Exploring and Examining Antidepressant Prescribing and Doses used in Primary Care, in Scotland, to Treat Depression

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Publications

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Abstract

Background

Antidepressant prescribing continues to rise. Selective serotonin reuptake inhibitor (SSRI) use, increased long-term prescribing, and higher doses are contributing to current growth. The majority of antidepressants are prescribed to treat depression.

Aim

To explore and examine the use of SSRI doses and dose-response effects for the treatment of depression, for adults, in primary care.

Method

An inter-related three study approach was used. A cross-sectional quantitative analysis exploring patient-level factors associated with prescribed daily doses of SSRIs. A qualitative interview study exploring what influences GPs' use of specific antidepressants and doses. Lastly, a systematic literature review of reviews examining SSRI dose response-effects for efficacy, acceptability and tolerability for acute phase (≤12 weeks) treatment of depression.

Results

The quantitative analysis found that higher SSRI doses were significantly associated with, in descending order of magnitude, individual practice attended, being prescribed the same SSRI for ≥2 years and living in a more deprived area.

GPs' treatment of depression involved ethical and professional imperatives of 'doing the right thing' for individuals by striving to achieve the 'right care fit'. Factors influencing prescribing and doses varied over time from first presentation, to initiation and longer-term treatment. Many were unaware that higher SSRI doses lacked greater efficacy, and onset of action occurred within 1-2 weeks; preferring to wait 8-12 weeks before altering treatment. Ongoing pressures to maintain prescribing, few perceived continuation problems and

lack of proactive medication review, all combined to further drive prescribing growth over time.

Forty-two reviews met inclusion criteria. The majority indicated that SSRIs demonstrated ceiling effects for efficacy; standard doses being non-inferior to higher doses. Higher doses were associated with more adverse events.

Conclusion

Although GPs strive ‘to do the right thing’ to help people, better promotion of SSRI dose limitations may help to optimise patient care, reduce prescribing and avoidable ADEs.

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Abbreviations

ADE	Adverse drug effect
ADM	Antidepressant medicine
B-Z	Benzodiazepine and/or z-hypnotic
CCA	Corrected covered area
CHCP	Community Healthcare Partnership
CHI	Community Health Index
CMHT	Community mental health team
COPD	Chronic obstructive pulmonary disease
DDD	Defined daily doses
DSM	Diagnostic and Statistical Manual of Mental Disorders
EMA	European Medicines Agency
FDA	Food and Drug Agency
GPASS	General Practice Administration System Scotland
HEAT	Health improvement, Efficacy, governance, Access to services and Treatment
HSCP	Health and Social Care Partnership
GP	General practitioner
GSK	GlaxoSmithKline
ICD	the International Classification of Diseases
ISD	Information Services Division, Scotland
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
NHSGGC	National Health Service Greater Glasgow and Clyde
NICE	National Institute for Health and Care Excellence
MAOI	Monoamine oxidase inhibitors
MDD	Major depressive disorder
NTI	National Therapeutic Indicators
OCD	Obsessional compulsive disorder
PIS	Prescribing Information System
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
PRISMS	Prescribing and Information System for Scotland
QOF	Quality Outcomes Framework
RAMESES	Realist And MEta-narrative Evidence Syntheses: Evolving Standards

ROBIS	Risk of Bias in Systematic Reviews
SIMD	Scottish Index of Multiple Deprivation
SMC	Scottish Medicines Consortium
SNRI	Serotonin and noradrenaline re-uptake inhibitor
SSRI	Selective serotonin re-uptake inhibitor
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TCA	Tricyclic antidepressant
WHO	World Health Organization

Chapter 1

1. Introduction and thesis overview

1.1 Why antidepressants and primary care?

Antidepressant prescribing and use has grown significantly over the last 50 years.[1-4] A range of factors are known to have contributed to this growth: the introduction of newer antidepressants in the 1970s and 1980s; followed by various treat depression campaigns; changes in public attitudes towards mental health treatment and more recently, increased long-term use.[4-9] This growth in use however has not been without its controversies: whether antidepressants are effective or not for the treatment of depression; the role that the pharmaceutical industry has had in influencing the definition of depressive disorder; reporting bias; missing data in clinical trials; and antidepressant associated self-harms.[10-14] While antidepressants are effective for the treatment of a range of mental and non-mental health conditions the majority are prescribed by general practitioners (GPs) in primary care for the treatment of depression.[15-17]

Previous studies have assessed local, regional and national prescribing patterns and trends using the number of antidepressant prescriptions, as well as patient factors such as demographics, deprivation, diseases and conditions experienced by those populations.[4, 18-20] Others have considered GP and general practice factors related to prescribers and practice populations,[20, 21] as well as exploring peoples' lived experience, and GPs' professional experience regarding antidepressant prescribing, treatment and depression management.[8, 22-25] A few studies have also considered other prescribing trends in relation to antidepressant use such as antibiotics, benzodiazepine and/or z-hypnotic (B-Z) use.[20, 26]

However, as a pharmacist working in general practice, and from my previous regional strategic and large-scale intervention work, I was aware that higher selective serotonin reuptake inhibitor (SSRI) doses were routinely being prescribed to treat depression.[17] This is of concern as SSRIs account for more than half the antidepressant prescriptions issued in Scotland, and the use of

higher SSRI doses may cause more adverse drug effects (ADEs) and avoidable harms without greater efficacy, and may further drive up antidepressant prescribing volumes.[27]

The use of higher SSRI doses for some conditions such as post-traumatic stress disorder or obsessive compulsive disorder (OCD) may be appropriate.[28, 29] For the majority of people however, who receive antidepressants to treat and manage depression, the use of higher doses may be less appropriate and may lead to people needlessly experiencing avoidable ADEs and harms. The prescribing of these higher doses may have resulted from GPs in the past being criticised for prescribing subtherapeutic doses of tricyclic antidepressants (TCAs) by psychiatrists and others.[30] However, there has been little research carried out to understand this trend towards prescribing increased doses of SSRIs. Such that I wanted to explore and understand the use of higher SSRI doses, and the reasons behind GPs prescribing decisions. Therefore, the aim of this PhD thesis and interlinking studies was to explore and examine antidepressant prescribing and doses used in primary care, in Scotland, to treat depression; and to answer the following research questions:

- What patient factors are associated with the prescribed daily dose of SSRIs for the treatment of depression, in adults, in primary care?
- What influences prescribers' use of specific antidepressants and doses for the treatment of depression, in adults, in primary care?
- Are higher SSRI doses more effective than lower doses for the treatment of depression, in adults, in primary care?

It was considered necessary to use multiple-methods to address the overarching aim to explore and examine antidepressant prescribing and SSRI doses used for the treatment of depression in primary care.

1.2 Thesis overview

Chapter 2 presents a historical narrative review outlining the changes in psychiatry; the diagnosis of depression; the development of antidepressants, their use and marketing; as well as societies' attitudes towards antidepressant use since the 1950s. Chapter 3 will then outline how antidepressant

prescribing is measured, and present and summarise factors which are known to influence antidepressant prescribing, as well as outlining the limitation of previous studies within and outwith Scotland.

Chapter 4 presents the overarching methodological rationale and ethical considerations for the sequence of interlinking studies in this thesis. It is known that a range of factors may or may not influence the identification and treatment of depression, with or without the prescribing of an antidepressant. It was therefore considered necessary to use three different methodologies to address each research question sequentially. Firstly, a quantitative cross-sectional study involving a regression analysis to explore and assess the impact of patient-level factors which may or may not be associated with the use of higher SSRI doses for the treatment of depression. Secondly, a qualitative interview study that explores and captures GPs' experiences and rationale for prescribing higher antidepressant doses, and draws on their insights and perspectives on the findings of the regression analysis. Thirdly a systematic literature review of reviews and narrative synthesis that re-assesses the broader published literature examining SSRI dose-response effects in relation to the treatment of depression, in adults.

Chapters 5 to 7, present the background, methods, results and considers the strengths, limitations and findings within the context of current and evolving literature for the logistic regression analysis, semi-structured GP interview study, and the systematic review of reviews respectively. Finally, chapter 8 summarises the main findings of this thesis and considers the strengths and limitations of the thesis, and the implications for practice, policy, education and future research. Lastly, the chapter will reflect on the potential and actual impact of this thesis to furthering the understanding of antidepressant prescribing and doses used for the treatment of depression for adults in primary care

Chapter 2

2. Antidepressant development: a historical narrative review

Antidepressants have grown to become one of the most commonly prescribed drugs in the world.[2, 3, 31, 32] In recent times this has resulted in 13% of the population over 12 years old being prescribed an antidepressant between 2011 and 2014 in the US, and 17% of the population of England and Scotland receiving one or more antidepressant prescription in 2018/19[i].[27, 33-35]

While it has taken seven decades to get to this point, there are a number of key factors which have contributed to the rise of antidepressant prescribing. Firstly, psychiatry and depression, then secondly the discovery of pharmacological compounds with mood elevating effects in the 1950s that became known as the antidepressants. Further development of antidepressants through the decades was fuelled by the theory that antidepressants' catecholamines effects provided their efficacy, and that a lack of these neurotransmitters caused depression.

Thirdly, the rise of biological psychiatry and the greater standardisation of psychiatric diagnoses within diagnostic manuals by 1980. The advent of the SSRIs in the 1980s and the UK wide Defeat Depression Campaign of the 1990s. All of which meant that it became easier to identify, categorise and treat clinical depression. Globally, depression is now identified and consistently ranked as one of the leading causes of years lived with disability for more than a generation.[36-38] By 2004 depression was estimated to be the leading cause of burden of disease in high-income and middle income countries, and third major cause in low-income countries. It is now estimated to be the number one leading cause of burden of disease worldwide by 2030.[37]

Fourthly, the expansion of antidepressant prescribing to treat non-depressive disorders and non-psychiatric conditions, has also contributed to the growth in use. Finally, the 2000s saw changes in public and media attitudes to depression and mental health, as well as an increase in long-term prescribing

[i]Scotland 2018/19, 936,000 people received ≥1 antidepressant prescription, and the population of Scotland was 5,438,100.[27, 32]

and the use of higher licensed[ii] doses for the treatment of depression in primary care.

To examine antidepressants further it is necessary to first consider the practice of psychiatry and the concept of depression prior to the emergence of antidepressants.

2.1 Psychiatry and depression

Prior to the mid-19th century 'depression' was generally referred to as melancholia. Melancholia represented a range of psychiatric disorders and states of mind such as psychoses, anxiety, paranoia, delusions, and normal emotions such as worry, fear and sadness and even included epilepsy.[39] In the late 19th century however, melancholia was defined by psychodynamic psychiatrists as a range of vegetative symptoms, delusions, and hallucinations.[40] This differs from current clinical practice where these symptoms would be key features of a psychotic illness which may be associated with schizophrenia, bipolar illness or severe depression.

The psychodynamic psychiatrists sought to understand psychological disturbances using analytical therapies that explored the deep recesses of each individual's biography, as repressed intra-psychic experiences were considered to have caused the disturbance. Standardisation of diagnosis was impossible because individual biographical context varied from person to person, and the same symptom(s) could indicate different disorders or the same disorders could present itself through different symptoms, [41] thus creating a high level of diagnostic diversity. The analyst tended to treat the psychological disturbances using non-specific methods of psychotherapy, and while the use of drugs was generally discouraged, drugs were often used.[41]

[ii] Licensed use, refers to conditions and disorders that a medicine; including the dose and preparation(s), has been approved for use by regulating authorities e.g. Medicines and Healthcare products Regulatory Agency (MHRA) in the UK, European Medicines Agency (EMA) for the European Union, Food and Drug Agency (FDA) in the USA, etc.

