating and flatulence predominantly also had a positive diagnosis of small intestinal bacterial overgrowth (SIBO). They also found that older age and the female sex seemed to be predicting factors for SIBO. Spiegel *et al.* (2008) also speculated about a possible link between SIBO and IBS through PPI use, the latter enhancing various forms of SIBO by eliminating gastric acid (see 3.2.1.5).

Given the fact that diarrhoea, together with other serotonergic side effects, is associated with some SSRIs, including fluoxetine (Beasley *et al.* 2000), and constipation is a common side effect of TCAs (Wiese 2011), the expectation was that a lower prevalence of constipation would be seen in participants on SSRIs and a higher prevalence of constipation in participants on TCAs. SSRIs did however, not make a difference in the prevalence of constipation (see Table 10), however, four of the individual items listed according to the Manning criteria for IBS were found significantly higher in the group on SSRIs (p values ranges from 0.0001 to 0.0336). These results could be explained by the functions of 5HT receptors responsible to enhance peristalsis (including 5-HT_{1p} and 5-$HT_{4)}$. It was found that the expression of serotonin transporter (SERT) is decreased in the bowel in inflammation and IBS therefor SSRIs could induce excessive 5HT function in the gut of IBS patients (Mayer *et al.* 2001).

The researcher's study also found a lower prevalence of constipation in participants on TCAs compared to those participants not on TCA treatment (see Table 11). This finding might be related to lower dosages used in the elderly, but may also indicate that constipation might be improved at these presumably lower doses. As this study did not record dosages, this explanation needs to be further investigated. There was no difference in the prevalence of individual IBS items between the two groups.

6.1.2 Medication use

The high use of antidepressants and anxiolytics and the broader group of GI medication contributed largely to the medication use in this study population (see Figure 3). The majority of the participants on antidepressants were using their antidepressants for longer than a year. The same was true for anxiolytics (see Table 12). It was not recorded in this study whether such use was controlled and motivated by a physician, or prescribed *ad lib* to the patient who then decided themselves how often they used it and for how long. Given the high scheduling of these central nervous system drugs, it is assumed that the former conditions apply.

With regard to effectiveness of medication, GI medication was regarded as less effective by the participants (see Table 16) while compliance with antidepressant therapy was the highest (see Table 17).

6.1.2.1 Antidepressant and anxiolytic use

The results of the researcher's study showed a high prevalence of antidepressant (34.5%) and anxiolytic use (22.5%) (see Figure 3). SSRI use was found by far the highest (22.0%) among the antidepressants (see Table 5). TCAs were also widely used, amitriptyline being by far the most commonly prescribed in this group (see Table 13).

Antidepressant use in the study population was much higher and anxiolytic use much lower compared to a study by Craig *et al.* (2003) that found antidepressant use of 12.0% and anxiolytic use of 33% in various elderly populations (> 65 years). Similar to the study by Craig *et al.* (2003) the current study also found antidepressant use to be significantly higher in females than in males ($p<0.05$) (see Table 13).

6.1.2.1.1 Selective serotonin re-uptake inhibitors and irritable bowel syndrome symptoms

The researcher's study found that a diagnosis of IBS was significantly more common in participants on SSRI treatment than in those not on SSRIs (Fisher's exact test, $p= 0.0191$) (see Table 10). This may suggest that SSRIs are not effective for IBS or that it worsens IBS. The numbers are however too small to draw a conclusion. Nevertheless, the finding may be in line with the findings of Mayer *et al*. (2001) who provided evidence that the expression of the serotonin transporter (SERT) is decreased in the bowel in the presence of inflammation and IBS. SSRIs may therefor be expected to be less efffective on at least GI symptoms in the presence of inflammation.

Vahedi *et al.* (2005) found that low dose fluoxetine was significantly more effective in IBS-C and had prolonged effect. It is possible that although SSRIs

are effective for the treatment of depression, at the same time are causing or maintaining GI symptoms consistent of IBS-D (Shah & Pimentel 2014) (see 3.2.1.5).

Fluoxetine is not routinely recommended in the elderly, because of its long half-life and prolonged side effects. Paroxetine is also not recommended in the elderly as its anticholinergic effects are the greatest of all the SSRIs. SSRIs recommended for use in the elderly due to their safety profile are citalopram, escitalopram and sertraline (Baldwin as cited in Wiese 2011). These drugs have, however, not been tested with regard to efficacy in the treatment of IBS. SSRIs nevertheless are generally preferred above TCAs.

6.1.2.1.2 Tricyclic antidepressants and irritable bowel syndrome symptoms

TCAs were used in more than 30% (see Table 13) of participants on antidepressants in the researcher's study, amitriptyline being used in 70% (see Table 15) of such cases. There was not a statistically significant difference in IBS diagnosis and individual IBS symptoms in participants on TCA treatment than in those not on TCAs although some individual IBS symptoms appeared to be slightly higher in the group of participants on TCAs except abdominal pain relieved by passing stools (Chi2 test, p=1.0000) (see Table 11). Thoua *et al.* (2009) demonstrated that amitriptyline reduces stress-induced electrical hypersensitivity. The sample size in the current population was small and the dose and indication was not taken into consideration. TCAs are, however, not recommended as first line treatment in the elderly as their side effects are a concern in this age group (Nobili *et al.* 2011). Side effects of TCAs in the elderly include falls and fractures caused by postural hypotension, cardiovascular problems and anticholinergic side effects that may include constipation, dry mouth, delirium and urinary retention. If a TCA is, however, chosen as a second-line medication, then nortriptyline and

desipramine are recommended as these are less likely to cause anticholinergic side effects (Baldwin as cited in Wiese 2011). The recommended starting dose for amitriptyline in the treatment of IBS is 10 mg gradually increased over weeks with a maximum dosage of 30 mg daily (Nagari & Thomas 2014).

Though It is clear from the literature that TCAs benefit IBS, paroxetine will still be the drug of choice in the elderly due to the combination of the safety of an SSRI and strong anticholinergic effects usually seen with TCAs.

6.1.2.1.3 Benzodiazepines

Forty one participants, 20.5% of this study population, were using BZD as chronic medication. A visible bloated belly symptom was higher in the group of participants that were on BZD (43.9%) than in the group that were not on BZD (30.8%), but this difference was not clinically significant (p=0.1135) (see Table 14). The same was true for all the other individual IBS symptoms except for "feeling of incomplete emptying". Alessi-Severini *et al*. (2013) showed BZD use to be above 10% in both community and personal care homes in a Canadian province. A study by Gleason *et al.* (1998) revealed that among 5,181 participants (65 years and older), 511 (9.9%) were taking at least one BZD. At approximately double this prevalence, the prevalence of BZD used in the researcher's study should therefore be seen as high. This result highlights the importance and necessity to keep on training and informing doctors on BZD prescription terms and the dangers of using these drugs in the case of the elderly. Clinicians should consider the risk of fractures associated with BZD use among the elderly population and the risk of dependence with long term use of BZDs, specifically in those with severe depression (Xing *et al*. 2014) as well as the detrimental effect of BZD use on cognitive function in older individuals (Paterniti *et al.* 2002).

The results of the study do not show a significant difference in the occurrence of IBS symptoms between those participants on BZDs compared to those participants not using BZD's (p= 0.6890) (see Table 14). BZDs does not affect GI motility and therefor is not expected to affect IBS positively or negatively.

6.1.2.2 Gastrointestinal medication use

The overall prevalence of GI medication use was found to be 33.5% (see Figure 3), with PPIs being prescribed in more than half of these cases (see Table 6).

6.1.2.2.1 Proton pump inhibitors

PPIs are not specifically indicated for IBS, but are prescribed in many cases where GI symptoms are described that are associated with IBS (Keszthelyi *et al*. 2012). Proton pump inhibitors relieve symptoms of acid reflux or gastro-oesophageal reflux disease (GORD), as well as for peptic or stomach ulcers and in the treatment of damage to the lower esophagus caused by acid reflux (Heidelbough 2012). These conditions are also associated with abdominal bloating, one of the Manning criteria identified symptoms of IBS.

The prevalence of PPI use was found to be 17.5% in this study population (see Table 6). Most of these cases (76%) were using PPI's for 1 year or longer (see Table 9). Individual symptoms of IBS were found to be high in the group using anti acid secretory drugs (see Table 8), of which the PPI's represented the major component.

There are uncertainties about the effects of long term use of PPIs as new studies are suggesting a possible increase in stomach acid over the long term (Vesper *et al*. 2009). The long term use of proton pump inhibitors is not recommended. A study by Vesper *et al.* (2009) found that preliminary studies suggested that proton pump inhibitors could be responsible for affecting the natural environment of *Lactobacili* and *Streptococci* species by targeting the P-type ATPases of these bacteria in the oral cavity and upper aero-digestive tract.

The use of PPIs in the elderly are associated with significant functional deterioration, attributed to factors such as increased risk for infections and antibiotic resistance; increased risk for cardiovascular events and fractures; serious drug interactions and nutritional deficiencies (Corsonello *et al.* 2014). The development of osteoporosis is of particular concern in long term use of PPIs in the elderly (Metz & Richter 2008).

6.1.3 Co-prescribing

One hundred and seventeen participants, (58.5%) were co-prescribed at least one or more GI, antidepressant or anxiolytic medication with other groups of medication (see Figure 4), whereas only 62 (31.0%) participants were not co-prescribed for GI, antidepressant or anxiolytic medication with other medication (see Figure 3).

Implications of co-prescription include the effect of antidepressants, especially SSRIs on the cytochrome P450-system (Hemeryck & Belpaire 2002) and the interaction of CYP450 (Meyer 1996) with PPIs (Lau & Gurbel 2009).
Fluoxetine (like paroxetine) potently inhibits CYP2D6 and has a moderate effect on CYP3A4-activity (Hemeryck & Belpaire 2002). The latter authors concluded that care should be exercised when using fluoxetine as the inhibitory effects on CYP450-activity might continue for weeks after fluoxetine therapy has been discontinued due to the long half-lives of both the parent compound and the metabolite norfluoxetine. Both paroxetine and fluoxetine are also substrates for CYP2D6 and therefore may inhibit their own metabolism (Crewe *et al.* 1992).

PPIs have varied effects on CYP450 enzymes, but omeprazole specifically has the potential for numerous drug-interactions. Omeprazole causes inhibition of especially CYP2C19, as well as inhibition of CYP2C8 and CYP2C9 and induction of CYP1A2 (Meyer as cited in Humphries & Merritt 1999). Newer PPIs, like pantoprazole and rabeprazole have less potential for drug interactions.

6.1.4 Probiotic use

The study shows a relatively low level of probiotic use (2.5%) (see Table 5). In particular, none of the participants diagnosed with IBS were using probiotics. Probiotics seem promising in the treatment of IBS, as it was found by several studies to decrease inflammation (Kosiewicz *et al*. 2014; Luo *et al.* 2014). It was also found to alter gene expression in the brain (Bravo *et al*. 2011) and in this way it might be addressing the suggested common origin for the co-morbidity of IBS, depression and anxiety. Bravo *et al.* showed that *Lactobacillus rhamnosus* (JB-1) can alter GABAB1b mRNA expression in the brain with increases in cortical regions (cingulate and prelimbic) and associated reductions in expression in the hippocampus, amygdala, and locus coeruleus. Other discoveries of their study include that *L. rhamnosus* (JB-1) reduced GABAAα2 mRNA expression in the prefrontal cortex and amygdala

but increased GABAAα2 in the hippocampus. The benefit of probiotics in depression and anxiety was clarified in their study by concluding that *L. rhamnosus* (JB-1) reduced stress-induced corticosterone and anxiety- and depression-related behaviour.

As such, probiotics has been suggested as a method to improve the action of antidepressants (Luo *et al*. 2014). Hamilton-Miller (2004) pointed out the potential utility of robiotics and prebiotics to counteract malnutrition, lactose intolerance and constipation in elderly individuals. (See 3.2.3). Their clinical utility in IBS and depression in the elderly however, needs to be confirmed by clinical trials.

6.2 THE CLINICAL SIGNIFICANCE OF THE FINDINGS

The researcher's study found a high prevalence of GI medication, antidepressant and anxiolytic use in the population of retirement village residents. These medication groups therefore contribute largely to polypharmacy in the study population. The higher prevalence of individual symptoms of IBS in conjunction with antidepressants found may indicate an association between the diagnosis of depression and IBS symptoms or may indicate a medication effect. Similar results for IBS symptoms with PPI use may indicate the presence of a dysbiosis brought on by chronic suppression of gastric acid secretion.

6.3 LIMITATIONS AND BIASES OF THIS STUDY

The results should be seen in the context of the study population of relatively affluent residents of retirement villages in previously exclusively white residential areas. The relative affluence is deduced from the level of medical scheme cover (92%) that is significantly higher than the average for the South African population (18.4%) (Statistics South Africa 2013). The results therefore cannot be generalized with regard to the South African population as a whole, as the prevalence of IBS could be very different in a different socio-economic group and/or cultural group. It may, however, serve as a point of reference for similar studies in elderly populations.

Only residents that gave informed consent participated, therefore some participants were excluded, based on whether they 'felt' like it or not. One of the symptoms related to the diagnosis for depression based on symptoms in this study was the loss of enjoyment of activities that were enjoyed before.
Our questionnaire did not provide a means of evaluating dosages of medication used. The benefit of anti-cholinergic drugs like TCAs in the treatment of IBS could be dose dependant and therefor the recording of dosages in this study would have been an advantage.

The definitive diagnosis of IBS occurs after exclusion of organic disease. As the researcher did not perform special investigations on participants, the diagnosis of IBS by means of the Manning criteria should be regarded with caution. One participant that was diagnosed with IBS reported blood mixed with stools and three of the participants diagnosed with IBS reported weight loss. These symptoms may indicate the presence of organic disease. The Manning criteria also do not include constipation as part of the diagnosis criteria for IBS.

The association between chronic PPI use and individual IBS symptoms has the potential for confounding by indication.

6.4 RECOMMENDATIONS

1. Clinicians should be made aware of the potential for potential co-occurrence of IBS, depression and anxiety and the potential influence of treatment for these conditions on one another.

2. Further research is needed regarding the link between high prevalence of individual IBS symptoms and PPI use as well as antidepressant use and items of the Manning criteria.

3. The high prevalence of PPI and SSRI use in this population and the prolonged use of these medications shows a need for guidelines on the use of these drugs in the case of the elderly, considering their longterm effects and potential for drug interactions.

4. Further research should focus on the possible dose-dependent benefit of paroxetine in the treament of IBS in the elderly.

5. Further research is needed with regard to the use of probiotics and antidepressants for IBS as well as the first choice of SSRI and the effect of chronic PPIs on the microbiota.

6.5 CONCLUSION

The study bring to light some of the complexities that polypharmacy in the elderly poses to prescribers. It also prompts researchers to take into account the background medication use of their study populations when assessing the prevalence of IBS.

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SUMMARY

KEY TERMS: Irritable bowel syndrome, depression, anxiety, elderly, antidepressants, anxiolytics, proton pump inhibitors, brain-gut axis, co-morbidity, pharmacotherapy.

Introduction:

Irritable bowel syndrome (IBS), depression and anxiety are very common disorders in the general population. The co-occurrence of these conditions are often reported in literature. The accumulation of physical and mental pathology; social and physical stressors; and polypharmacy with advancing age may contribute to higher prevalence of these conditions in elderly populations, both individually or in combination. Data for depression prevalence in the elderly in South Africa is available, but there is no data on the prevalence of anxiety and IBS in this population. Further, the existing literature does not report on the influence of medication use on these conditions. Based on the results of other studies, the expectation was to find a high prevalence of IBS, depression and anxiety, its co-occurrence as well as a high level of overlap in medication use for these conditions.

Aim and objectives:

The aim of this study was to determine the prevalence and co-morbidity of IBS, depression and anxiety in retirement village residents against the background of the pattern of medication used for these conditions.

Specific objectives of the study were the assessment of current symptoms of IBS, depression and anxiety and the assessment of the use of antidepressants, anxiolytics and gastrointestinal (GI) medications that might influence the symptoms of IBS.

Methods:

Two hundred ambulant residents older than 50 years were recruited from 2 retirement villages in an urban setting in South Africa by means of convenience sampling. A cross-sectional observational study was performed with a questionnaire. The questionnaire consisted of two standardized instruments: the Manning criteria for assessing IBS symptoms; and the Hospital Anxiety and Depression Scale (HADS) for the assessment of anxiety and depression. The questionnaire was supplemented by custom-designed questions to evaluate medication use.

Results:

The prevalence of IBS, depression and anxiety were found to be 4.5%, 3.0% and 4.5%, respectively and the overlap of these conditions with each other were seen in the majority of anxiety and depression cases.

Sixty-nine participants (34.5%) reported antidepressant use. Selective serotonin re-uptake inhibitors (SSRIs) were used by 63.8% and tricyclic antidepressants (TCAs) by 33.3% of participants reporting antidepressant medication use. SSRIs were thus used by 22.0% and TCAs by 11.0% of the total study population, fluoxetine and amitriptyline being used in the majority of such cases. Forty-one participants (20.5%) reported the current use of benzodiazepines (BZDs).

Proton pump inhibitors (PPIs) were the most commonly used GI medication (17.5%). Participants taking PPIs were more likely to experience the symptom of “a visible bloated belly” and other individual symptoms of IBS than those who were not taking PPIs and these differences were statistically significant.

The majority of participants using antidepressants, anxiolytics and PPIs were taking these for a period of one year or longer.

Individual symptoms of IBS, listed on the Manning criteria, were more common in individuals taking antidepressants than in those not taking antidepressants and these differences were statistically significant. Four of the 6 Manning criteria were more common in the group of participants using SSRIs than in the group that was not using SSRIs. The presence of IBS symptoms in participants on BZDs was not significanty different from IBS symptoms in those not taking BZDs.

The prevalence of constipation was higher in the group of participants taking SSRIs than in those not taking SSRIs and lower in the group of participants taking TCAs than in those not taking TCAs, but there was no clear association between constipation and use of the target medication groups.

Conclusion:

The lower than expected prevalence of IBS, depression and anxiety occurred against the background of a high level of prolonged antidepressant, anxiolytic and proton pump inhibitor use. The high prevalence of chronic PPI and SSRI use in this population highlights the need for clear guidelines on the use of these drugs, taking into account the long term effects and potential drug-drug interactions.

OPSOMMING

SLEUTELTERME: Prikkelbare dermsindroom, depressie, angs, bejaarde, antidepressante, angswerende medikasie, protonpomp-inhibeerders, brein-maag as, ko-morbiditeit, farmakoterapie.