The early 20th century however, saw greater international standardisation of definitions for diseases and causes of death in order to meet the statistical needs of a range of organisations such as health insurers, hospitals, public health bodies.[42, 43] In 1900, The Health Organization of the League of Nations developed the International Classification of Causes of Death to allow comparisons across countries and societies, and across time. Over the years the International Classification of Causes of Death became the International Classification of Diseases (ICD) and included illnesses that did not necessarily cause death. Standards for psychiatric disorders were included in the sixth revision (ICD-6) in 1948.[44]

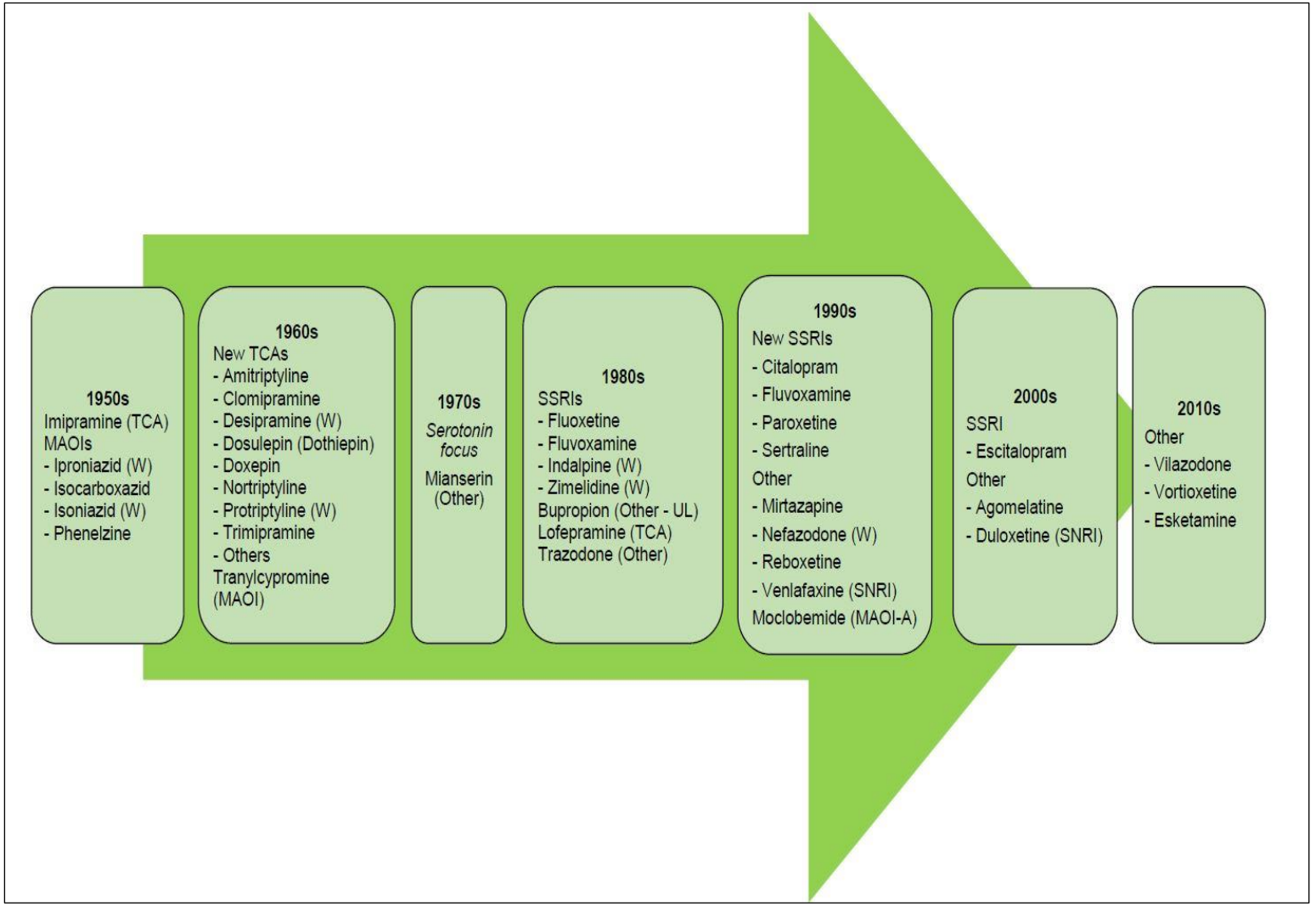
In 1952, the American Psychiatric Association produced their own version of the standards as the Diagnostic and Statistical Manual of Mental Disorders first edition (DSM-I). In line with psychodynamic theory of the time depression was viewed as a psychotic disorder which was chronic and severe in nature with gross misinterpretations of reality, delusions, hallucinations and vegetative states which more typified inpatients. Yet, psychodynamic psychiatrists considered that anxiety was the central psychoneurotic condition, underlying depression and other conditions, and that, *'The chief characteristic of these disorders is 'anxiety' which may be directly felt and expressed or which may be unconsciously and automatically controlled by the utilization of various psychological defense mechanisms.'*.[41]

Despite the attempts at standardisation, a high level of diagnostic diversity and variance continued on both sides of the Atlantic. So much, so that this led some to comment that *'the profession was unable to define even the most basic conditions'* or provide standardised treatments for specific conditions, such as depression.[41, 45, 46] However, the concept of depression and its management gradually changed between 1950 and 1980 with the advent of antidepressants, the catecholamine theory, the rise of biological psychiatry and greater diagnostic standardisation.

2.2 Antidepressants: the early years, 1950s to 1970s

The first pharmacological agents to be called ‘antidepressants’ were identified in the 1950s. Since then, a range of antidepressants have emerged (Figure 1). Prior to this, depression was treated with a range of remedies, medicaments and therapies from purgatives and laxatives, to opioids and then stimulants such as amphetamine, as well as electroconvulsive therapy.[39, 47, 48] Shortly after the war Charpentier and colleagues at Rhône Poulenc in France synthesised and tested a series of phenothiazine amines that were found to have antihistamine effects; the most potent of which was promethazine.[49] Promethazine was also shown to have sedative and anti-nausea central nervous system effects, all of which made it a therapeutic and marketing success.

Figure 1. Antidepressant development and availability by decade



MAOI: monoamine oxidase inhibitor. SNRI: serotonin and noradrenaline re-uptake inhibitor. SSRI: selective serotonin re-uptake inhibitor. TCA: tricyclic antidepressant. UL: unlicensed in UK. W: withdrawn in UK. Other: antidepressants that are not classed as MAOI, SSRI or TCA. Note: Dates of drug availability vary by date of licencing in different countries e.g., clomipramine late 1960s in US, and 1970 in the UK.

Promethazine's success led to the synthesis of more phenothiazine amines for their possible central nervous system effects and resulted in promazine and chlorpromazine being identified. Chlorpromazine demonstrated a range of effects: antiemetic, hypotension, changes in cardiac rhythm, antimuscarinic effects, and sedation, it was initially used in combination with barbiturates to potentiate their sedating effects for 'sleep cures' for the treatment of schizophrenia. Chlorpromazine was then tested as monotherapy for schizophrenia and produced 'spectacular' effects and became the first antipsychotic.[49, 50] Chlorpromazine's therapeutic and commercial success then led to significant investment in synthesising and developing 'me-too' phenothiazine amine derivatives and resulted in the development of imipramine (the first TCA) in 1951 as an antipsychotic.[49]

Dr Roland Kuhn, a Swiss psychiatrist, was looking for an alternative antipsychotic, as his hospital no longer received the *'ostentatiously expensive'* chlorpromazine for testing.[51] Kuhn approached Geigy Pharmaceuticals for the opportunity to test new compounds, and was given imipramine. He started testing it in patients, and within three years had treated more than 500 patients with a range of psychiatric conditions.[52] Although imipramine was considered less effective for the treatment of schizophrenia, remarkable improvements were seen in his patients with endogenous depression that exhibited mental and motor retardation, and only caused minor adverse effects.[49, 52, 53] However, Kuhn also reported that a homosexual man's '*desires became strikingly less prominent during treatment'*, another man was cured of impotence, and patients with chronic depression for years were cured within two to three days of starting imipramine.[52]

At the same time Hoffman-La Roche in the US were synthesising hydralazine derivatives and produced iproniazid in 1951. As tuberculosis was a major public health issue at this time it was routine practice for pharmaceutical companies to test new compounds against tuberculosis bacteria and iproniazid was found to have effective antituberculosis properties. Within a few weeks of being synthesised it was being used to treat patients in early 1952.[54] Soon clinicians started to observe that patients receiving the new drug were experiencing: insomnia, anxiety, agitation, euphoria and/or subexcitation, so

much so that the newspapers described these as wonder drugs as patients were *'dancing in the halls tho' there were holes in their lungs*'.[54, 55] At the time these adverse effects nearly led to iproniazid's withdrawal from the market, however it remained as a treatment for tuberculosis as it was more effective than isoniazid for bone and joint disease.[54]

Attempts were then made to use the euphoric adverse effects therapeutically in a small select group (n=20) of debilitated, fatigued and exhausted patients with rheumatoid arthritis and in people with a range of mental illnesses.[55] Twelve of the patients experienced a feeling of wellbeing, increased energy and appetite, and a reduction in sleep requirements, and were reported to have commented: *"I have not felt so good in so many years"; "I still cannot believe how few pills can make such a difference";* and *"I cannot sleep now but I do not mind being awake*". Unfortunately, the study failed to report on the other 8 patients. A larger study (n=87) of iproniazid use in patients with melancholia, indicated that 70% of patients achieved good to excellent remission rates, and a 50-70% reduction in the need for electroconvulsive therapy, with the main adverse effects being weight gain and hypotension.[56]

Salzer and Laurie tested isoniazid in patients (n=40) with mixed depressive states with some positive effects being seen within one to three weeks, and 70% of patients responding after 3 (range 1 to 6) months of treatment.[57] Unlike the other studies they were clearer about exclusion criteria, doses used and study method, as well as study and drug limitations. However, as with other early studies, there was a lack of clarity on which patients received treatment as inpatients or outpatients, but it appears that some or all of the participants in the two later studies were outpatients.[52, 55-57] More importantly however, they also highlighted some of the challenges of interpreting the results due to uncontrollable variables, placebo effects, spontaneous remission and exacerbations, and the effects of concomitant psychotherapy, all of which remain as challenges within current research and clinical practice to this day.

2.2.1 Catecholamine theory

The exact mechanism for antidepressants' effects in depression in the 1950s was unclear, and still remains so. However, iproniazid and isoniazid were known to inhibit monoamine synthesis in the tuberculosis causing Mycobacterium bacteria. It was demonstrated that iproniazid had monoamine oxidase inhibitor (MAOI) effects in humans by the end of 1952, and led to this term being used to categorise this group of antidepressants.[53, 54]

The MAOI effects were shown to be irreversible for both MAO-A and -B, therefore blocking the metabolic degradation of noradrenaline, dopamine and serotonin (5-hyrdroxytryptamine) and increasing the levels of these catecholamines both within and outwith the central nervous system. Iproniazid was withdrawn from the market in 1961 as it caused hepatotoxicity.[53] Another significant problem was sudden life-threatening hypertensive crisis due to interactions with tyramine rich foods, such as mature cheese (e.g. parmesan), salami, beer, red wine, which limited their use. Tyramine is a catecholamine precursor that when ingested by people receiving MAOIs leads to a sudden surge in noradrenaline and adrenaline production which can cause a sudden increase in blood pressure causing nausea, vomiting, migraine and ultimately death.[53, 58]

In 1965 it was postulated that imipramine had non-MAOI effects on catecholamines. The urinary excretion of vanillylmandelic acid, a noradrenaline metabolite, was reduced in patients taking imipramine which may have led to increased intracellular noradrenaline relieving depressive symptoms. As MAOIs and imipramine both led to the elevation of noradrenaline, adrenaline and dopamine, and reserpine depleted catecholamines and caused depressive like symptoms, it was therefore theorised that depression was caused by low levels of catecholamines.[59, 60] However, Schildkraut et al.[59] were very clear in acknowledging that this was just a theory, and could not be confirmed or refuted. Yet the 'catecholamine hypothesis' became widely accepted as the main mechanism of action for antidepressants, and cause of depressive illness due to a 'chemical imbalance' and 'chemical deficit'.[59-61]

2.2.2 The rise of the tricyclic antidepressants

The 1960s saw the synthesis of new TCAs, starting with amitriptyline, Figure 1. The demethylation of amitriptyline and imipramine produced desipramine and nortriptyline respectively; both of which are also active metabolites of their parent compounds when taken by humans.[49] But there were more TCAs to come with dosulepin (dothiepin), doxepin, trimipramine and others[iii]. It was hoped that these new compounds would be more effective, have a faster speed of effect, with less ADEs to improve tolerance and concordance.[62] While there were attempts to reduce ADEs with each new compound, the adverse effects of TCAs were still not as severe as sudden life-threatening hypertensive crisis or liver damage caused by MAOIs, therefore TCAs rose to dominate the antidepressant market by the early 1960s.

However, it later emerged that TCA overdoses were associated with higher fatality rates than MAOIs, with amitriptyline and dosulepin demonstrating a higher mortality risk than other TCAs.[63, 64] This was due to their sedating and cardiac QTc[iv] prolonging effects which are associated with ventricular tachycardia and sudden cardiac death.[65] It was not until lofepramine was developed, and came to the market in the 1980s, that there was a TCA that provided antidepressant effects with less sedation and adverse cardiac effects. As a result there have been significantly fewer lofepramine associated fatalities, and lofepramine remains the preferred option when a TCA is indicated for the treatment of depression.[63, 64, 66, 67]

Clomipramine was developed by Ciba-Geigy in the late 1960s. Unlike the other TCAs its antidepressant effects are predominantly due to serotonin transport re-uptake inhibition.[68] However, due to Ciba-Geigy owning imipramine and amitriptyline, and clomipramine not being licensed for depression by the US Food and Drug Agency (FDA), it was marketed as an effective treatment for OCD.[69] Nonetheless, there was great interest in serotonin's role in depression

[iii] There are many more: butriptyline, opipramol, maprotiline etc. Figure 1 lists the most common ones for the UK.

[iv] QT interval on an electrocardiogram describes the manifestation of ventricular depolarization and repolarization. The QT interval is influenced by heart rate therefore the QT interval should be measured for rate correction allowing the calculation of the corrected QT interval (QTc). Bazett's formula is considered the gold standard for QTc calculation.[63]

as some thought that noradrenaline was responsible for the *'psycho-energetic and motor stimulating effects of antidepressants, but not for their mood-elevating actions'*.[70] Therefore by intensifying the effects of non-noradrenaline neurotransmitters, such as serotonin, it was theorised that it may be possible to improve a patient's mood without the motor stimulating effects. Investigating and pursuing pharmacological methods of increasing serotonin appeared to be a rational option for developing new antidepressants, and ultimately led to the development of the SSRIs in the 1970s and 1980s.[70, 71]

2.2.3 Concern with tricyclic antidepressants

In the late 1960s, GPs were being encouraged to treat depression, however concerns and questions started to be raised regarding the large increases in antidepressant and psychotropic prescribing in the UK by GPs.[72-74] This led to the Department of Health and Social Security to sponsor Dr Peter Parish to research and explore psychotropic prescribing in general practice. It was unclear if the Department of Health and Social Security's concerns and motivations were purely financial or not, and even though data were available and emerging for TCA related overdoses and deaths, the study only considered the role of barbiturates and benzodiazepines in overdose.[1, 64] However, the study's findings highlighted factors in general practice that were influencing prescribing as well as raising questions regarding the influence of drug companies on GP prescribing of antidepressants.

Parish called for continuing professional development and education related to mental health; possibly in part to counter balance the influences of the pharmaceutical companies.[1]

'Responsible and appropriate prescribing can only be promoted by a system of continuous therapeutic education.' (Part 7, page 70).[1]

'Recognized efficacy must dictate the use of most drugs; however, evaluation of a drug's efficacy in general practice is often subjective so that no matter how objective the original clinical assessment of a particular drug, when it is launched into general practice, it succeeds or fails on value judgements strengthened by the various influences involved in drug promotion. It is therefore reasonable to hypothesize that sales promotion exercises the greatest

influence upon general practitioners to prescribe a particular drug. The drug companies are the main source of therapeutic information and are responsible for the diffusion of their information to the prescribing doctor.' (Part 7, page 69).[1]

However, Parish and others recognised the difference between trial settings and clinical practice, and highlighted the challenges of identifying and appropriately diagnosing depression and other psychiatric disorders in general practice, specialist settings and the psychiatric profession as a whole (see Section 2.3).[1, 45, 46]

'There is much confusion however in recognizing and defining anxiety and depression; further, the number of products launched onto the market for the treatment of these disorders is equally confusing.' (Part 7, page 69).[1]

'The overall degree of psychopathology rated for this patient is significantly different (at the .001 level) between the British (who rate low) and the American psychiatrists (who rate high).' (page 238).[46]

2.3 Biological psychiatry, diagnostic criteria and greater standardisation

The rise of biological psychiatry in the 1960s and 1970s, at the demise of psychodynamic psychiatry, was mainly driven by the explosion in psychopharmacological treatment options and the need for greater standardisation of diagnosis and disorders.

The first 70 years of the 20th century experienced an explosion in psychopharmacology with the development of amphetamines, barbiturates, antipsychotics, antidepressants and benzodiazepines, etc. that relieved a range of symptoms and conditions from anxiety to psychosis.[47, 49, 50, 75, 76] The efficacy of these new therapeutic entities drove psychiatry and neuropsychiatrists to explore, rationalise and hypothesize about their biological effects, the causes of mental illness, and develop biomedical models of illness.[44, 59, 60, 77, 78]

At this time however, there were questions and tensions regarding the legitimacy of psychiatry as a profession on both sides of the Atlantic. In part this was due to the psychodynamic psychiatry approach that resulted in diagnostic variability, a lack of reliability and continuity, and led some to comment that, *'the profession was unable to define even the most basic conditions'.*[41, 45, 46] It therefore became harder to justify to governments, health insurers and other funders that psychiatrists were treating specific diseases and not tenuous concepts of 'displacement' or 'conversion'. This further weakened psychodynamic psychiatry's credibility and promoted biological psychiatry with their standard biomedical models of illness, diagnostic criteria, standardised terminology and treatments.[41, 43, 44, 77, 78] By 1980 biological psychiatry was the prevailing school of thought that influenced the development of ICD-9 (1979) and DSM-III (1980). This significantly changed the clinical landscape for psychiatry, standardising diagnostic criteria, treatment of mental illness, research and policy in Westernised societies.[12, 40]

To qualify as having major depressive disorder the DSM-III required that patients had one or more core signs and/or symptoms: dysphoric mood or a loss of interest or pleasure in usual activities, and that four or more of the following key signs and/or symptoms were present: 1) poor appetite or significant change in weight, 2) insomnia or hypersomnia, 3) psychomotor agitation or retardation, 4) decreased sexual drive, 5) fatigue or loss of energy, 7) feelings of worthlessness, self-reproach, or excessive or inappropriate guilt, 8) diminished ability to think or concentrate or indecisiveness, 9) recurrent thoughts of death or suicidal ideation or suicide attempt, for two weeks or more.[40] It was also considered that the more symptoms people exhibited, the more severe their depression was, however they were limited in quantifying the severity of depression.

Whilst efforts were being made to standardise and categorise diagnoses, depression rating and screening scales were also being developed and validated e.g. the Hamilton Depression Rating Scale (HAM-D_{17}) in 1960 and Montgomery-Åsberg Depression Rating Scale (MADRS) in 1979, as well as the Hospital Anxiety and Depression Scale (HADS) in 1983.[79-82] Although these rating scales were primarily developed to assess the change in symptoms

associated with antidepressant use, they provided an objective measure of depression severity. But there are challenges to using such rating scales in routine practice due to the time taken to complete, the number of questions and the requirement for semi-structured clinician-rated interviews.[83, 84] To overcome this, self-administered rating scales that could be completed by patients were developed e.g. the Public Health Questionnaire, in 1999.[84, 85] Yet, even today a large proportion of clinicians still consider these rating scales to be of limited use and value due to: the time needed to complete them; being seen as an unnecessary intrusion into the consultation; and/or they question the value and validity of the results.[86, 87] Conversely, patients have reported that they find the rating scale useful, and see them as an efficient and structured supplement to medical judgement; providing a tangible measure of their condition.[86-89]

The move in thinking to biological psychiatry enabled depression to be considered as a clearer concept; reducing some of the variation in diagnosis and treatment. So much so that, it is now routinely termed a 'common mental health condition'. This label however, fails to capture the significant personal and societal burden and challenges that depression causes, as it is an often a recurring, debilitating and potentially lethal illness that requires effective management. Despite all of the advances discussed above, significant challenges remain in the diagnosis and treatment of depression.[90, 91]

2.4 The rise of the SSRI-era

Following the development of clomipramine and the serotonin hypothesis of depression, the 1970s and 1980s saw the development of second generation antidepressant compounds that aimed to specifically inhibit serotonin re-uptake.[70, 71] The first SSRI to come to market was zimelidine from Astra-AB in early 1982, but it was withdrawn from use in 1983 as a small number of patients developed Guillain-Barré syndrome with its use.[92, 93] The second was fluoxetine (Prozac) in 1988 which became the number one selling drug in North America by the middle of the 1990s. Fluoxetine's success encouraged other

manufactures to develop and launch their 'me-too' SSRIs: citalopram, fluvoxamine, paroxetine and sertraline.

Unlike the MAOIs and the early TCAs, attempts were made to more rigorously assess the efficacy and adverse effects of SSRIs for treating depression. In line with other medical disciplines the following were used: placebo controlled and active controlled randomised controlled trials; standardised diagnostic criteria according to the DSM-III and subsequent revisions; assessment of illness severity using standardised rating scales; and regular assessment of participants' progress against standard criteria.

SSRIs were shown to be effective for the treatment of depression,[15, 94, 95] and demonstrated an early onset of action within 1-2 weeks, as with other antidepressants.[66, 96-98] Their main therapeutic advantages over MAOIs and TCAs were that they were better tolerated with fewer dropouts and ADEs, had fewer major interactions, and were safer in overdose.[62, 63] Another advantage was that SSRI starting doses were therapeutic doses for the treatment of depression. Unlike TCAs that needed to be titrated to therapeutic doses due to tolerance issues.[99, 100]

2.4.1 Clinical practice and the Defeat Depression Campaign

In response to GPs being seen as under diagnosing and under treating depression, the Royal Colleges of Psychiatrists and General Practitioners designed and ran the Defeat Depression Campaign from 1992 to 1996.[9, 30, 99, 101] The campaign aimed to educate GPs to better recognize and manage depression in primary care. At the same time significant efforts were being made across all areas of medicine to deliver evidence-based medicine, and improve the continuity of patient care and outcomes. This influenced the inclusion of specific drug treatments in local drug formularies and supported the development of clinical guidelines e.g. British Association of Psychopharmacology guidelines for treating depression with antidepressants, 1993.[102-104]

During this period there was significant growth in SSRI prescribing (Figure 2).[4] This may have been due to a greater move to applying evidence-based medicine, formulary inclusion and guideline development, the licensing of SSRI

for an increasing range of anxiety disorders: OCD, panic disorder, post-traumatic stress disorder.[100, 102, 104-107] At the same time there was a shift in psychiatric practice, that saw the closure of asylums – acute psychiatric hospitals – and an increased provision of care in the community.[108, 109] This move to care in the community however, was unlikely to have had an impact on overall antidepressant prescribing and SSRI use, as the numbers of patients being moved to community were a small proportion of the general population, and antidepressant prescribing had been growing since the mid-1980s (Figure 2 and Figure 3).[4, 27, 72, 110, 111]

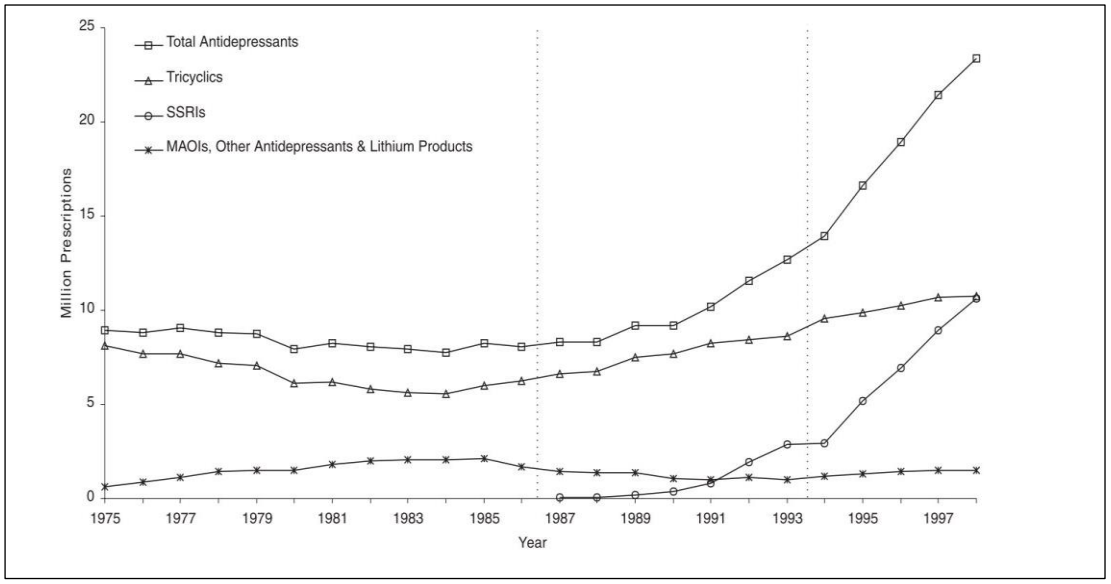


Figure 2. Antidepressant prescribing in the United Kingdom, 1975–1998 (from Middleton et al. 2001)[4]

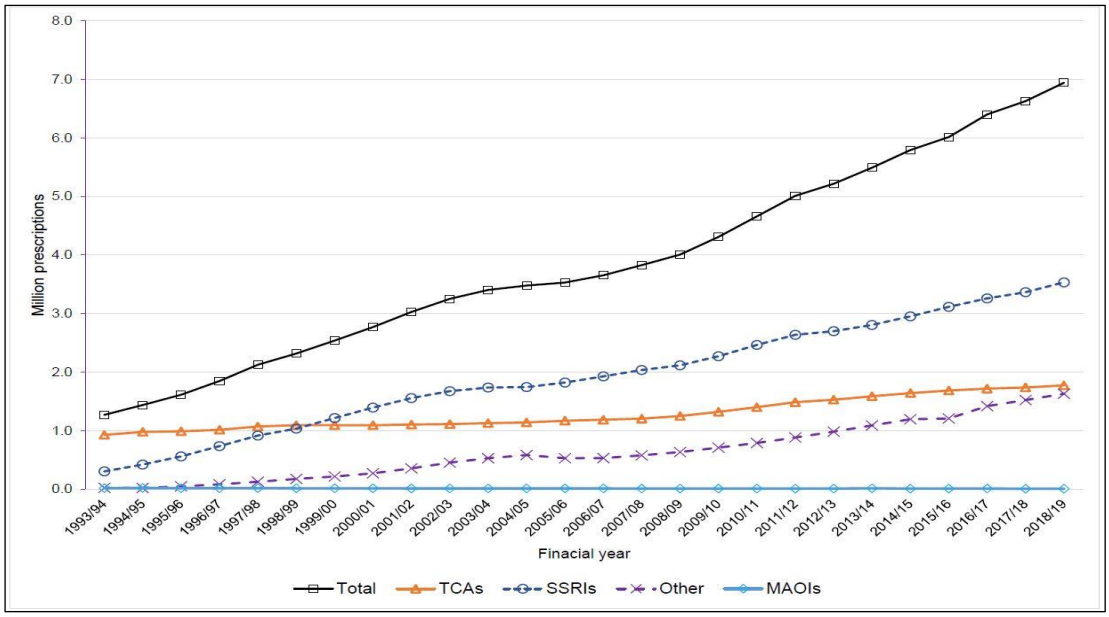


Figure 3. Antidepressant prescriptions numbers, Scotland 1993/1994 to 2018/19

The 1990s also saw the development and promotion of new second generation compounds with multiple neurotransmitter effects, such as: venlafaxine, the first serotonin and noradrenaline re-uptake inhibitor (SNRI) with its dose dependent serotonin, noradrenaline and dopamine effects; mirtazapine, with its serotonin and noradrenaline effects; and moclobemide a MAOI.[112] Unlike previous MAOIs that irreversibly inhibited MAO-A and -B, moclobemide was a reversible inhibitor of MAO-A at therapeutic doses. This meant that MAO-B remained active and available to metabolise tyramine, minimising the risk of hypertensive crisis.[113] While these new entities demonstrated different ADE profiles to previous antidepressants, they were shown to provide similar antidepressant effects.[15, 66, 95]