Inleiding:

Prikkelbare dermsindroom (PDS), depressie en angs is baie algemene toestande in die algemene populasie. Die gesamentlikie voorkoms van hierdie toestande word dikwels in die literatuur gerapporteer. Die akkummulasie van fisiese en geestes patologie, sosiale en fisiese stressore; en polifarmasie met toenemende ouderdom mag bydra tot ‘n hoër prevalensie van hierdie toestande in bejaarde populasies; beide as enkel toestande of in kombinasie. Data vir die prevalensie van depressie in bejaardes in Suid Afrika is beskikbaar, maar daar is geen data oor die prevalensie van PDS in hierdie populasie nie. Verder rapporteer die bestaande literatuur ook nie oor die invloed van medikasie gebruik op hierdie toestande nie. Gebaseer op die resultate van ander studies, was die verwagting om ‘n hoë prevalensie van PDS, depressie en angs; die gesamentlike voorkoms daarvan; sowel as ‘n hoë vlak van oorvleueling in medikasie gebruik vir hierdie toestande te vind.

Doel en mikpunte:

Die doel van hierdie studie was om die prevalensie en ko-morbiditeit van PDS, depressie en angs in die inwoners van aftree oorde teen die agtergrond van die gebruik van die patroon van medikasie gebruik vir hierdie toestande te bepaal.

Die spesifieke mikpunte van die studie was die bepaling van teenwoordige simptome van PDS, depressie en angs en die vasstelling van die gebruik van antidepressante, angswerende en maagdermmedikasie wat die simptome van PDS mag beïnvloed.

Metodes:

Twee honderd ambulante inwoners ouer as 50 jaar is van 2 aftree oorde in ‘n stedelike omgewing in Suid Afrika gewerf deur middel van ‘n gerieflikheidsteekproefneming. ‘n Kruisdeursnee waarnemingstudie is met ‘n vraelys onderneem. Die vraelys het bestaan uit twee gestandaardiseerde instrumente: die Manning kriteria vir die vasstelling van PDS simptome; en die “Hospital Anxiety and Depression Scale” (HADS) vir die bepaling van angs en depressie. Die vraelys is aangevul deur doelgerigte ontwerpte vrae om medikasiegebruik te evalueer.

Resultate:

Die prevalensie van PDS, depressie en angs is bevind om 4.5%, 3.0% en 4.5% onderskeidelik te wees en die gelyktydige voorkoms van hierdie toestande is gesien in die meerderheid van angs en depressie gevalle.

Nege-en-sestig deelnemers (34.5%) het die gebruik van antidepressante gerapporteer. Selektiewe serotonien heropname inhibeerders (SSRIs) is gebruik deur 63.8% en trisikliese antidepressante (TCAs) deur 33.3% in deelnemers wat antidepressant gebruik geraporteer het. SSRIs is dus deur 22.0% van die studiebevolking gebruik en TCAs deur 11.0%, met fluoxetine en amitriptilien in die meerderheid van sulke gevalle, onderskeidelik. Een-en-veertig deelnemers (20.5%) het die huidige gebruik van bensodiasepiene (BZDs) gerapporteer.

Protonpomp-inhibeerders (PPIs) was die mees algemeen gebruikte maagdermmedikasie (17.5 %). Deelnemers wat PPIs geneem het, was meer geneig om die simptoom van “n sigbare geswelde buik” of ander individuele simptome van PDS te ervaar as die wat nie PPIs geneem het nie en hierdie verskille was statisties beduidend.

Die meerderheid van die deelnemers wat antidepressante, angsiolitika en PPIs geneem het, het die middels vir 1 jaar of langer geneem.

Individuele simptome van PDS wat as items in die Manning kriteria verskyn, was meer algemeen in individue wat antidepressante gebruik het as in die wat nie antidepressante geneem het nie en hierdie verskille was statisties beduidend. Vier van die 6 Manning kriteria was meer algemeen in individue wat SSRIs gebruik het as in die wat nie SSRIs geneem het nie en hierdie verskille was ook statisties beduidend. Die voorkoms van PDS simptome in deelnemers wat BZDs gebruik het was nie beduidend anders as die simptome van IBS in deelnemers wat nie BZDs gebruik het nie.

Die voorkoms van konstipasie was meer algemeen in die groep deelnemers wat SSRIs geneem het as in die groep deelnemers wat nie SSRIs gebruik het nie en minder algemeen in deelnemers wat TCAs gebruik het as in deelnemers wat nie TCAs geneem het nie, maar daar was geen duidelike assosiasie tussen konstipasie en die gebruik van die teiken medikasie groepe nie.

Gevolgtrekking:

Die laer as verwagte prevalensie van PDS, depressie en angs wat in hierdie studie gerapporteer word moet gesien word teen die agtergrond van hoë vlakke van chroniese gebruik van antidepressante, angswerende medikasie en protonpomp-inhibeerders. Die hoë voorkoms van PPI en SSRI gebruik in hierdie populasie en die langdurige gebruik van hierdie medisyne beklemtoon die behoefte vir duidelike riglyne oor die gebruik van hierdie medisyne in die geval van bejaardes, met in ag neming die langtermyn effekte en potensiaal vir middel-middel interaksies.

APPENDIX D

The association and treatment of gut problems, depression and anxiety in residents of a retirement village

For office use only: File number: ……

QUESTIONNAIRE
Please write in BLACK or BLUE ink.
Please write in CAPITAL LETTERS.
Please IGNORE the numbered BLOCKS on the RIGHT

SECTION A
EXCLUSION CRITERIA:

Circle the correct option.

Which of the following are applicable to you?

Any condition that confines you to bed for prolonged periods.	Yes	No
Have you been diagnosed with cancer of any part of the digestive system?	Yes	No
Small or large bowel removal or partial removal	Yes	No
Stomach removal or partial removal?	Yes	No
Has any other part of your digestive system been removed (Appendix and galbladder excluded)	Yes	No
Are you under 50 years?	Yes	No
Are you above 85 years?	Yes	No

If answered No to all of the above questions, please continue with section B

SECTION B
PLEASE IGNORE THE NUMBERED BLOCKS ON THE RIGHT
(FOR OFFICE USE ONLY)

☐☐☐☐ 1-4

DEMOGRAPHIC INFORMATION

1. Please indicate your age: ☐☐ 5-6

……years

DO YOU BELONG TO A MEDICAL SCHEME? ☐ 7

1.Yes 2.No

MEDICAL HISTORY

Are you currently on treatment for any of the following?

Circle the correct answer.

2. Depression Yes No ☐ 8

<14 days	15 days to 6 months	>6 months to 1 year	>1 year
1.	2.	3.	4.

☐ 9

3. Anxiety Yes No ☐ 10

<14 days	15 days to 6 months	>6 months to 1 year	>1 year
1.	2.	3.	4.

☐ 11

4. Alzheimer Yes No ☐ 12

<14 days	15 days to 6 months	>6 months to 1 year	>1 year
1.	2.	3.	4.

☐ 13

5. Parkinsonism Yes No ☐ 14

<14 days	15 days to 6 months	>6 months to 1 year	>1 year
1.	2.	3.	4.

☐ 15

6. Epilepsy Yes No ☐ 16

<14 days	15 days to 6 months	>6 months to 1 year	>1 year
1.	2.	3.	4.

☐ 17

7. Bipolar mood disorder Yes No ☐ 18

<14 days	15 days to 6 months	>6 months to 1 year	>1 year
1.	2.	3.	4.

☐ 19

8. Other nervous system disorder Yes No ☐ 20

<14 days	15 days to 6 months	>6 months to 1 year	>1 year
1.	2.	3.	4.

☐ 21

Did you experience weight loss over the past 3 months? ☐ 22
1. Yes 2. No

If so, please specify.....

1. < 3kg over 3 months
2. > 3kg over 3 months
3. > 6kg over 3 months
4. > 12kg over 3 months ☐ 23

Has one of the following organs been removed?

1. Gal bladder 1. Yes 2. No ☐ 24
2. Appendix 1. Yes 2. No ☐ 25
3. Uterus 1. Yes 2. No ☐ 26

Do you suffer from diseases of any of the following organs?

1. Heart 1. Yes 2. No ☐ 27

2. Lung 1. Yes 2. No ☐ 28

3. Kidney 1. Yes 2. No ☐ 29

4.Diabetes Mellitus 1. Yes 2.No ☐ 30

Have you been previously diagnosed with any of the following conditions?

1.Fribromyalgia 1. Yes 2. No ☐ 31

2.Chronic fatigue syndrome 1. Yes 2. No ☐ 32

3.Regular migraine 1. Yes 2. No ☐ 33

4.Regular bladder infection 1. Yes 2. No ☐ 34

5.Pressure leak 1. Yes 2. No ☐ 35

6.Dismenoree 1. Yes 2. No ☐ 36

7. Urinary incontinence 1. Yes 2. No ☐ 37

Are you currently on treatment for any of the following conditions?

1. Inflammatory bowel disease: Crohn's or ulcerative colitis

1. Yes 2. No ☐ 38

Less than 1 year 1.	About 5 years 2.	About 10 years 3.	About 15 years 4.	About 20 years 5.

☐ 39

2. Peptic ulcer 1.Yes 2. No ☐ 40

Less than 1 year 1.	About 5 years 2.	About 10 years 3.	About 15 years 4.	About 20 years 5.