Another factor which is sometimes considered to have influenced the increase in antidepressants during the 1990s, is the reduction in benzodiazepine use. By the late 1960s benzodiazepines like diazepam (Valium) and nitrazepam (Mogadon) had surplanted the barbiturates (branded as Milltown in the USA, and Equanil in the UK) as the drugs of choice for the treatment of anxiety,

depression and a ‘hotch-potch’ of other conditions; benzodiazepines dominated psychotropic prescribing until[v] the advent of the SSRIs.[1, 41, 50, 114]

Some may claim that SSRIs came to replace benzodiazepines in the UK and elsewhere, yet a combination of factors contributed to their decline. Primarily it became more apparent that benzodiazepines were only effective for the short-term treatment of anxiety and/or insomnia, with resistance developing within 3-14 days of continued use.[75] The increasing concerns about addiction and dependence led the UK Committee on the Safety of Medicines[vi] to publish a series of warnings regarding their safety, between 1980 and 1988.[115, 116] While these warnings contributed to the initial growth in z-hypnotic prescribing in the 1990s, as these were considered as a safer alternative,[117, 118] however it became apparent that z-hypnotics caused similar resistance, addiction and dependence issues.[119-123] Therefore, due to B-Zs limited efficacy and ADE risks, a range of activities have been utilised to minimise inappropriate use and reduce B-Z-related harms from the 1980s to the present.[124-127] Over the years these interventions have contributed to reductions in B-Z use, but may have also contributed to the increased use of alternatives such as sedating antihistamines, antipsychotics and sedating antidepressants e.g. low dose trazodone or mirtazapine,[128-130] as well as a small increase in SSRI prescribing to treat anxiety disorders.

Finally as DSM has evolved and expanded, to now include more than 300 psychiatric disorders, and surreptitiously included grief; a normal life-event that typically runs its course within 2 to 6 months and requires no treatment, as a feature of major depressive disorder in DSM-5 in 2013.[12, 131] Leading pharmaceutical companies targeting normal life stressors and associated anxiety as new mental health disorders.[12, 67, 132, 133] All combine create a demand and overwhelming pressures to prescribe antidepressant and further fuel prescribing growth.

[v] Up to 1 in 8 adults received a benzodiazepine in the UK in the 1970s.[112]
[vi] Fore runner to the MHRA, the licensing body for the UK.

2.4.2 SSRI 'off-license' use, controversies and concerns

'Off-license' use, or 'off-label' use is where a medicine is prescribed for use outwith its license, such as simply crushing a tablet, or using medicines where a product license has not been sought. Unlicensed use on the other hand, is where there is a lack of evidence for the use of a medicine for the treatment of a specific condition.[100, 134] While some 'off-license' antidepressant use may be appropriate and supported by a large body of evidence, others are not.

For example TCAs have been tested in clinical trials and used 'off-label' to treat neuropathic pain associated with diabetes, back pain, and migraines.[106, 107, 135] There is a larger body of evidence to support TCAs use for the management of neuropathic pain from the mid-1990s onwards.[16] However, TCAs were off-patent at the time of these studies, available as cheap generic medicines, that no pharmaceutical companies were going to invest in to gain marketing authorisations and licenses for. There was no money in treating these specific conditions, and they would not recoup the cost of licensing.

Conversely, some pharmaceutical companies such a GlaxoSmithKline (GSK) actively promoted their antidepressant paroxetine (Paxil in the US, and Seroxat in the UK) in the US for the unlicensed treatment of depression in children. This led to GSK receiving a $2 million fine in the US in 2004.[136, 137] The controversy does not stop there, GSK suppressed negative study findings that demonstrated paroxetine was ineffective in treating depression in children, and reportedly considered that, *'it would be commercially unacceptable to include a statement that efficacy had not been demonstrated, as this would undermine the profile of paroxetine'.*[138, 139] While this was clearly unethical and put children at risk, the Medicines and Healthcare products Regulatory Agency (MHRA) acknowledged at the time UK law was too weak, *'The legislation in force at the time was not sufficiently strong or comprehensive as to require companies to inform the regulator of safety information when the drug was being used for, or tested outside its licensed indications.'*[140]

More controversially, at the same time it started to emerge that antidepressants were possibly associated with a higher risk of suicidality in children and adolescents, and that led the US and EU regulators to issue safety warnings in

2003/04.[141] However the reduction in antidepressant use, due to the warnings, was associated with an increase in observed suicides.[141] Nonetheless further investigations demonstrated that people under 25 years of age were the highest risk of antidepressant associated suicides, and those over 25 years of age experienced an associated reduction in suicide risk with antidepressant use.[142, 143]

Yet, more controversies emerged regarding the validity of some pharmaceutical company's study findings, that data submitted to the FDA were not easily available to prescribers, researchers and patients, and the selective publication of positive study findings.[13] Although Turner et al. did comment that the publication bias could have been due to *'a failure to submit manuscripts on the part of authors and sponsors [or due to] decisions by journal editors and reviewers not to publish, or both.'*.[13] Lastly, there was the recurring theme that antidepressants were ineffective for the treatment of depression,[10, 144] despite multiple reviews demonstrating their efficacy.[15, 95, 145]

2.4.3 Direct and indirect marketing

Since the development of pharmaceutical products, numerous strategies have been used to influence opinion leaders and target prescribers. One such strategy was the use of international multicentre randomised controlled trials which had a handful of participants at each site. Although such studies could easily be conducted in one site or clinic, in one country or town. These studies were used to capture the interest of the opinion leaders who would prescribe and use the drug(s) in their clinics. This indirectly promoted the drug for inclusion in formularies and guidelines, and increased their use in the wider community. While a full in-depth review of these tactics are outwith the scope of this thesis, there are a few factors that will be considered.

There were a number of key factors which made the marketing of SSRIs a success: 1) DSM-III and ICD-9 standardised classification of depression; 2) the catecholamine theory; 3) the Defeat Depression Campaign in the UK; 4) SSRIs are as effective as MAOIs, TCAs and SNRIs, but better tolerated and safer; 5) inclusion in local and regional formularies, and national guidelines; 6) the swing from benzodiazepines to antidepressants for the treatment of emotional distress

7) direct-to-consumer advertisement in the US; and 8) the professional and lay media.

Diagnostic classifications and the catecholamine theory, as already discussed above, provided the ideal biological models and story on which to define the problem 'depression', the cause of the problem 'a chemical imbalance/deficit' and provide the quick solution, 'an antidepressant'. This simple story was relentlessly marketed by the pharmaceutical companies to prescribers, and picked up by the mass media as non-medical commentators started to report *'90% cure rates'*, where others saw antidepressants as social accoutrements.[146, 147] In the UK this was coupled with the Royal Colleges of General Practice and Psychiatry Defeat Depression campaign, and guidelines that promoted the diagnosis and use of antidepressants as part of routine treatment in general practice. These encouraged a move away from inappropriate benzodiazepine use, and influenced a range of specialists and generalists working in primary and secondary care settings.[1, 41, 104, 148, 149]

Prescribers are not immune to the effects of drug companies and the mass media. It is known that those who have less industry contact are more likely to prescribe in line with guidelines and formularies, have higher rates of generic prescribing and are more cost-effective prescribers.[1, 148, 150, 151] The professional media however are full of advertisements with the majority of clinical journals relying on the revenue for viability. While some advertisers make the claim that these adverts and articles provide prescribers with valuable information, it has been well documented that numerous advertising claims are inaccurate or unfounded; not adhering to the pharmaceutical industry's own code of conduct or that of national and international legislative administrative and licensing bodies such as the FDA in the US, MHRA for the UK or the European Medicines Agency (EMA) for the European Union.[152, 153] Occasionally some regulatory bodies have fined the companies for deliberately misleading prescribers and the public,[136] or they have avoided prosecution as the law was, '*not sufficiently strong or comprehensive as to require companies to inform the regulator of safety information'*.[140]

In 1997 in the US, the pharmaceutical industry achieved a major coup, and were sanctioned to advertise prescription drugs directly to the public.[154] Direct-to-consumer advertising allowed the drug companies to circumvent guidelines, formularies and prescribers who may limit drug use, while legitimising product promotion to potential patients through the mass media as health education, awareness and promotion. These advertisements did not always match the clinical evidence base, and often disadvantaged patients by rarely highlighting non-drug alternatives or self-management options.[61, 154, 155] Unsurprisingly perhaps, evidence is lacking for direct-to-consumer-advertising improving patient disease awareness or education. However, patient requests for medications does affect physicians prescribing choice, and may play a role in the over prescribing and use of antidepressants.[156, 157]

The 2000s saw the launch of some new therapeutic entities: agomelatine, vilazodone, vortioxetine, the 'me-too' SNRI duloxetine, and a 'new' SSRI escitalopram.[15, 95] Unfortunately, none of these antidepressants were any more effective than those currently available. Escitalopram for instance was not new, but appeared at a time of mass 'evergreening' patent extension strategies by a number of pharmaceutical companies.[158-160] Such strategies involve 1) developing and promoting a 'new and improved formulation' e.g. Zoton capsules to Zoton fastabs, Seroquel tablets to Seroquel XL extended release tablets, etc., etc., 2) promoting an active metabolite of the parent drug e.g. desipramine from amitriptyline, 3) promoting the active isomer of the original drug as a 'new' entity having less ADEs or greater efficacy e.g. cetirizine to levocetirizine, citalopram to escitalopram, etc. All of which provide no greater efficacy or benefits to patients or society, but are significantly more expensive.

Escitalopram is the s-enantiomer[vii] of citalopram and is responsible for citalopram's serotonin effects.[158, 159, 161-163] Advocates of escitalopram used findings from meta-analyses to promote and suggest that escitalopram was more effective and better tolerated than other second generation

[vii] Some drug molecules exist as two mirror image forms known enantiomers. A 50:50 mixture of the two enantiomers is known as a racemic mixture. It is common that one of the enantiomers is responsible for much of the drugs pharmacological effects, while the other may be inactive or even harmful.[157] Such that 2mg of citalopram contains 1mg of S-citalopram and 1mg of R-citalopram.

antidepressants.[15, 164, 165] These meta-analyses did not evaluate dose-response effects and/or consider the fact that comparator antidepressants were not prescribed at comparable doses i.e. higher doses of SSRIs which are known to cause more ADEs and are associated with higher dropout rates; or low doses of SNRIs that do not exert their dual serotonin and noradrenaline effects, making them less effective.[166-168]

While a range of marketing strategies have been used to directly and indirectly target prescribers and patients to use more antidepressants, some of the growth in use may be due to indirect effects of mass media reporting and changes in professional and public attitudes to depression and emotional distress treatment.

2.5 Attitudes to mental illness and treatment

There are wide variations in attitudes and opinions regarding depression and the use antidepressants. For some it can be differences in opinion regarding mental health problems, the concept of depression and stigma.[23, 25, 169] For others it is the use of antidepressants, the medicalisation of society, and peoples' reliance on medicines. Furthermore, for others, there are concerns about pharmaceutical companies' actions and 'bad pharma'.[39, 138, 169-172]

There has been a number of public health campaigns in the UK and elsewhere to improve peoples' awareness of mental health issues and de-stigmatise these conditions.[7, 173] These campaigns have achieved modest effects on peoples' awareness and attitudes to depression, but it is unclear what impact they have had on peoples' health seeking behaviours – going to their GP or counsellor and engaging with treatment.[173] The recent Time to Change campaign in England focused on peoples' attitudes towards mental health problems and was shown to significantly improve peoples' mental health knowledge, reduce stigma, and possibly increase peoples' positive attitudes to seeking professional help.[7]

At the same time UK newspapers, such as the Times and Daily Mail, have demonstrated a two to threefold increase in the number of mental health articles, and an upward trend in depression related articles between 1992 and 2006; from 28% to 37%.[174] There has also been an increasing number of 'good news' stories explaining and exploring depression, or providing advocacy and support, and a reduction in 'bad news' stories that were likely to contribute to mental health stigma.[174]

GPs have also acknowledged that the Defeat Depression campaign had a sustainable positive impact on GPs' attitudes and clinical practice with approximately 40% of respondents indicating that they had made significant changes to their practice.[9, 175] Other GPs acknowledged that they were more attuned to identifying and treating depressive symptoms, due to the campaign. They also believed that patients had a 'simple' perception of depression and some had unrealistic expectations of 'happiness' and quality of life; expecting a 'quick-fix' solution for their problems, which in part lead to medicalisation of unhappiness and further increases in antidepressant prescribing.[8, 170, 176]

In one study, potential patients i.e. people that were not receiving treatment for depression, indicated that while they were sympathetic to people with depression, they were reluctant to seek professional help for themselves due to the stigma associated with mental health problems.[177] If, however, treatment was needed they would prefer counselling to antidepressants; 30% of participants considered antidepressants to be ineffective and 78% considered them to be addictive.[177] In another study patients who had actually received antidepressants for depression describe their depression journey and changes in attitude with time, from 'hitting rock bottom', to seeking help from their GP, their fears of stigmatisation and concerns about antidepressant addiction and ADEs.[23, 25] Many described cautiously starting, stopping, restarting, and experimenting with antidepressants and their effects until they became expert patients by experience and made the decision to continue treatment when they found it helpful. They described a new challenge once they completed a course of treatment; the fear of discontinuing antidepressants and becoming unwell again,[23, 25] which GPs have also acknowledged as one of their fears and one of the major barriers to discontinuing antidepressants.[178, 179]

There are many differing attitudes and opinions regarding antidepressants: from pro-drug enthusiasts, to pragmatists and anti-drug lobbyists.[39, 138, 170-172, 180] The reasons for these positions are wide and varied, sometimes it is due to peoples personal lived experiences in relation to antidepressant benefits and harms. Other times it may be due to the preferred treatment options favouring non-pharmacological options over everything else, or vice a versa; attitudes and opinions may be polarised due to the actions of some pharmaceutical companies, and the potential medicalisation of society. No matter what, antidepressants can and do help some people; offering an option in the treatment of moderate to severe depression as one aspect of a complex multifaceted intervention.[66, 67, 181-183]

2.6 The new millennium

The noughties have continued to see a rise in antidepressant prescribing and use internationally. Concerns about the number of people receiving antidepressants in the UK led the Scottish Government, in 2007, to set Health improvement, Efficacy, governance, Access to services and Treatment (HEAT) targets for National Health Service (NHS) Boards in Scotland to: 1) Reduce the annual rate of increase of defined daily dose per capita of antidepressants to zero by 2009/10, and 2) Put in place the required support framework to achieve a 10% reduction in future years.[184] At the same time the Government in England introduced the Improving Access to Psychological Therapies programme in 2008 to try and reduce antidepressant prescribing, and subsequently the Scottish Government developed the access to psychological therapies HEAT targets in 2010.[184, 185] However, in Scotland, the antidepressant HEAT targets were not met, in part due to poor target design, limited knowledge about antidepressant prescribing and use, as well as limited action within some health boards.[184, 186] Despite greater access to psychological services in Scotland and England there has been no, or little, impact on antidepressant use and growth.[185, 187, 188] In part this may be due to current depression guidelines advising that antidepressants and psychological therapies are used in combination to treat moderate to severe depression.[66, 67]

Prescribing has also continued to rise, in the absence of a clear increase in incidence or prevalence of depression in the UK.[5, 189] Some may argue that this is due to the increasing range of mental and non-mental health conditions that antidepressants are used to treat, such as anxiety disorders, menopausal flushing, neuropathic pain, etc.,[16, 106, 107] however the majority (60-85%) of antidepressants continue to be prescribed to treat depression.[17, 31, 190]

Some of this more recent growth has been due to more people receiving antidepressants; now estimated at 5-17% of adults in Europe and USA annually.[27, 33, 35, 191, 192] But some of the growth is due to increased long-term use,[5, 6] with up to 50% of people in the UK now receiving long-term antidepressants for more than 2 years.[5, 17, 33] It is unclear if this is due to greater compliance with clinical guidelines by prescribers, or patients accepting and/or expecting treatment with an antidepressant long-term.[23, 25] It may be due to the fact that some people experience intolerable withdrawal/discontinuation[viii] effects and they are unable to stop their antidepressant.[193-195] While total antidepressant prescriptions have continued to rise there has been some reduction in the prescribing of individual SSRIs, specifically escitalopram and citalopram. This is due to: 1) Cost containment strategies, early to mid-2000s, to minimise escitalopram use as it provided no greater benefits than other SSRIs see Section 2.4.2,[158-160, 163, 196, 197] and 2) The 2011 MHRA warning that there is a dose-response effect with greater QTc prolongation as escitalopram and citalopram doses are increased, and the reduction of the maximum licensed doses.[196, 198]

Other potential explanations for the increase in overall prescribing may be the lack of regular review. It is now known that the frequency of review and number of people being reviewed decreases as the duration of antidepressant treatment increases in general practice.[199, 200] Another factor may be the use of

[viii] The term 'discontinuation symptoms' is used to describe symptoms experienced on stopping medicines that are not drugs of dependence, although there are important semantic differences in the terms 'discontinuation' and 'withdrawal' symptoms – the latter implying addiction, the former does not. While the distinction is important for precise medical terminology, it is irrelevant when it comes to personal experiences and how an individual may describe their signs and symptoms.[311] Therefore for simplicity and clarity withdrawal is used as the standard term throughout this thesis to describe this phenomenon.

higher antidepressant doses,[17, 191, 199, 201] that may influence the overall prescribing volumes, see Section 3.1.[17, 191, 201] While the use of higher antidepressant doses may be appropriate for some patients, with some drugs, it may be inappropriate for others.

2.7 Antidepressant doses for the treatment of depression

As outlined above there are four main classes of antidepressants, all of which are thought to exert their antidepressant effects by influencing neurotransmitters: SSRIs being highly specific for inhibiting serotonin transporter reuptake and increasing pre-synaptic serotonin levels; TCAs having mixed serotonin, noradrenaline, histamine and muscarinic effects that vary between individual TCAs; MOAIs increasing serotonin, noradrenaline and dopamine; and other antidepressants having a range of serotonin, noradrenaline, dopamine, histamine, muscarinic and melatonin effects that also vary between individual drugs.[68]

In recent times there has been an increase in the routine use of higher licensed SSRI doses for the treatment of depression in primary care.[17, 191, 201] While the use of higher licensed doses of TCAs or SNRIs may be appropriate, to provide multiple neurotransmitter effects, the ADE profile has often meant higher doses have not been achieved or tolerated.[166, 202] However, SSRI's have historically been prescribed at therapeutic doses,[30, 99] and the rationale for pursuing similar strategies with SSRI dose increases is unclear.

SSRIs are highly selective for inhibiting serotonin transporter reuptake with low affinity for serotonin, adrenergic, dopaminergic and histamine receptors.[168, 202, 203] Previous studies involving humans have demonstrated that standard doses for a range of SSRIs provide more than 76-85% serotonin transporter occupancy, and demonstrate a hyperbolic relationship between SSRI dose and transporter occupancy, Figure 4 and Table 1.[203-205] Therefore, the rationale for increasing SSRI doses for the treatment of depression is of questionable value and/or benefit to patients, as the serotonin reuptake transporter receptors are already highly occupied and there is little or no space for more drug to act.

Conversely, TCAs and SNRIs demonstrate changes in serotonin, noradrenaline and dopamine effects as doses are increased.[168, 202] Venlafaxine for example exhibits predominantly serotonin effects at doses <150mg per day, with noradrenaline effects becoming significant from 150mg per day, and dopamine reuptake inhibition above 225mg per day.[68] Therefore TCAs and SNRIs demonstrate dose-response effects for efficacy due to their multiple receptor effects with higher doses being more effective where they are tolerated.[166, 168]

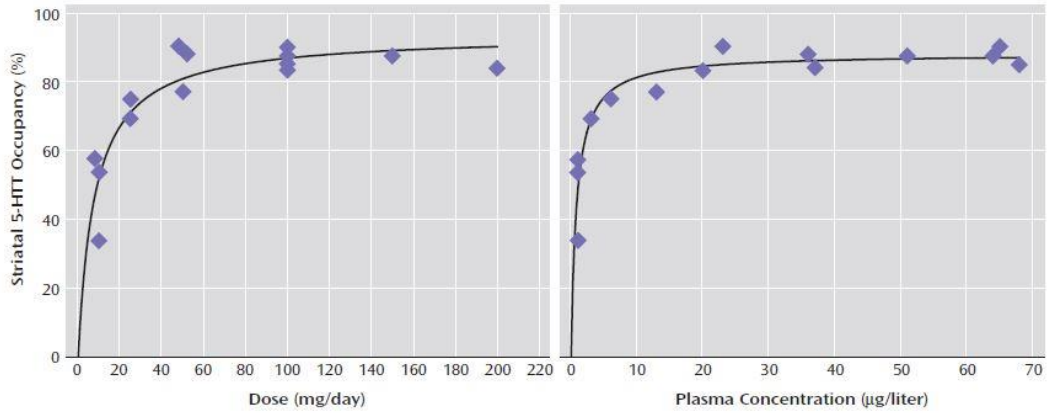


Figure 4. Relationship between striatal serotonin transporter (5-HTT) occupancy and dose and plasma concentration of sertraline in people with depression (n=14) (from Meyer 2004)[203]

Table 1. Antidepressant serotonin transporter occupancy

	Brain region	SERT occupancy (%)†	Daily dose (mg)	Defined daily dose*
Escitalopram	Midbrain	82	10	1
Citalopram	Striatum	81	20	1
Fluoxetine	Striatum	76	20	1
Fluvoxamine	Thalamus	85	50	0.5
Sertraline	Striatum	85	50	1

SERT: serotonin transporter.
† Summarised from Kasper et al. 2009, Meyer 204 and Suhara et al. 2003.[203-205]
*As defined by the World Health Organization.[206]

As previously discussed, traditionally GPs have prescribed subtherapeutic doses of TCAs for the treatment of depression, and have been criticised for doing so by psychiatrists and others.[30, 99] In part this may have been due to a lack of knowledge or patients not tolerating higher TCA doses due to ADEs or even prescribers fear of causing adverse effects.[95, 207, 208] However as with

SNRIs, higher TCA doses can be more effective for treating depression,[166, 209] and while some guidelines highlight the limitations of increasing SSRI doses[66, 210] the majority do not, and promote the general message to increase the dose.[67, 181, 182] Therefore 'push the dose' prescribing has become a routine approach, and while in part this may be due to the doses used in clinical trials and different prescribing cultures i.e. higher SSRI doses more commonly prescribed in North American studies compared with European studies,[211, 212] it may also be in response to patients' expectations of higher doses being more effective.[22]

Chapter 3

3. Prescribing measures and variations

Internationally there are variations in how medicines prescribing is measured. Firstly, this may be due to how patients access their medicines from specialist clinics or their GP, and whether these appointments are covered by insurance policies or require full or part-payment directly from the patient. Secondly, the duration of the prescription whether they are for 28, 56 or 84 days, or longer, and how these prescriptions are dispensed. For example, someone that has received a prescription for 84 days treatment, may receive one dispensing for 84 days or three dispensings at monthly intervals, and while these prescriptions are for the same duration they may be counted differently depending on the healthcare system. Thirdly, data capture can and does vary with the healthcare system and different regional administrations within the same country. This thesis therefore focuses on and uses prescribing data from one health system the NHS in Scotland.

3.1 Measuring prescribing in Scotland

In line with other medicines in the UK the majority of antidepressants are prescribed and paid for via NHS services. The UK NHS is taxpayer funded and devolved in the home nations; the NHS in Scotland is distinct from the other home nations, both in management and policy. NHS services in Scotland are provided via 14 geographical health boards covering a population of 5.3 million people across a land mass of 30,414 square miles, ranging from highly rural to highly urbanised areas, with large variations in socioeconomic deprivation. All NHS patients in Scotland are assigned a Community Health Index (CHI) number that acts as a unique identifier and provides information on sex and date of birth.[213]

The majority of patients in Scotland are registered with one of the 932 general practices. Since the number of general practices has reduced over the years and the population has increased slightly, this has led to an increase in average

practice list size. This is largely driven by practice mergers and a trend towards larger practices with more GPs serving a larger number of patients.[214] There are however a very small minority of patients that may not be currently registered with general practices such as the homeless, tourists and people residing in secure facilities such as prisons or forensic units.