☐ 41

3.Esophageal reflux disease 1. Yes 2. No ☐ 42

Less than 1 year 1.	About 5 years 2.	About 10 years 3.	About 15 years 4.	About 20 years 5.

☐ 43

GASTRO INTESTINAL SYMPTOMS

Which of the following symptoms do you have?

Circle the option, which is applicable and indicate the duration of the condition:

9. Abdominal pain relieved by passing stools 1.Yes 2. No ☐ 44

Less than 1 year 1.	About 5 years 2.	About 10 years 3.	About 15 years 4.	About 20 years 5.

☐ 45

10. Looser stools with onset of pain 1.Yes 2.No ☐ 46

Less than 1 year 1.	About 5 years 2.	About 10 years 3.	About 15 years 4.	About 20 years 5.

☐ 47

11. Feeling of incomplete emptying 1.Yes 2. No ☐ 48

Less than 1 year 1.	About 5 years 2.	About 10 years 3.	About 15 years 4.	About 20 years 5.

☐ 49

12. Constipation 1. Yes 2. No ☐ 50

Less than 1 year 1.	About 5 years 2.	About 10 years 3.	About 15 years 4.	About 20 years 5.

☐

51

13. More frequent stools with onset of pain 1.Yes 2.No ☐ 52

Less than 1 year 1.	About 5 years 2.	About 10 years 3.	About 15 years 4.	About 20 years 5.

☐ 53

14. Phlegm in stool 1. Yes 2. No ☐ 54

Less than 1 year 1.	About 5 years 2.	About 10 years 3.	About 15 years 4.	About 20 years 5.

☐ 55

15. Visible bloated belly 1. Yes 2. No ☐ 56

Less than 1 year 1.	About 5 years 2.	About 10 years 3.	About 15 years 4.	About 20 years 5.

☐ 57

16. Blood mixed with stools 1. Yes 2. No ☐ 58

Less than 1 year 1.	About 5 years 2.	About 10 years 3.	About 15 years 4.	About 20 years 5.

☐ 59

17. Stools float on water Yes No ☐ 60

Less than 1 year 1.	About 5 years 2.	About 10 years 3.	About 15 years 4.	About 20 years 5.

☐ 61

MEDICATION HISTORY

Do you use any of the following antidepressants currently?

Indicate the frequency of use currently:

ANTIDEPRESSANT MEDICINE DURATION

List of Medicines	Only when necessary 1.	None 2.	<14 days 3.	15 days to 6 months 4.	>6 months to 1 year 5.	> 1 year 6.
Adco-mirteron						☐ 62
Adco-talomil						☐ 63
Aropax						☐ 64
Cilift						☐ 65
Cipramil						☐ 66
Citraz						☐ 67
Cymbalta						☐ 68
Deparoc						☐ 69
Depnil						☐ 70
Depramil						☐ 71

List of Medicines Only when necessary 1.	None 2.	<14 days 3.	15 days to 6 months 4.	>6 months to 1 year 5.	> 1 year 6.
Efexor					☐ 72
Ethipra-mine					☐ 73
Herbex nerve					☐ 74
Lantanon					☐ 75
Lexamil					☐ 76
Lilly-Fluoxetine					☐ 77
Lorien					☐ 78
Luvox					☐ 79
Molipaxin					☐ 80
Nuzak					☐ 81
Paxil					☐ 82
Prezac					☐ 83

List of Medicines Only when necessary 1.	None 2.	<14 days 3.	15 days to 6 months 4.	>6 months to 1 year 5.	> 1 year 6.
Ranflocs					☐ 84
Remeron					☐ 85
Rezac					☐ 86
Serra-press					☐ 87
Serdep					☐ 88
Serlife					☐ 89
Thaden					☐ 90
Tofranil					☐ 91
Trepil-line					☐ 92
Wellbu-trin					☐ 93
Zoloft					☐ 94

Indicate the relief on the antidepressant therapy:

☐ 95

Circle the correct option.

1. None, I still am depressed all of the time
2. I still feel depressed most of the time, but some days I don't feel depressed
3. I only feel depressed on certain days when there is a cause
4. I have no symptoms of depression

How do you use your antidepressant medication?
Circle the correct answer:

1. Exactly as prescribed ☐ 96
2. Full dose when I feel I need it ☐ 97
3. Half a dose ☐ 98
4. I will sometimes take double the dose when symptoms are bad ☐ 99
5. I sometimes forget to take a dose ☐ 100
6. Other ☐ 1

Do you use any of the following stomach medication currently?
Indicate the frequency of use currently:

STOMACH MEDICINE	DURATION				
List of Medi-Cines	Only when needed 1.	None 2.	<14 days 3.	15 days to 6 months 4.	>6 months to 1 year 5.	> 1 year 6.
Adco-omepra-zole					☐ 2
Altosec					☐ 3
Asacol					☐ 4
Bevis-pas					☐ 5
Busco-pan					☐ 6
Cimeti-dine					☐ 7
Clopa-mon					☐ 8
Colofac					☐ 9
Contro-loc					☐ 10
Contro-met					☐ 11

List of Medi- cines Only when needed 1.	None 2.	<14 days 3.	15 days to 6 months 4.	>6 months to 1 year 5.	> 1 year 6.
Cytotec					☐ 12
Denol					☐ 13
Dulcolax					☐ 14
Fybogel					☐ 15
Gelacid					☐ 16
Histak					☐ 17
Hyospas- mol					☐ 18
Ibero- gast					☐ 19
Lacson					☐ 20
Lancap					☐ 21
Lanso- loc					☐ 22
Lanzor					☐ 23
Laxette					☐

					24
List of Medi- cines Only when needed 1.	None 2.	<14 days 3.	15 days to 6 months 4.	>6 months to 1 year 5.	> 1 year 6.
Lenamet					☐ 25
Lopera- mide					☐ 26
Losec					☐ 27
Molko- san					☐ 28
Mayo- gel					☐ 29
Maxo- lon					☐ 30
Movi- col					☐ 31
Ten Herbs					☐ 32
Nexiam					☐ 33
Omez					☐ 34
Panto- cid					☐ 35
Panto- loc					☐ 36

List of Medi-cines	Only when needed 1.	None 2.	<14 days 3.	15 days to 6 months 4.	>6 months to 1 year 5.	> 1 year 6.
Pariet						☐ 37
Pentasa						☐ 38
Probiotic						☐ 39
Rani-hexal						☐ 40
Salazo-pyrin						☐ 41
Sandoz-omepra-zole						☐ 42
Scopex						☐ 43
Spasmo-gel						☐ 44
Topzole						☐ 45
Ulsanic						☐ 46
Ultak						☐ 47
Vomi-don						☐ 48

List of Medi-cines	Only when needed 1.	None 2.	<14 days 3.	15 days to 6 months 4.	>6 months to 1 year 5.	> 1 year 6.
Zantac						☐ 49

IF YOU TAKE ANY MEDICINE FOR THE STOMACH, ANSWER THE FOLLOWING QUESTIONS:

Circle the correct option:
Indicate the relief on the Stomach medication

☐ 50

1. none, I still experience stomach problems more than 3 times a week
2. I still have (more than once a week) problems with my stomach
3. I have (less than once a week) problems with my stomach
4. No symptoms

How do you use your stomach medication?

1. Exactly as prescribed ☐ 51
2. Full dose when I feel I need it ☐ 52
3. Half a dose ☐ 53
4. I will sometimes take double the dose when symptoms are bad ☐ 54
5. I sometimes forget to take a dose ☐

6. Other 55 ☐ 56

Do you use any of the following medicine for anxiety currently? Indicate the frequency of use currently:

ANTI ANXIETY MEDICINE — DURATION

List of Medicines Only when necessary 1.	None 2.	<14 days 3.	15 days to 6 months 4.	>6 months to 1 year 5.	> 1 year 6.
Pax					☐ 57
Serepax					☐ 58
Purata					☐ 59
Ativan					☐ 60
Tranqipam					☐ 61
Xanor					☐ 62
Adco-Alzam					☐ 63
Azor					☐ 64

List of Medi-cines Only when necessary 1.	None 2.	<14 days 3.	15 days to 6 months 4.	>6 months to 1 year 5.	> 1 year 6.
Zopax					☐ 65
Brazepam					☐ 66
Sandoz-Bro-mazepam					☐ 67
Urbanol					☐ 68
Aterax					☐ 69
Stresam					☐ 70
Dormicum					☐ 71
Imovane					☐ 72
Alchera					☐ 73
Sandoz – Zopiclone					☐ 74
Z-Dorm					☐ 75
Zopigen					☐ 76

List of Medi-cines	Only when necessary 1.	None 2.	<14 days 3.	15 days to 6 months 4.	>6 months to 1 year 5.	> 1 year 6.
Adco-Zopimed						☐ 77
Zopivane						☐ 78
Stilnox						☐ 79
Adco-Zolpidem						☐ 80
Ivedal						☐ 81
Zolnox						☐ 82
Zolpi-hexal						☐ 83
Beta-sleep						☐ 84
Somnil						☐ 85
Herbex nerve						☐ 86

Circle the correct option:

Indicate the relief on the anxiety medication ☐ 87

1. none, I still get very anxious almost every day
2. I still experience (more than twice a week) anxiety
3. I feel calm and relaxed most of the time

How do you use your anxiety medication?