When measuring prescribing in Scotland, there are four different categories of antidepressants which are licensed and prescribed for a variety of mental health and non-mental health conditions:

- **SSRIs** account for the majority of antidepressant prescriptions; 51% to 53% over the last decade.[188] They are used to treat depression, as well as other conditions such as general anxiety disorder, OCD, eating disorders, and menopausal flushes.
- **TCAs** (26% to 31%) are primarily used as the first pharmacological option for the treatment of neuropathic pain e.g. associated with diabetes, back pain or to prevent migraines. They are also used to a lesser extent to treat depression when SSRIs have not worked or patients have treatment resistant depression, and clomipramine can also be used for the treatment of OCD.
- **Other antidepressants** (16% to 24%), are drugs that do not fit any of the other categories: the SNRIs (venlafaxine and duloxetine), mirtazapine, trazodone, reboxetine, flupenthixol, tryptophan, agomelatine and voritoxetine. These are used to treat depression and/or anxiety disorders, with trazodone more commonly being used to treat insomnia, tryptophan for treatment resistant depression and flupentixol for depression with psychotic features.
- **MAOIs** (0.1% to 0.3%) are effective for the treatment of severe depression and may be used where SSRIs, TCAs and other antidepressants have been ineffective, but they are now used infrequently because of their adverse effect profile, possible interactions with other medicines and the need for dietary restrictions.

As already acknowledged, in Scotland the majority of antidepressants are prescribed by GPs in primary care, either as the initiating prescriber or on the

advice of mental health or non-mental health specialists. A small proportion are prescribed by other health care professionals that are non-medical prescribers (e.g. nurses and pharmacists), Out of Hours services, and specialist outpatient services.

Within Scotland, information on all NHS prescriptions dispensed in primary care are captured by National Prescribing Datamarts: Prescribing and Information System for Scotland (PRISMS) and Prescribing Information System (PIS). PRISMS and PIS are web-based applications providing information for all primary care dispensed prescriptions. They can be interrogated to provide national, regional and practice-level prescribing reports with PIS providing access to individual patient-level prescription information.[215, 216] PRISMS and PIS data informs the annual 'Medicines used in Mental Health' report by Information Services Division (ISD) Scotland which provides information on prescribing trends, costs and limited demographic information for groups receiving dispensed prescriptions [link]. The 'Medicines used in Mental Health' report is unique, in that other specialities such as: cardiology, neurology or respiratory do not have similar reports scrutinising their prescribing.[27]

3.1.1 Prescribing measures

There are multiple methods for measuring prescription data, see Figures 5 to 7.[27] As with all measures there are strengths and limitations in their use. Similar methods are used to measure prescribing across the UK, Europe, North America and Australasia however data collection methods can and do differ.[2, 3, 31, 32]

- **Items** – The number of prescription items e.g. one prescription for mirtazapine is one item (Figure 5). This can demonstrate overall trends, but does not take account of the number of days such as 7, 14, 28, 56 or more days, or quantity of medicine on a prescription.

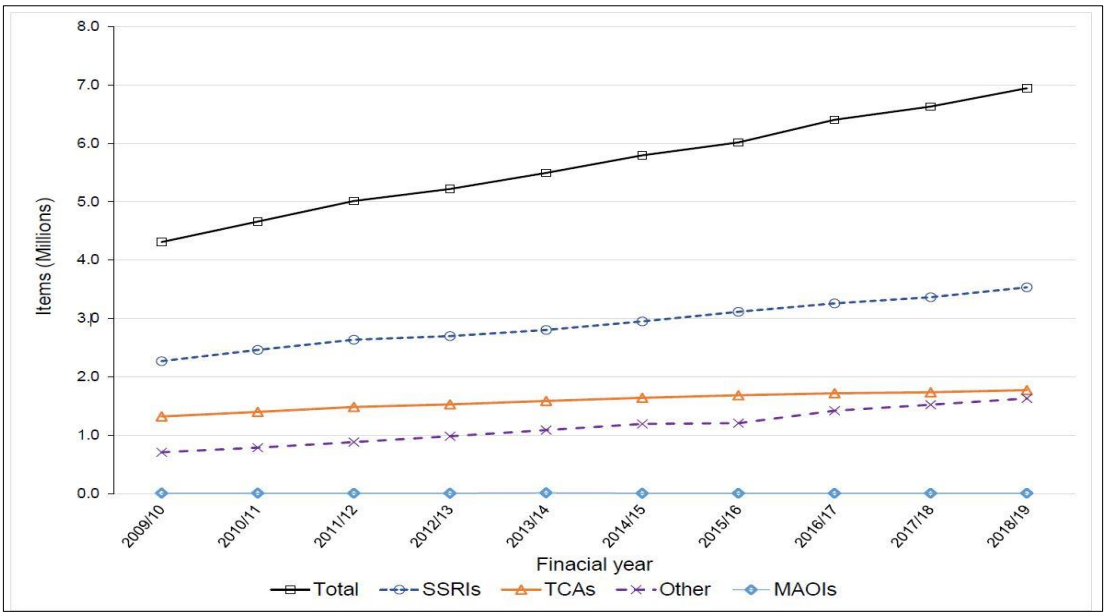


Figure 5. Antidepressant items by financial year, Scotland 09/10 to 18/19 (from ISD 2019)[27]

- **Gross Ingredient Cost** – Provides good financial procurement information, however it is usually necessary to look at data in more detail to identify underlying drivers of changes in cost trends. The costs of antidepressants rose from £32 million in 2009/10 to £42 million in 2018/19.[27] However significant changes in drug and/or preparation costs can have a large impact on the overall costs nationally, some of which may be avoidable e.g. very low volume drugs such as trazodone liquid increased by £7.1million per

annum (a 440% increase from 2013 to 2019), or some TCAs (dosulepin, nortriptyline, trimipramine) from 2013 (Figure 6).[27, 217]

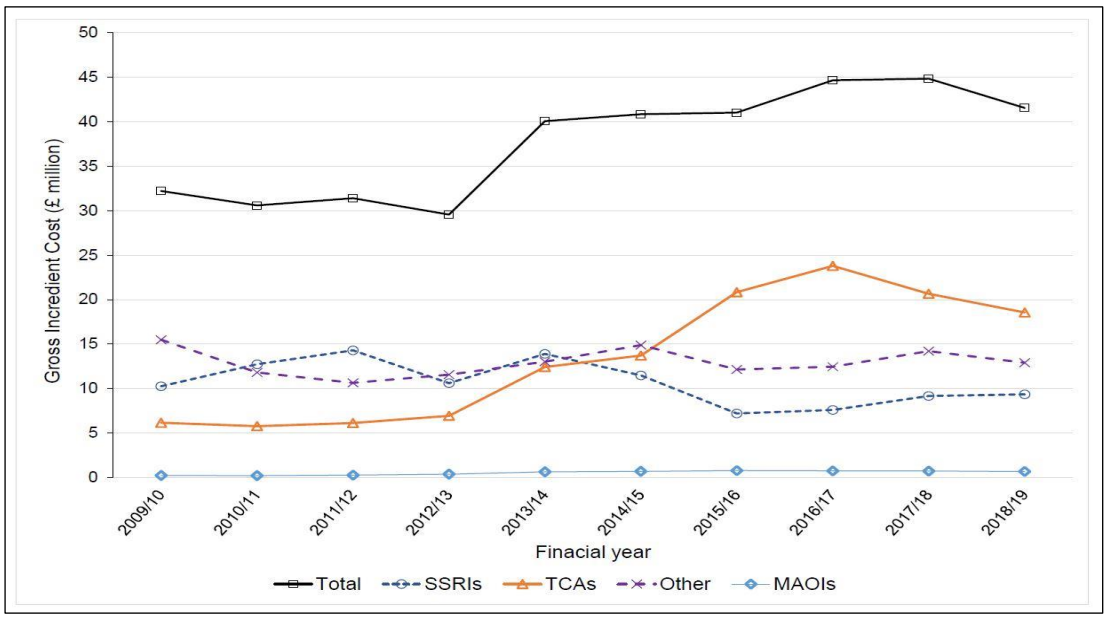


Figure 6. Antidepressant Gross Ingredient Cost (£m) by financial year, Scotland 2009/10 to 2018/19 (from ISD 2019)[27]

- **Time period** – This may over or under inflate prescribing data depending which period is used. Christmas and Easter holidays are periods when people order more prescriptions in advance inflating prescribing volumes during these periods, such that December will be higher than other months and January lower than other months. Using a 12 month time periods, where an individual receives one or more prescriptions does not inform us if the medicines have been continued for 12 months, but may inflate statistics especially where drugs are poorly tolerated. Such variations need to be considered in some studies as it is know that up to 60% of people treated for depression stop their antidepressants early.[218]
- **Patient numbers** – Identification of patient numbers has been enabled since 2010/11 by inclusion of patients CHI number on prescriptions. The CHI number acts as a unique identifier containing details of gender and date of birth allowing limited demographic data to be analysed with prescription data for dispensed medicines. Prescription CHI capture is >95%.[216] However, it does not provide information regarding the medicine's indication

or whether the medicine was actually taken, and may over- or under-inflate use if used with inappropriate measures e.g. number of people receiving one or more prescriptions in a 12 month period.

- **Defined daily doses (DDD)** – DDDs are units of measurement defined by the World Health Organization as 'the assumed average maintenance dose per day for a drug used for its main indication in adults'. DDDs do not necessarily reflect the recommended or prescribed daily dose but allow a convenient method to compare prescribing volumes between organisations such as health boards and general practices.[206] Therefore, they are usually quoted as a rate e.g. 10 DDDs/1000 population to enable comparison (Figure 7). Scotland's population information is taken from the National Record of Scotland and is based on the population aged 15 and over.[27] Unfortunately, the DDDs cannot account for different doses used for different conditions. For instance, therapeutic doses of a TCA may equal 2 DDDs for the treatment of depression, whereas it would be 0.2 DDDs for treating neuropathic pain. However, SSRI DDDs are consistent with therapeutic doses for depression treatment: citalopram, fluoxetine and paroxetine 20mg daily, sertraline 50mg daily and escitalopram 10mg daily. Only fluvoxamine, which is very rarely prescribed in Scotland, has a dose range of 50mg to 100mg which does not match its DDD of 100mg.

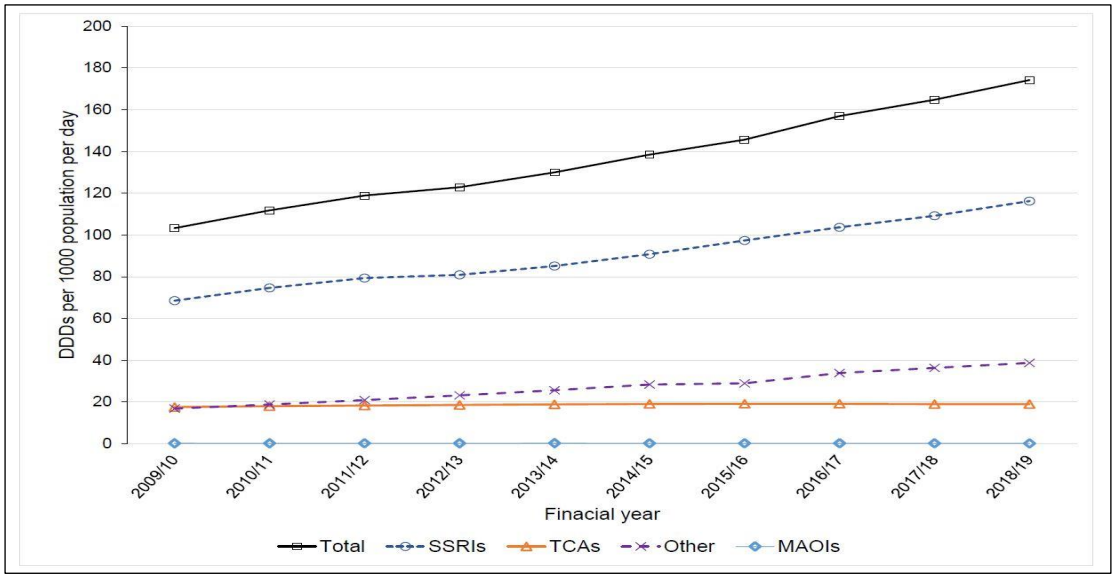


Figure 7. Antidepressant defined daily doses (DDDs) per 1000 population per day by financial year, Scotland 2009/10 to 2018/19 (from ISD 2019)[27]

3.1.2 Data quality

Overall the quality of prescribing data that is routinely collected in Scotland is high; enabling analysts to overcome known data limitations with other UK and European databases.[219] This is due to data quality control, electronic transmission of data within Scotland, CHI capture and years of experience refining prescription analysis and systems.[216] Awareness of the strengths and limitations of different data sources and measures of prescribing, and the flexibility to use a variety of measures, combined with local clinician insight, puts Scotland in a unique position in the world.

As with all data however, there are limitations and weaknesses as PRISMS and PIS data systems are not linked to routine patient-level diagnostic information. For a brief period of time in Scotland the Quality Outcomes Framework (QOF), associated with the general practice medical contract, set contractual obligations that patients newly diagnosed with depression were to have their diagnosis and follow up review (within 12 weeks of diagnosis) electronically Read Coded[ix].[220] Unfortunately, a large proportion of patients were not electronically coded as requested by QOF or as part of routine practice,[90, 190, 221] and it has not yet been possible to link QOF and PIS data.

PRISMS and PIS data are also limited as it is unknown if the patient complied and actually took the medicine regularly as prescribed. GP-level prescribing data from these datamarts are not always representative of an individual GP's prescribing. Prescriptions may be initiated and issued under a colleague's prescriber code, the prescriber code being linked to the patient's registered GP, rather than the initiating GP or non-medical prescriber e.g. a general practice pharmacist.

3.2 Variations in antidepressant prescribing

While it has already been acknowledged that drug availability, the advent of biological psychiatry, pharmaceutical company marketing, and inclusion in

[ix] Read Codes are a standard hierarchical classification system for recording patient medical information in UK primary care.[220]

guidelines and formularies has promoted and driven the use of antidepressant over the years, it is also known that there are variations in antidepressant prescribing and use. In part these variations are associated with the population and patient-level factors; variations in general practice and GP-level characteristics; as well as policy and healthcare system factors, which are discussed in more depth below.

3.2.1 Population and patient-level factors

It is known that higher socioeconomic deprivation is associated with higher antidepressant prescribing, DDD volumes and number of people receiving antidepressants (Figure 8).[27] In part this is due to common mental health problems such as depression, being more prevalent in areas of higher socioeconomic deprivation, as well as an associated increase in incidence and prevalence as the number of physical morbidities and long-term conditions increase (Figure 9).[21, 222-224] Although these associations are bidirectional in nature; overall the use of antidepressants and other medicines are higher in areas of higher deprivation where there are greater health needs.[225, 226] While better housing is associated with lower rates of prescribing, indices of crime and education were not associated with antidepressant prescribing in a previous UK study.[18] All of which may contribute to geographical variations at regional and national levels (Figure 10).[18, 27]

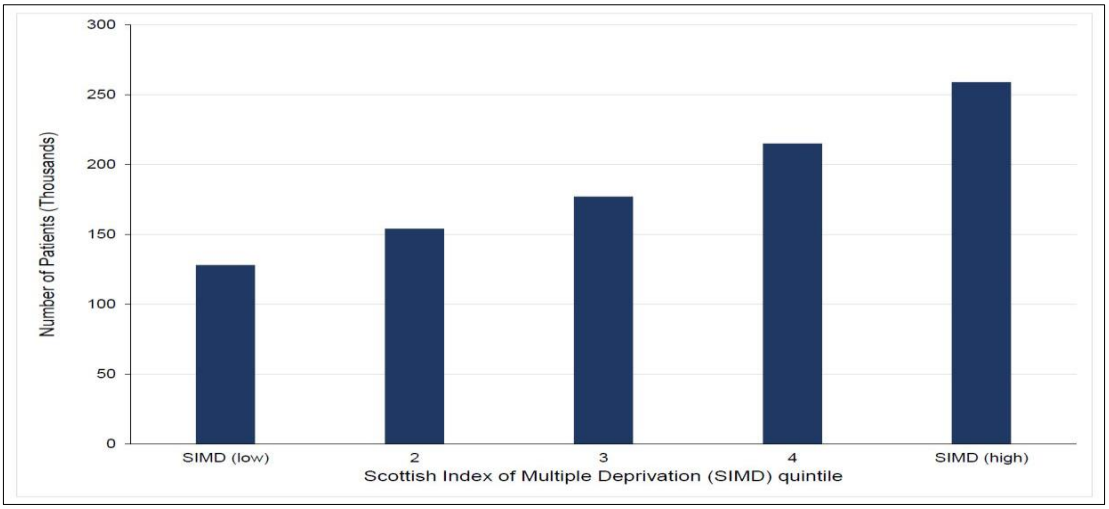


Figure 8. Number of patients receiving one or more antidepressant prescriptions by Scottish Index of Multiple Deprivation, Scotland 2018/19 (from ISD 2019)[27]

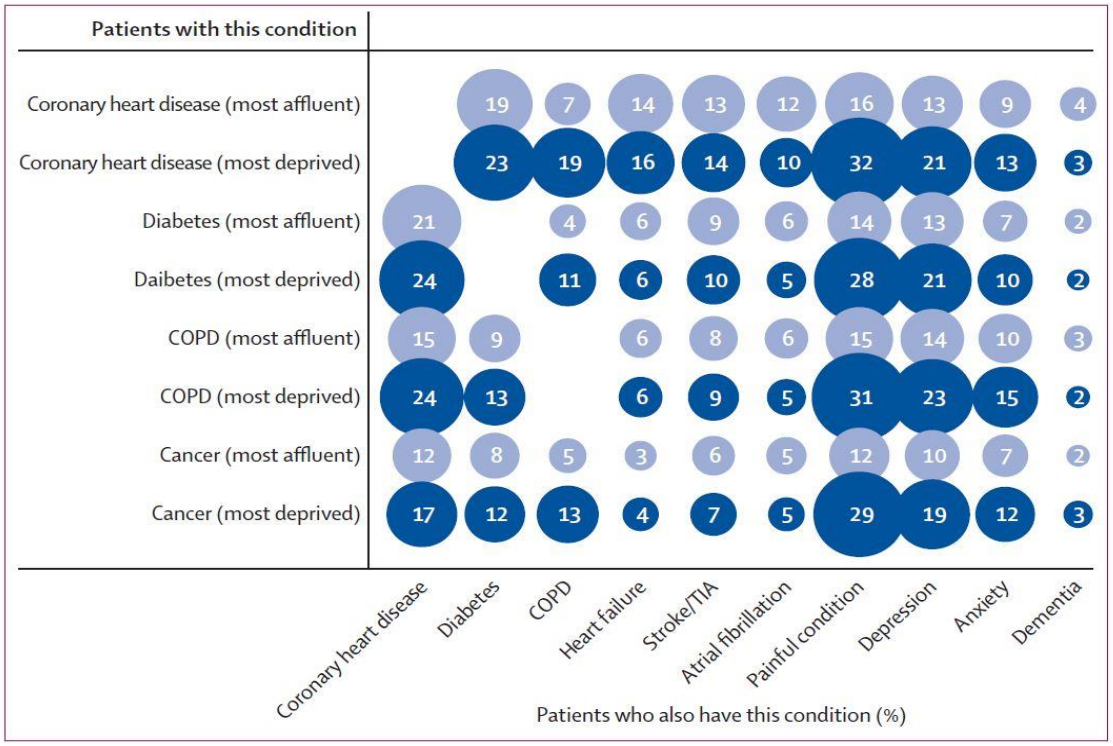


Figure 9. Comorbidities comparison between most affluent and most deprived deciles (from Barnett et al.)[222]

COPD: chronic obstructive pulmonary disease. TIA: transient ischaemic attack.

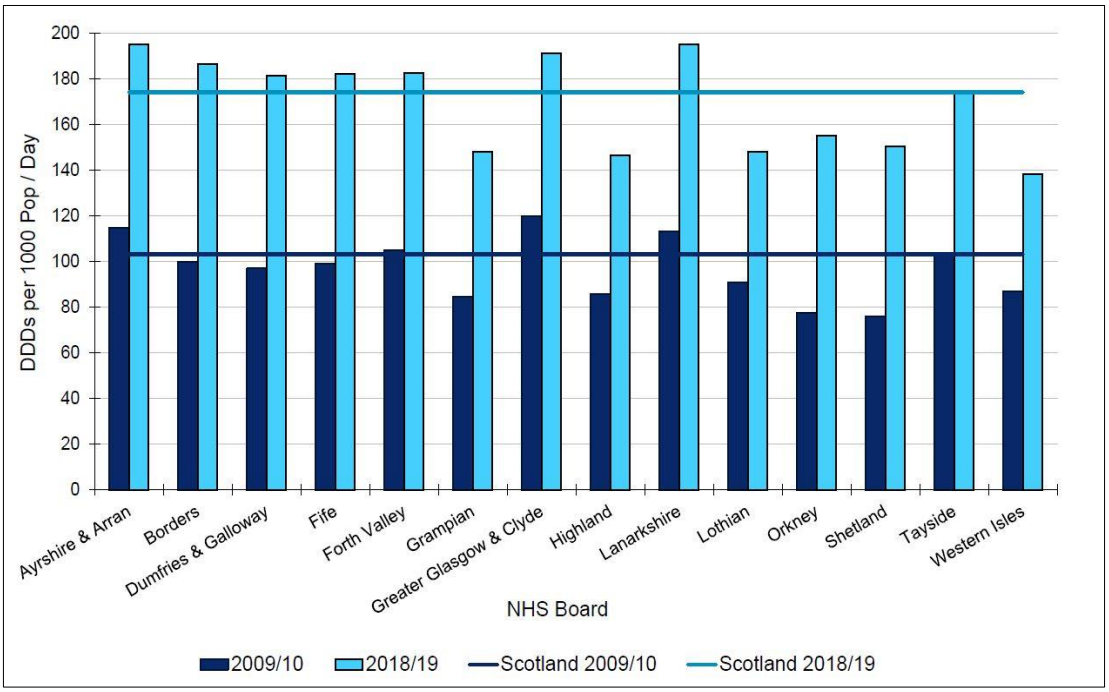


Figure 10. Antidepressant defined daily doses (DDDs) per 1000 population (aged 15+) per day, by health board (from ISD 2019)[27]

Variations in population ethnicity and density are also known to be associated with varying levels of antidepressant prescribing within multicultural societies. This does however vary by ethnic group and population density.[19, 21, 227, 228] Some black, Asian and minority ethnic groups are up to four times less likely to be diagnosed with depression or be prescribed an antidepressant, and while Caribbean populations have similar rates of depression as their white British counter parts, they are less likely to be prescribed an antidepressant.[227]

Gender is also known to be associated with antidepressant prescribing and use. Females are more likely to be prescribed antidepressants, which may be associated with a greater willingness to engage with health services and receive treatment. Female patients have on average 50% more general practice consultations, are twice as likely be diagnosed with depression and receive twice as many antidepressants as males.[5, 6, 188, 229, 230] Antidepressant prescribing also varies by age, showing binomial peaks at 50-54 years old and 85-89 years old (Figure 11).[27] However, it is unclear if any of these factors influence antidepressant doses used to treat depression.

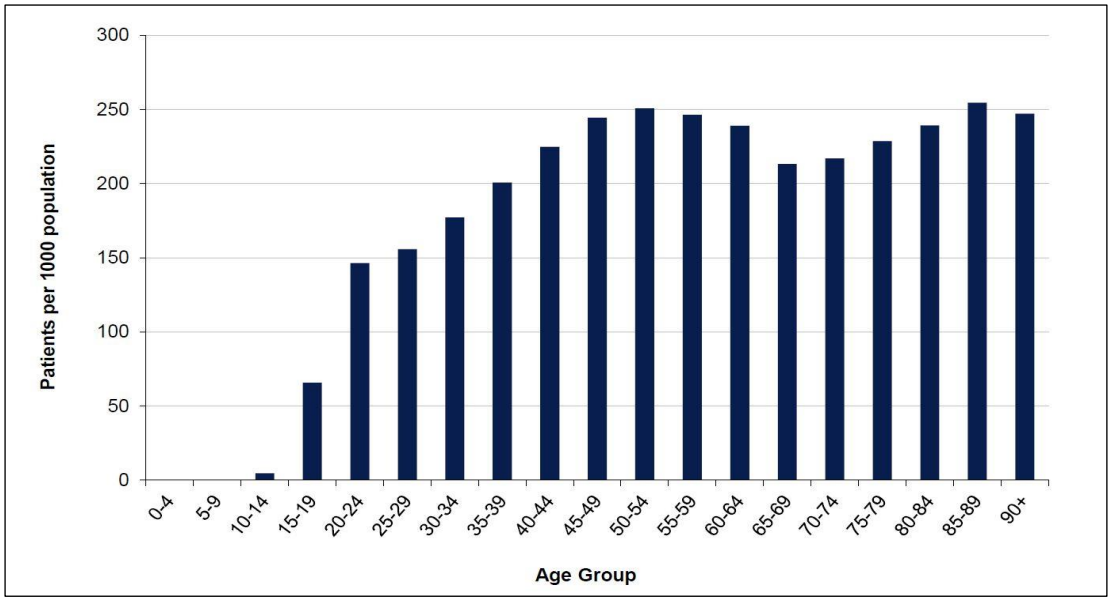


Figure 11. Number of patients by age group per 1000, receiving ≥1 antidepressant prescription, Scotland 2018/19 (from ISD 2019)[27]

3.2.2 General practice and GP-level factors

Just as there are large variations in antidepressant prescribing at regional levels, there are also significant variations at general practice-level with a 5 fold variation between the lowest and highest antidepressant prescribing practices in Scotland.[20, 21] Hull et al.[20] demonstrated in their multivariant model from a London population that 57% of the variation was associated with: where GPs qualified; the proportion of registered female patients, older (>65 years) patients, and the list size per full time GP. Practices with larger south Asian populations and south Asian qualified GPs were lower prescribers, conversely UK born and trained GPs, training practices and higher deprivation were associated with higher prescribing. Morrison et al.[21] demonstrated that 49% of the variation in prescribing was associated practice factors. Higher prescribing practices were associated with, in descending order of influence: a greater burden of illness and long-term conditions, which was highly correlated with deprivation and the single most influential factor; urban location; and greater proportion of female GPs. Lower prescribing practices were associated with being single handed practices; having a larger than average list size; a greater proportion of GPs born outside of the UK; more rural; having a higher proportion of patients from ethnic minority groups; older GPs; and the availability of psychological therapies. However, the proportion of GPs qualified outside the UK, being a training practice or QOF points attainment were not associated with antidepressant prescribing volumes in this study.