1. Exactly as prescribed ☐ 88
2. Full dose when I feel I need it ☐ 89
3. Half a dose ☐ 90
4. I will sometimes take double the dose when symptoms are bad ☐ 91
5. I sometimes forget to take a dose ☐ 92
6. Other ☐ 93

ARE YOU CURRENTLY ON ANY OTHER MEDICATION?

MEDICINE 1 ☐94☐95

(For office use only):
Block 1: class
Block 2: sub-class for drug

Duration:

<14 dae	15 dae tot 6 maande	>6 maande tot 1 jaar	> 1 jaar	Slegs wanneer nodig
1.	2.	3.	4.	5.

☐96

MEDICINE 2 ☐97☐98

(For office use only):
Block 1: class
Block 2: sub-class for drug

Duration:

☐99

<14 dae	15 dae tot 6 maande	>6 maande tot 1 jaar	> 1 jaar	Slegs wanneer nodig
1.	2.	3.	4.	5.

MEDICINE 3 ☐100☐1

(For office use only):
Block 1: class
Block 2: sub-class for drug

Duration:

☐2

<14 dae	15 dae tot 6 maande	>6 maande tot 1 jaar	> 1 jaar	Slegs wanneer nodig
1.	2.	3.	4.	5.

MEDICINE 4 ☐3☐4

(For office use only):
Block 1: class
Block 2: sub-class for drug

Duration:

☐5

<14 dae	15 dae tot 6 maande	>6 maande tot 1 jaar	> 1 jaar	Slegs wanneer nodig
1.	2.	3.	4.	5.

MEDICINE 5 ☐6☐7

(For office use only):
Block 1: class
Block 2: sub-class for drug

Duration:

☐8

<14 dae	15 dae tot 6 maande	>6 maande tot 1 jaar	> 1 jaar	Slegs wanneer nodig
1.	2.	3.	4.	5.

MEDICINE 6 ☐9☐10

(For office use only):
Block 1: class
Block 2: sub-class for drug

Duration:

☐11

<14 dae	15 dae tot 6 maande	>6 maande tot 1 jaar	> 1 jaar	Slegs wanneer nodig
1.	2.	3.	4.	5.

MEDICINE 7 ☐12☐13

(For office use only):
Block 1: class
Block 2: sub-class for drug

Duration:

☐14

<14 dae	15 dae tot 6 maande	>6 maande tot 1 jaar	> 1 jaar	Slegs wanneer nodig
1.	2.	3.	4.	5.

MEDICINE 8 ☐15☐16

(For office use only):
Block 1: class
Block 2: sub-class for drug

Duration:

☐17

<14 dae	15 dae tot 6 maande	>6 maande tot 1 jaar	> 1 jaar	Slegs wanneer nodig
1.	2.	3.	4.	5.

How often did you visit your doctor or health care facilities during the past six months?

Circle the correct option.

☐ 24

1. I did not visit
2. Once
3. 2-5 times
4. 6-11
5. 12 or more times

SUPPLEMENTS

List of supplements	< 14 days 1.	15 days to 6 months 2.	> 6 months to 1 year 3.	> 1 year 4.
Omega 3				☐ 25
Vitamin D3				☐ 26
Magnesium				☐ 27
Folate/Folic acid				☐ 28
Vitamin B CO				☐ 29

Kreatine				☐ 30
5-HTP				☐ 31
Theanine				☐ 32
List of supplements	< 14 days 1.	15 days to 6 months 2.	> 6 months to 1 year 3.	> 1 year 4.
Chromium				☐ 33
Zink				☐ 34
Prozen				☐ 35
Procydin				☐ 36
Omega 6				☐ 37
Melatonin				☐ 38

Other Yes ☐ 39

Please specify which other supplements you are taking……
……
……

Circle the reply which comes closest to how you have been feeling in the past week. Don't take too long over your replies; your immediate reaction to each item will probably be more accurate than a long thought out response.

I feel tensed or "wound up": ☐ 40
3. Most of the time
2. A lot of the time
1. From time to time,occasionally
0. Not at all

I still enjoy the things I used to enjoy: ☐ 41
0. Definitely as much
1. Not quite so much
2. Only a little
3. Hardly at all

I get a sort of frightened feeling as if something awful is about to happen: ☐ 42
3. Very definitely and quite badly
2. Yes, but not too badly
1. A little, but it doesn't worry me
0. Not at all

I can laugh and see the funny side of things: ☐ 43
0. As much as I always could
1. Not quite so much now
2. Definitely not so much now
3. Not at all

Worrying thoughts go through my mind: ☐ 44
3. A great deal of the time
2. A lot of the time
1. From time to time but not too often
0. Only occasionally

I feel cheerful: ☐ 45
3. Not at all
2. Not often
1. Sometimes
0. Most of the time

I can sit at ease and feel relaxed: ☐ 46

0. Definitely
1. Usually
2. Not often
3. Not at all

I feel as if I am slowed down: ☐ 47

3. Nearly all the time
2. Very often
1. Sometimes
0. Not at all

I get a sort of frightened feeling like 'butterflies' in the stomach: ☐ 48

0. Not at all
1. Occasionally
2. Quite often
3. Very often

I have lost interest in my appearance: [4

3. Definitely
2. I don't take so much care as I should
1. I may not take quite as much care
0. I take just as much care as ever

I feel restless as if I have to be on the move: [5(

3. Very much indeed
2. Quite a lot
1. Not very much
0. Not at all

I look forward with enjoyment things: [5

0. As much as ever I did
1. Rather less than I used to
2. Definitely less than I used to
3. Hardly at all

I get sudden feelings of panic: ☐ 52

3. Very often indeed
2. Quite often
1. Not very often
0. Not at all

I can enjoy a good book or radio or TV programme: ☐ 53

0. Often
1. Sometimes
2. Not often
3. Very seldom

Thank you for your participation!

APPENDIX B: ETHICS COMMITTEE APPROVAL

UNIVERSITY OF THE FREE STATE
UNIVERSITEIT VAN DIE VRYSTAAT
YUNIVESITHI YA FREISTATA
UFS UV

Research Division
Internal Post Box G40
☎(051) 4052812
Fax (051) 4444359

E-mail address: StraussHS@ufs.ac.za

Ms H Strauss/hv

2013-06-07

REC Reference nr 230408-011
IRB nr 00006240

MS A TROMP
DEPT OF PHARMACOLOY
FACULTY OF HEALTH SCIENCES
UFS

Dear Ms Tromp

ECUFS NR 84/2013
MS A TROMP **DEPT OF PHARMACOLOGY**
PROJECT TITLE: CO MORBIDITY OF AND TREATMENT FOR IRRITABLE BOWEL SYNDROME, DEPRESSION AND ANXIETY IN RESIDENTS OF A RETIREMENT VILLAGE.

- You are hereby kindly informed that the Ethics Committee approved the above project at the meeting held on 4 June 2013.
- Committee guidance documents: Declaration of Helsinki, ICH, GCP and MRC Guidelines on Bio Medical Research. Clinical Trial Guidelines 2000 Department of Health RSA; Ethics in Health Research: Principles Structure and Processes Department of Health RSA 2004; Guidelines for Good Practice in the Conduct of Clinical Trials with Human Participants in South Africa, Second Edition (2006); the Constitution of the Ethics Committee of the Faculty of Health Sciences and the Guidelines of the SA Medicines Control Council as well as Laws and Regulations with regard to the Control of Medicines.
- Any amendment, extension or other modifications to the protocol must be submitted to the Ethics Committee for approval.
- The Committee must be informed of any serious adverse event and/or termination of the study.
- A progress report should be submitted within one year of approval of long term studies and a final report at completion of both short term and long term studies.
- Kindly refer to the ETOVS/ECUFS reference number in correspondence to the Ethics Committee secretariat.

Yours faithfully

.....
PROF WH KRUGER
CHAIR: ETHICS COMMITTEE

Cc **Dr P van Zyl**

APPENDIX C: CONSENT FORMS

Dear manager of ..... retirement village,

We, A. Tromp and Dr. PM van Zyl are researchers from the University of the Free State. We are conducting a research study with the title :
"Co morbidity of and treatment for irritable bowel syndrome, depression and anxiety in residents of a retirement village". The goal of this study is to investigate the link between depression, anxiety and gastro intestinal problems and the implications for treatment.
We undertake to get individual informed consent form each participant. The research involves the filling of a questionare.

Your facility are asked to participate in a research study titled: "Co morbidity of and treatment for irritable bowel syndrome, depression and anxiety in residents of a retirement village".
You have been informed about the study by Heidi Tromp.
You may contact Heidi Tromp at 0763746870 any time if you have questions about the research.

You may contact the Secretariat of the Ethics Committee of the Faculty of Health Sciences, UFS at telephone number (051) 4052812 if you have any questions about the rights as a research facility.

The facility's participation in this research is voluntary, and you will not be penalized or lose benefits if you refuse to participate or decide to terminate participation.

If you agree to participate, you will be given a signed copy of this document as well as the participant information sheet, which is a written summary of the research.

The research study, including the above information has been verbally described to me. I understand what ..... retirement village's involvement in the study means and I voluntarily give permission for conducting of the research at our facility.

Signature of manager at .....retirement village Date

Signature of Wittness 14/11/13
Date

Signature of Translator (Where applicable) Date

Dear manager of Striata retirement village,

We, A. Tromp and Dr. PM van Zyl are researchers from the University of the Free State. We are conducting a research study with the title :
"Co morbidity of and treatment for irritable bowel syndrome, depression and anxiety in residents of a retirement village". The goal of this study is to investigate the link between depression, anxiety and gastro intestinal problems and the implications for treatment.
We undertake to get individual informed consent form each participant. The research involves the filling of a questionare.

Your facility are asked to participate in a research study titled: "Co morbidity of and treatment for irritable bowel syndrome, depression and anxiety in residents of a retirement village".
You have been informed about the study by Heidi Tromp.
You may contact Heidi Tromp at 0763746870 any time if you have questions about the research.

You may contact the Secretariat of the Ethics Committee of the Faculty of Health Sciences, UFS at telephone number (051) 4052812 if you have any questions about the rights as a research facility.

The facility's participation in this research is voluntary, and you will not be penalized or lose benefits if you refuse to participate or decide to terminate participation.

If you agree to participate, you will be given a signed copy of this document as well as the participant information sheet, which is a written summary of the research.

The research study, including the above information has been verbally described to me. I understand what Striata retirement village's involvement in the study means and I voluntarily give permission for conducting of the research at our facility.

Signature of manager at Striata retirement village — Date: 2013-05-20

Signature of Witness — Date: 20.5.13

Signature of Translator (Where applicable) — Date

Die gelyktydige voorkoms en behandeling vir brein-en spysverteringskanaal verwante probleme in inwonders in 'n aftree oord:

Beste deelnemer,

Ons, A. Tromp en Dr. PM. van Zyl is navorsers aan die Universiteit van die Vrystaat. Ons onderneem 'n navorsing studie met die titel: "Co morbidity of and treatment for irritable bowel syndrome, depression and anxiety in residents in a retirement village".

Die doel van ons studie is om die gelyktydige voorkoms van gastrointestinale probleme, depressie en angs te ondersoek asook die implikasies vir die behandeling van hierdie toestande. Ons onderneem om individuele ingeligte toestemming te verkry van elke deelnemer. Die navorsing behels die invul van 'n vorm wat omtrent 20 minute tot 'n maksimum van een uur sal duur.

U mag die sekretariaat van die etiekkomitee van die fakulteit Gesondheidswetenskappe, UV by telefoon nommer (051) 4052812 skakel indien u enige navrae wil rig rakende u deelname.

Daar is geen risiko betrokke by die navorsing nie. U sal nie betaal word nie. U deelname aan hierdie navorsing is vrywilliglik, en u sal nie gepenaliseer word of voordele verloor as u weier om deel te neem of besluit om te ontrek nie.

Indien u instem om deel te neem, sal u 'n getekende afskrif van hierdie dokument ontvang sowel as die inligtingsvorm vir deelnemers, wat 'n geskrewe opsomming is van die navorsing.

Die navorsing studie, insluitende die bostaande inligting is verbaal aan my verduidelik. Ek verstaan wat my betrokkenheid in die studie behels en ek aanvaar vrywilliglik om deel te neem.

Handtekening van deelnemer Datum

Handtekening van getuie Datum

Handtekening van tolk Datum

(Waar van toepassing) Navorsers kan geskakel word by die Universiteit van die Vrystaat: 0763746870

APPENDIX D: PERMISSION LETTER FOR HADS

GL-ASSESSMENT
Telephone 0845 602 1937 opt 1
Fax 0845 601 5358
E-mail: info@gl-assessment.co.uk
www.gl-assessment.co.uk

Welcome to GL-Assessment
Thank you for completing the GL-Assessment Registration Form
You have been entered onto our confidential registration list

To:	Adelheit Tromp	Account No:	128191
From:	Customer Services	Qualification Code:	10110
Date:	20 September 2012	Reader No:	158512

Your Qualification Code is 10110

This code allows us to see which tests are available to you based on your qualifications.

We would be very grateful if you could quote both your **Account Number**, and **Qualification Code**, whenever you order from us. This will enable us to process your orders quickly and efficiently. Please notify us of any changes in your details so we can keep our records up-to-date.

If you have any enquiries, please contact

Customer Services on 0845 602 1937 opt 1
Alternatively, you can e-mail us at information@gl-assessment.co.uk

For International Customers please call +44 (0) 208 996 8440

SUMMARY OF RAW DATA

Nr	A	G	GI	PPI	LAX	OGI	AD	SSRI	TCA	Other AD	ANX	BZD	Other ANX	IBS	DEP	A	PRS	LSP	FIE	CON	MFP	PS	BLO	BLE	SFW
1	83	F	N		I		N				Y			N	N	N	N	N	N	Y	N	N	N	N	N
2	59	F	N				N				N			N	N	N	N	N	N	Y	N	N	N	N	N
3	83	F	N				N				N			N	N	Y	N	N	Y	Y	N	N	N	N	N
4	77	M	N				N				N			N	N	N	N	N	N	N	N	N	N	N	N
5	72	F	N				N				N			N	N	N	N	N	N	Y	N	N	N	N	N
6	72	M	N				Y		Y		N			N	N	N	N	N	N	N	N	N	N	N	N
7	73	F	Y	Y			Y	Y			Y	Y		N	N	N	N	N	Y	N	N	N	Y	N	N
8	74	F	N				N				N			N	N	N	N	N	N	N	N	N	N	N	N
9	80	F	Y			Y	N				N			N	N	Y	N	N	Y	Y	N	N	N	N	N
10	61	F	N				N				N			N	N	N	N	N	N	N	N	N	N	N	N
11	76	F	Y	Y		Y	N				N			Y	N	N	Y	Y	Y	Y	Y	N	Y	N	N
12	77	M	N				N				N			N	N	N	N	N	N	N	N	Y	N	N	N
13	81	F	Y	Y		Y	Y		Y		N			N	N	N	N	N	N	N	N	N	Y	N	N
14	83	F	Y	Y			Y		Y		N			N	N	N	N	Y	Y	Y	Y	N	Y	N	N
15	73	F	N				Y	Y			N			N	N	N	N	N	N	Y	N	N	Y	N	N
16	78	F	N				N				N			N	N	N	N	N	N	N	N	N	N	N	N
17	83	M	N				N				N			N	N	N	N	N	N	N	N	N	N	N	N
18	73	F	Y		Y		Y	Y			N			N	N	N	Y	N	Y	Y	Y	N	Y	N	Y
19	61	F	N				Y	Y			N			N	N	N	Y	N	N	N	Y	N	Y	N	N
20	78	F	N				N				N			N	N	N	N	N	Y	Y	N	N	Y	N	Y
21	68	F	Y	Y			Y		Y	Y	Y	Y		N	Y	N	N	N	N	Y	N	N	N	N	N
22	80	F	N				Y	Y			N			N	N	N	N	N	N	N	N	N	N	N	N
23	76	F	Y	Y			Y	Y			Y	Y		Y	N	N	Y	Y	Y	N	N	N	Y	N	N
24	80	F	N				N				N			N	N	N	N	N	N	Y	N	N	N	N	N

A: Age **G:** Gender **GI:** Gastrointestinal medication use **PPI:** Proton pump inhibitor **LAX:** Laxative ; **OGI:** Other gastro-intestinal medication **AD:**Anti: antidepressant use ; **SSRI:** Selective serotonin re-uptake inhibitor ; **TCA:** tricyclic antidepressant; **Other AD**: Other antidepressant **ANX**: Anxiolytic use **BZD**: Benzodiazepine **Other ANX**: Other anxiolytic **IBS**: irritable bowel syndrome; **DEP**:depression; **A:** anxiety; **PRS:** abdominal pain relieved by passing stools; **LSP:** Looser stools wih onset of pain; **FIE:** feeling of incomplete emptying; **CON:** Constipation; **MFP:** more frequent stools with onset of pain; **PS:** phlegm in stool; **BLO:** visible boated belly; **BLE;** blood mixed with stools **SFW:** Stools float on water

Nr	A	G	GI	PPI	LAX	OGI	AD	SSRI	TCA	Other AD	ANX	BZD	Other ANX	IBS	DEP	A	PRS	LSP	FIE	CON	MFP	PS	BLO	BLE	SFW
25	78	M	N				Y	Y			N			Y	Y	Y	Y	Y	N	Y	Y	N	Y	N	N
26	55	M	N				N				N			N	N	N	N	N	N	N	N	N	N	N	N
27	79	F	N				N				N			N	N	N	N	N	Y	Y	N	N	Y	N	N
28	69	M	N				N				N			N	N	N	N	N	N	N	N	N	N	N	N
29	75	F	N				N				Y	Y		N	N	N	Y	N	Y	Y	N	N	N	Y	N
30	85	F	N				Y				N			N	N	N	N	N	N	N	N	N	N	N	N
31	75	M	Y		Y		N				N			N	N	N	N	N	N	Y	N	N	N	N	N
32	68	F	N				Y	Y			Y	Y		N	N	N	N	N	N	N	N	N	N	N	N
33	81	F	Y		Y		N				Y	Y		N	N	N	N	N	N	N	N	N	N	N	N
34	79	F	Y			Y	N				N			N	N	N	N	N	N	N	N	N	N	N	N
35	73	F	Y	Y			Y	Y			N			N	N	N	N	N	N	N	N	N	N	N	N
36	85	F	Y		Y		N				N			N	N	N	N	N	Y	Y	N	N	Y	N	N
37	80	F	Y			Y	Y	Y			N			N	N	N	N	N	N	Y	N	N	N	N	N
38	80	F	N				Y	Y			N			N	N	N	N	N	N	N	N	N	N	N	N
39	62	F	Y	Y			Y	Y	Y		N			Y	N	Y	Y	Y	Y	Y	Y	N	Y	N	N
40	85	F	N				N				N			N	N	N	N	N	N	N	N	N	N	N	N
41	71	F	N				N				N			N	N	N	N	N	N	N	N	N	N	N	N
42	63	F	Y	Y			Y			Y	N			N	N	N	N	N	N	Y	N	N	N	N	N
43	81	F	N				N				N			N	N	N	N	N	N	N	N	N	N	N	N
44	66	F	N				N				N			N	N	N	N	N	N	N	N	N	N	N	N
45	80	M	N				N				N			N	N	N	N	N	N	Y	N	N	N	Y	N
46	79	M	N				N				N			N	N	N	N	N	N	N	N	N	N	N	N
47	84	F	Y		Y		Y	Y	Y		Y	Y		N	N	N	N	N	Y	Y	N	N	Y	N	N
48	84	M	N				N				N			N	N	N	N	N	N	N	N	N	N	N	N
49	71	M	N				N				N			N	N	N	N	N	N	Y	N	N	N	N	N
50	68	F	Y	Y			N				Y	Y		N	N	N	N	N	Y	Y	N	N	Y	N	N

A: Age **G:** Gender **GI:** Gastrointestinal medication use **PPI:** Proton pump inhibitor **LAX:** Laxative ; **OGI:** Other gastro-intestinal medication **AD:**Anti: antidepressant use ; **SSRI:** Selective serotonin re-uptake inhibitor ; **TCA:** tricyclic antidepressant; **Other AD**: Other antidepressant **ANX**: Anxiolytic use **BZD**: Benzodiazepine **Other ANX**: Other anxiolytic **IBS**: irritable bowel syndrome; **DEP**:depression; **A:** anxiety; **PRS:** abdominal pain relieved by passing stools; **LSP:** Looser stools wih onset of pain; **FIE:** feeling of incomplete emptying; **CON:** Constipation; **MFP:** more frequent stools with onset of pain; **PS:** phlegm in stool; **BLO:** visible boated belly; **BLE;** blood mixed with stools **SFW:** Stools float on water

Nr	A	G	GI	PPI	LAX	OGI	AD	SSRI	TCA	Other AD	ANX	BZD	Other ANX	IBS	DEP	A	PRS	LSP	FIE	CON	MFP	PS	BLO	BLE	SFW
51	85	F	Y			Y	N				N			N	N	N	N	N	N	Y	N	N	Y	N	N
52	85	F	Y		Y		N				N			N	N	N	N	N	N	N	N	N	N	N	N
53	75	F	N				N				N			N	N	N	N	N	N	N	N	N	N	N	N
54	80	F	N				N				N			N	N	N	N	N	N	Y	N	N	Y	N	N
55	79	F	Y		Y		N				N			N	N	Y	N	N	Y	Y	N	N	Y	N	N
56	74	F	Y			Y	N				Y		Y	N	N	N	N	N	N	N	N	N	N	N	N
57	73	F	N				N				N			N	N	N	N	N	N	Y	N	N	N	N	N
58	70	F	N				N				Y	Y		N	N	N	N	N	N	N	N	N	N	N	N
59	76	M	N				N				N			N	N	N	N	N	N	N	N	N	Y	N	N
60	64	F	Y			Y	Y	Y			Y	Y		N	N	N	N	N	Y	Y	N	N	Y	N	N
61	78	F	N				N				N			N	N	N	N	N	N	N	N	N	N	N	N
62	75	F	N				Y				N			N	N	N	N	N	N	N	N	N	N	N	N
63	78	F	N				Y		Y		Y	Y		N	N	N	N	Y	Y	N	Y	N	Y	N	N
64	81	F	N				N				N			N	N	N	N	N	N	N	N	N	N	N	N
65	80	F	Y	Y			Y	Y			N			N	N	N	N	N	N	N	N	N	N	N	N
66	69	F	N				N				Y	Y		N	N	N	N	N	N	N	N	N	Y	N	N
67	69	F	N				Y	Y			Y	Y		N	N	N	N	N	N	N	N	N	N	N	N
68	82	F	N				N				N			N	N	N	N	N	N	N	N	N	N	N	N
69	66	F	N				Y		Y		N			N	N	N	N	N	N	N	N	N	N	N	N
70	72	M	N				N				N			N	N	N	N	N	N	N	N	N	N	N	N
71	85	F	N				Y	Y			N			N	N	N	N	N	N	N	N	N	N	N	N
72	73	M	N				N				N			N	N	N	N	N	N	Y	N	N	N	N	N
73	83	F	N				N				N			N	N	N	N	N	N	Y	N	N	Y	N	Y
74	73	F	N				N				N			N	N	N	N	N	N	N	N	N	N	N	N

A: Age **G:** Gender **GI:** Gastrointestinal medication use **PPI:** Proton pump inhibitor **LAX:** Laxative ; **OGI:** Other gastro-intestinal medication **AD:**Anti: antidepressant use ; **SSRI:** Selective serotonin re-uptake inhibitor ; **TCA:** tricyclic antidepressant; **Other AD**: Other antidepressant **ANX**: Anxiolytic use **BZD**: Benzodiazepine **Other ANX**: Other anxiolytic **IBS**: irritable bowel syndrome; **DEP**:depression; **A:** anxiety; **PRS:** abdominal pain relieved by passing stools; **LSP:** Looser stools wih onset of pain; **FIE:** feeling of incomplete emptying; **CON:** Constipation; **MFP:** more frequent stools with onset of pain; **PS:** phlegm in stool; **BLO:** visible boated belly; **BLE;** blood mixed with stools **SFW:** Stools float on water

Nr	A	G	GI	PPI	LAX	OGI	AD	SSRI	TCA	Other AD	ANX	BZD	Other ANX	IBS	DEP	A	PRS	LSP	FIE	CON	MFP	PS	BLO	BLE	SFW
75	75	M	N				N				N			N	N	N	N	N	N	N	N	N	N	N	N
76	75	M	N				N				N			N	N	N	N	N	N	N	N	N	N	N	N
77	80	F	N				N				N			N	N	N	N	N	N	N	N	N	N	N	N
78	71	F	N				N				N			N	N	N	N	N	N	N	N	N	N	N	N
79	76	F	Y	Y			Y	Y			Y	Y		N	N	N	N	N	N	N	N	N	N	N	N
80	79	M	N				N				N			N	N	N	N	N	N	Y	N	N	N	N	N
81	85	F	N				N				N			N	N	N	N	N	N	Y	N	N	Y	N	N
82	81	F	N				N				N			N	N	N	N	N	N	N	N	N	N	N	N
83	84	F	N				N				Y	Y		N	N	N	N	N	N	N	N	N	N	N	N
84	79	F	N				N				N			N	N	N	N	N	N	N	N	N	N	N	N
85	73	F	Y	Y			Y			Y	N			N	N	N	N	N	N	N	N	N	N	N	N
86	84	F	Y	Y		Y	Y	Y			Y	Y		N	N	N	Y	N	N	Y	N	N	Y	N	N
87	68	F	N				Y		Y		N			N	N	N	N	N	N	N	N	N	N	N	N
88	74	F	N				N				N			N	N	N	N	N	N	Y	N	N	N	N	Y
89	85	M	Y	Y			N				N			Y	N	N	Y	Y	Y	N	Y	Y	Y	Y	N
90	72	M	Y	Y			N				N			N	N	N	N	N	N	Y	N	N	Y	N	N
91	74	F	N				N				N			N	N	N	N	N	N	N	N	N	Y	N	N
92	80	M	N				N				N			N	N	N	N	N	N	N	N	N	N	N	N
93	84	F	N				N				Y	Y		N	N	N	N	N	N	N	N	N	N	N	N
94	68	F	Y			Y	Y	Y			N			N	N	N	Y	N	N	Y	Y	N	Y	N	N
95	85	F	Y	Y			N				N			N	N	N	N	N	N	N	N	N	N	N	N
96	78	F	Y			Y	N				N			N	N	N	N	N	N	Y	N	N	N	N	N
97	66	F	N				Y	Y			N			N	N	N	N	N	N	N	N	N	N	N	N
98	81	F	Y			Y	Y		Y		N			N	N	N	N	N	N	N	N	N	Y	N	N
99	84	M	Y		Y		N				N			Y	N	N	Y	Y	Y	Y	Y	N	Y	N	N
100	69	F	Y	Y		Y	Y	Y	Y	Y	N			N	N	N	N	N	N	N	N	N	N	N	N

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101	84	F	N				N				Y	Y		N	N	N	N	N	N	N	N	N	N	N	N
102	69	F	N				N				N			N	N	N	N	N	N	Y	N	N	Y	N	N
103	83	F	N				Y	Y			N			N	N	N	N	N	N	N	N	N	N	N	N
104	83	F	N				N				Y	Y		N	N	N	Y	N	N	Y	N	N	Y	N	N
105	75	F	N				Y	Y			N			N	Y	N	N	N	Y	Y	N	N	Y	N	N
106	80	M	N				N				N			N	N	N	N	N	N	N	N	N	N	N	N
107	75	F	N				N				N			N	N	N	N	N	N	Y	N	N	N	N	N
108	74	F	N				N				N			N	N	N	N	N	N	N	N	N	N	N	N
109	78	F	N				N				Y	Y		N	N	N	N	N	N	N	N	N	N	N	N
110	77	M	N				N				N			N	N	N	N	N	N	Y	N	N	N	N	N
111	70	F	N				N				Y	Y		N	N	N	N	N	N	N	N	N	N	N	N
112	70	M	Y			Y	Y		Y		N			N	N	N	N	N	N	N	N	N	Y	N	N
113	68	F	N				Y		Y		N			N	N	N	N	N	N	N	N	N	N	N	N
114	75	F	N				N				N			N	N	N	N	N	N	N	N	N	N	N	N
115	82	F	Y	Y			N				Y	Y		N	N	N	N	N	N	Y	N	N	N	N	N
116	73	F	N				N				N			N	N	N	N	N	N	Y	N	N	N	N	N
117	83	F	N				Y	Y			N			N	N	N	N	N	N	N	N	N	N	N	N
118	78	F	N				Y		Y		N			N	N	N	N	N	N	N	N	N	N	N	N
119	78	M	N				N				N			N	N	N	N	N	N	N	N	N	N	N	N
120	76	M	N				N				Y	Y		N	N	N	N	N	N	N	N	N	N	N	N
121	61	M	N				N				N			N	N	N	N	N	N	N	N	N	N	N	N
122	80	F	N				N				N			N	N	N	N	N	N	Y	N	N	Y	N	N
123	78	F	Y	Y			Y	Y			N			N	N	N	N	N	N	N	N	N	Y	N	N
124	73	F	Y	Y			N				N			Y	N	N	Y	Y	Y	Y	Y	N	Y	N	N

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125	80	M	N				N				N			N	N	N	N	N	Y	Y	Y	N	Y	Y	Y
126	76	M	Y		Y		N				N			N	N	N	N	N	N	Y	N	N	N	N	N
127	84	F	N				N				N			N	N	N	N	N	N	N	N	N	N	N	N
128	68	F	Y			Y	N				N			N	N	N	N	N	N	Y	N	N	N	N	N
129	85	M	Y		Y		N				N			N	N	N	N	N	N	N	N	N	N	N	N
130	65	M	N				N				N			N	N	N	N	N	N	N	N	N	N	N	N
131	75	M	Y			Y	N				N			N	N	N	N	N	N	N	N	N	Y	N	N
132	71	M	N				N				N			N	N	N	N	N	N	N	N	N	N	N	N
133	85	M	N				N				N			N	N	N	N	N	N	N	N	N	N	N	N
134	71	F	Y		Y	Y	Y		Y		Y	Y		N	N	N	N	N	Y	N	N	N	Y	Y	N
135	76	F	N				N				N			N	N	N	N	N	N	N	N	N	N	N	N
136	81	F	N				N				N			N	N	N	N	N	N	N	N	N	Y	N	N
137	73	M	N				Y		Y		N			N	N	N	N	N	N	N	N	N	Y	N	N
138	78	M	Y	Y			N				N			N	N	N	N	N	N	N	N	N	N	N	N
139	80	F	N				N				N			N	N	N	N	N	N	Y	N	N	N	N	N
140	74	F	N				N				N			N	N	N	N	N	Y	Y	N	N	Y	N	N
141	69	F	Y	Y			Y	Y			Y	Y		N	N	N	N	N	N	N	N	N	N	N	N
142	78	F	N				N				N			N	N	N	N	N	N	N	N	N	N	N	N
143	79	F	N				Y	Y			N			N	N	N	N	N	N	Y	N	N	N	N	N
144	77	F	Y	Y			N				N			N	N	N	N	N	N	N	N	N	Y	N	N
145	80	M	N				N				N			N	N	N	N	N	N	N	N	N	N	N	N
146	84	M	N				Y		Y		N			N	N	N	N	N	N	N	N	N	N	N	N
147	70	F	Y	Y	Y	Y	N				Y	Y		N	N	N	Y	N	Y	Y	N	N	Y	N	N
148	72	M	N				N				N			N	N	N	N	N	N	N	N	N	N	N	N
149	80	M	N				N				N			N	N	N	N	N	N	N	N	N	N	N	N
150	80	F	N				N				N			N	N	N	N	N	N	Y	N	N	N	N	N

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151	82	M	N				Y	Y			Y	Y		N	N	N	N	N	N	N	N	N	N	N	N
152	68	F	Y	Y			N				N			N	N	N	N	N	N	Y	N	N	Y	N	N
153	75	F	Y		Y		N				N			N	N	N	N	N	Y	Y	N	Y	Y	N	N
154	82	F	N				N				N			N	N	N	N	N	N	Y	N	N	N	N	N
155	90	F	N				Y		Y		N			N	N	N	N	N	N	N	N	N	N	N	Y
156	85	F	N				N				Y	Y		N	N	N	N	N	N	N	N	N	N	N	N
157	75	F	Y		Y		N				N			N	N	N	Y	N	Y	Y	N	N	Y	N	N
158	84	F	Y			Y	Y	Y			N			N	N	N	Y	N	Y	Y	N	N	N	N	Y
159	85	M	N				N				N			N	N	N	N	N	N	N	N	N	N	N	N
160	84	F	N				N				Y	Y		N	N	N	N	N	N	N	N	N	N	N	N
161	83	F	Y	Y			Y	Y			N			Y	N	N	Y	Y	Y	Y	Y	Y	Y	N	N
162	75	F	N				Y	Y	Y		N			N	N	N	Y	N	Y	N	N	N	N	N	N
163	70	F	N				N				N			N	N	N	N	N	N	N	N	N	N	N	N
164	75	F	N				Y	Y			N			N	N	N	N	N	N	Y	N	N	N	N	N
165	56	F	Y	Y			Y	Y			N			Y	Y	Y	Y	Y	N	N	Y	N	Y	N	N
166	83	M	N				Y	Y			Y	Y		N	N	N	N	N	N	Y	N	N	N	N	N
167	83	M	Y	Y			N				Y	Y		N	N	N	N	N	N	N	N	N	N	N	N
168	80	F	N				N				N			N	N	N	N	N	N	N	N	N	N	N	N
169	84	F	N				N				N			N	N	N	N	N	N	Y	N	N	Y	N	N
170	70	M	Y	Y			Y			Y	Y	Y		N	Y	Y	N	N	Y	Y	N	N	Y	N	N
171	67	F	N				N				N			N	N	N	N	N	N	N	N	N	N	N	N
172	75	F	Y		Y	Y	Y	Y	Y		N			N	N	N	Y	N	N	N	N	N	Y	N	N
173	73	M	Y	Y			N				N			N	N	N	N	N	N	N	N	N	N	N	N
174	83	F	Y	Y		Y	Y	Y			N			N	N	Y	N	Y	N	Y	Y	N	Y	N	N

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175	83	F	N				N				Y	Y		N	N	N	N	N	N	N	N	N	N	N
176	77	F	N				N				N			N	N	N	N	N	N	Y	N	N	N	N	N
177	76	F	Y	Y			N				Y	Y		N	Y	Y	N	N	Y	Y	Y	N	Y	N	Y
178	72	F	N				Y	Y			Y	Y		N	N	N	N	N	Y	Y	N	N	Y	N	N
179	70	F	Y		Y		Y		Y		Y	Y		N	N	N	N	N	Y	N	N	N	Y	N	Y
180	69	F	Y			Y	N				Y	Y		N	N	N	N	N	N	N	N	N	N	N	N
181	52	F	N				N				N			N	N	N	N	N	N	Y	N	N	N	N	N
182	73	F	Y	Y			N				Y	Y		N	N	N	N	N	N	N	N	N	N	N	N
183	84	F	N				N				N			N	N	N	N	N	N	N	N	N	N	N	N
184	74	F	N				N				N			N	N	N	N	Y	N	N	Y	N	N	N	N
185	72	M	Y		Y		Y	Y			N			N	N	N	Y	N	Y	Y	N	Y	Y	N	N
186	85	F	N				Y	Y			N			N	N	N	N	Y	N	N	N	Y	Y	N	N
187	65	M	N				Y			Y	Y	Y		N	N	N	Y	N	Y	Y	N	N	Y	N	N
188	80	F	Y		Y		N				N			N	N	N	Y	N	Y	Y	N	N	Y	N	N
189	74	F	N				Y	Y			N			N	N	N	N	N	N	N	N	N	N	N	N
190	77	F	N				Y		Y		Y	Y		N	N	N	N	N	Y	Y	N	N	N	N	N
191	83	F	N				N				N			N	N	N	N	N	N	N	N	N	N	N	N
192	82	F	N				Y		Y		N			N	N	N	N	N	N	N	N	N	N	N	N
193	79	F	N				N				N			N	N	N	N	N	N	N	N	N	N	N	N
194	76	F	N				N				N			N	N	N	N	N	N	N	N	N	N	N	N
195	61	F	N				Y	Y			Y	Y		N	N	N	Y	N	Y	Y	N	Y	Y	N	N
196	81	F	Y	Y			Y	Y			Y		Y	N	N	N	N	N	N	N	N	N	Y	N	N
197	79	F	N				N				N			N	N	N	N	N	N	Y	Y	N	Y	N	N
198	67	M	N				N				N			N	N	N	N	N	N	N	N	N	N	N	N
199	85	F	N				Y			Y	N			N	N	N	N	N	N	N	N	N	N	N	N
200	79	F	N				Y	Y			N			N	N	N	Y	N	N	N	N	N	Y	N	N

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