Interestingly, although Morrison et al. indicated that there was an association between lower prescribing of antidepressant and the availability of psychological therapies; since the introduction of Improving Access to Psychological Therapies in England, antidepressant prescribing has continued to increase.[185, 187] However, this may be due to clinicians adhering to National Institute for Health and Care Excellence (NICE) depression and/or anxiety guidelines, that promote stepped care, encouraging and supporting patients to use psychological therapies and antidepressants together for moderate to severe depression or anxiety.[67, 132]

At an individual GP-level within a general practice partnership, there are variations in prescribing between GPs, as one partner can be instrumental in

influencing variations in practice-level prescribing volumes between practices.[231] In part this may be due to colleagues within the practice feeling uncomfortable, and finding it somewhat or very difficult – rather than easy – to change their colleagues' prescriptions; especially in relation to antidepressants and other psychotropic medicines.[179] While some GPs have also highlighted that it can be,

'...easier to start [psychotropic medicines] than to stop [them],'.[179],

and that

'...we're [prescribers] probably not good enough, at the moment, is sort of the long-term managing and the coming-off part.'.[232]

Both of which may combine with a reduced frequency of review,[199] and contribute to the increase in long-term prescribing, and possibly the use of higher antidepressant doses, however previous studies have not considered these effects.[5, 233-237] Lastly, local consultants and opinion leaders can influence GPs' prescribing either by directly advising that patients are prescribed specific drugs and doses, or by GPs observing and replicating specialist's prescribing actions.[148, 151]

3.2.3 Policy

The NHS in Scotland has a number of structures in place to support the appropriate prescribing of medicines to optimise their safe, effective and cost-effective use, such as the Scottish Medicines Consortium (SMC), evidence based national and local clinical guidelines, and health board formularies with preferred choice medicines.

The SMC is part of Healthcare Improvement Scotland which is a national specialist health board that provides national advice on the clinical and cost-effectiveness of all new medicines that have received a license from the MHRA or the EMA, as well as reviewing new formulations of, and new ways to using, established medicines.[238] Before a medicine can be prescribed routinely in Scotland, it has to be accepted for use by SMC. Their advice is intended to help the health service plan for the quick, uniform introduction of beneficial treatments across the NHS in Scotland, allowing heath boards to plan their

budgets more effectively. Prior to the SMC being established, the 14 individual local Area Drug and Therapeutics Committees advised their respective NHS boards which products should be accepted for use in their area. The introduction of SMC in 2002 provided a single point of advice, reducing duplication of work and differences in availability of medicines across the NHS in Scotland. After considering the SMC's advice, when medicines are accepted as appropriate for use in routine practice, individual health boards can and do consider how or if the new medicines should be included in their local formularies. For instance, escitalopram and vortioxetine have been approved for some conditions by the SMC; however, not all health boards have included these medicines within their formularies which may limit use but not exclude use.[196]

Most of the clinical guidelines follow a stepped-care model which aims to match treatment to an individual's needs due to the severity of their illness. For example, in ascending order of severity: very mild illness may remit with minimal intervention known as 'watchful waiting' or 'active monitoring'; mild illness may require psychological therapies which are recommended for first-line treatment of mild depression and anxiety disorders. Whereas combination treatment with antidepressant and psychological therapies is recommended for moderate to severe illness, with SSRIs being recommended and prescribed as first-line pharmacological treatment.[67, 181, 210] For some health boards in Scotland, depression guidelines take the form of pharmacological algorithms recommending first-, second- and third-line antidepressant treatment options linked to drug formularies, rather than linking with or acknowledging non-pharmacological and non-medicalised interventions.

Formulary inclusion or exclusion of certain antidepressants may influence regional variations in use and/or prescribing costs. Newer antidepressants that provide similar effects and benefits to older medicines, but are significantly more expensive, may not be included some Scottish Health Boards' formularies but may be included in others. In some cases these non-formulary medicines have been switched to equivalent formulary options in Scotland and England.[196, 197] Formulary inclusion can also influence different prescribing measures such as inclusion of SSRIs which are better tolerated than TCAs,

leading to an increase in the number of antidepressant items (prescriptions).[4] These changes can also influence the number of DDDs being prescribed as therapeutic doses of SSRIs are larger than the majority of TCAs doses that are used; 1 DDD versus 0.5 to 0.75 DDDs respectively for the treatment of depression.[99] Therefore, better adherence to prescribing indicators (targets) and guidelines that promote formulary compliance with SSRIs will contribute to a rise in antidepressant prescribing as measured by DDDs.

In order to contain prescribing costs the NHS in Scotland at national and regional level has encouraged and promoted the use of generic prescribing for the majority of medicines, excluding those that require branded drugs or specific preparations as specified in prescribing guidelines[x]. In relation to SSRIs some have estimated that despite a 2.34 fold increase in SSRI prescribing between 2001 and 2017, generic prescribing has enabled a 74% reduction in SSRI expenditure.[196] In part some of this more recent growth is due to greater long-term use and the use of higher licenced doses of SSRI.[5, 17, 191]

3.3 Previous study limitations

SSRIs account for more than 50% of antidepressant prescriptions (Figure 5) and more than 65% of DDDs prescribed in Scotland (Figure 7),[27] and 43% to 76% of antidepressant prescriptions in North America, Europe and Australasia.[3, 31, 192, 201] The growth in long-term use coupled with the use of up to 40% higher SSRI doses for the treatment of depression will have a significant effect on antidepressant growth.[17, 191] Unfortunately, previous studies have not assessed the potential effect of increased SSRI doses contributing to overall antidepressant growth even although it is widely known that SSRI have contributed significantly to overall antidepressant growth over the last 30 years in the UK and elsewhere.

[x] For certain medicines there are variations in absorption between different preparation e.g. phenytoin capsules, tablets and liquid have large variations in absorption between preparations. Therefore as phenytoin is used to treat epilepsy changes in absorption may significant reduce or increase blood levels and the effectiveness of that medicine i.e. loss of epilepsy control, or higher blood levels causing avoidable adverse drug effects and hospitalisation.

All research methods and studies have limitations. However, studies examining antidepressant growth have been limited by a number of factors. Firstly, the majority of quantitative studies have used non-general practice based databases and practice-level variables.[5, 20, 21, 99, 191] These studies are limited since patient-level data for diagnoses is missing or not electronically recorded in the general practice systems which populate these larger databases e.g. General Practitioner Research Database.[90, 190, 221, 239] While other quantitative studies have focused on a specific cohort of patients such as people receiving long-term treatment,[17] or those receiving newly initiated treatment only.[218] Others have examined relationships between antidepressants, depression, and other drugs such as anxiolytic/hypnotic prescribing although they have not investigated potential associations between antidepressant doses and anxiolytic/hypnotic use when co-prescribed.[20, 26, 240]

Secondly, qualitative studies have explored factors influencing GP prescribing and patients' decisions to take and use antidepressants for depression,[8, 25] however to date only one study to my knowledge has commented, in passing, on expectations relating to antidepressants and prescribed doses.[22] Lastly, there is also the question regarding SSRI dose-response effects and depression treatment which has not been explored in large scale systematic reviews and meta-analyses,[10, 15, 145, 241] even though a pervious narrative review indicated that SSRIs appeared to have a flat dose-response effect for the treatment of depression, and higher doses were associated with a greater risk of ADEs.[166] Therefore, this thesis aims to explore and examine the use of SSRI doses and dose-response effects for the treatment of depression in primary care by addressing the following research questions:

- What patient factors are associated with the prescribed daily dose of SSRIs for the treatment of depression, in adults, in primary care?
- What influences prescribers' use of specific antidepressant and doses for the treatment of depression, in adults, in primary care?
- Are higher SSRI doses more effective than lower doses for the treatment of depression, in adults, in primary care?

Chapter 4

4. Methodological considerations

4.1 Theoretical framework and rationale for methodological approach

The overarching aim of this sequence of interlinking studies is, to explore and examine the use of SSRI doses and dose-response effects for the treatment of depression in primary care. A sequence of separate quantitative and qualitative studies is necessary to address the three research questions:

- What patient factors are associated with the prescribed daily dose of SSRIs for the treatment of depression, in adults, in primary care?
- What influences prescribers' use of specific antidepressants and doses for the treatment of depression, in adults, in primary care?
- Are higher SSRI doses more effective than lower doses for the treatment of depression, in adults, in primary care?

There are a range of philosophical paradigms which provide potential theoretical frameworks to guide and address these questions individually but possibly not collectively.

So what are philosophical paradigms? These are a set of philosophical assumptions and theoretical frameworks which underpin social research; they are a set of basic beliefs that guide the actions and define the worldview of the researcher.[242, 243] These paradigms are mainly philosophical in nature and are commonly comprised of a number of components. Ontology, the nature of reality and nature of being. Epistemology, the enquiry into nature and the scope of human knowledge – how we know the world, gain knowledge, and the relationship between the knowers and the known. Methodology, a shared understanding of the best means of gaining knowledge about the world.[242, 243]

There are a range of paradigms that help structure and organise social research such as positivism, empiricism, pragmatism, post-structuralism, constructivism, etc.[242] These theoretical constructs represent and provide

different perspectives on ontology, epistemology and methodology. For example positivism takes a 'factual' perspective; focusing on observations and measurements, and is often associated with quantitative methods and natural sciences. Positivism asserts that there is a truth and a reality out there that can be known through application of the particular research methods. Positivism also applies formalised language to communicate findings such as precision, generalisability, reliability and replicability. Whereas constructivism, is often associated with qualitative methods where the researcher relies on the participants' perspectives to develop an understanding of the phenomena or construct being explored, and uses less formal or precise terminology and language to communicate those findings. For constructivists, reality or truth is contentious as the social world and its phenomena are the product of social construction. Pragmatism as a research paradigm accepts that there can be single or multiple realities and that these can be accessed through social enquiry.[244] Pragmatism embraces the plurality of research methods; using the philosophical and/or methodological approach that fits and works best in developing and understanding of the issue being explored, and may employ both formal and/or informal language.[243] Now if we envisage these examples as a range of paradigms; positivism would be anchored at one end with constructivism at the other, while pragmatism would be positioned in the middle.

Pragmatism focuses on the consequences of research and the research question rather than the methods. It rejects the idea that a single scientific method can be used to investigate all issues; a single methodology may not adequately address the research question or problem and may limit understanding. Consequently, pragmatism is often associated with using mixed-methods or multiple-methods in order to adequately address the issue under investigation.[243] Pragmatists consider that 'reality' is not static, but changes at every turn of events or actions, and that the world is in a constant state of becoming. As Kaushik and Walsh states, *'this world is a world of unique human experiences in which, instead of universal truths, there are warranted beliefs, which shape as we repeatedly take actions in similar situations experiences the outcomes'*.[243] Therefore, if the situation of the action

changes, this may change an individual's experience and the outcome. Pragmatists also consider that no two people have exactly the same experiences, so their world views must differ; they may have a shared experience but differing degrees of shared beliefs.[243]

As already acknowledged above, as antidepressant use has developed over the years there have been a number of events and/or actions that are known to have influenced their use at specific points in time, however their use and factors influencing their use are still in a state of 'becoming'. For those reasons pragmatism was assessed and considered as an appropriate philosophical framework to enable the exploration and examination of antidepressant prescribing and doses used in primary care, in Scotland, to treat depression. This enabled a sequence of three interlinked studies to identify an understanding of: 1) patient factors that are associated with the prescribed daily dose of SSRIs; 2) what influences prescribers' use of specific antidepressants and doses; and 3) whether higher SSRI doses are more effective than lower doses for the treatment of depression, in adults, in primary care?

4.2 Setting

As already acknowledged the NHS is devolved in the home nations (Section 3.1). NHS Greater Glasgow and Clyde (NHSGGC) is the largest of the 14 health boards in Scotland providing healthcare services for a diverse population of approximately 1.2 million people across a varied urban area. In 2009 there were 269 general practices, reducing to 235 in 2020 due to a range of factors such as GPs retiring and general practice mergers. From a mental health perspective these practices are served by 18 Community Mental Health Teams (CMHTs) which support and/or treat people with mental health illness and/or difficulties in out-patient and domiciliary settings, providing more than simply out-patient psychiatric treatment to upwards of 18,000 patients annually. NHSGGC health board area is subdivided into six Health and Social Care Partnerships (HSCPs) along local council areas. Each HSCP brings together community primary care health services and social work services to support patients in the locality, with CMHTs working within and across HSCP boundaries.

4.3 Governance and ethical considerations

This thesis involved three interlinking studies:1) a quantitative cross-sectional analysis of individual patient-level factors and prescribed SSRI doses for depression treatment; 2) a qualitative study involving one-to-one semi-structured interviews with practicing GPs; and 3) a systematic literature review of reviews and narrative synthesis. There were a range of ethical considerations that varied slightly due to the different methodologies being used in each study.

4.3.1 Recruitment, informed consent and ethical considerations

The quantitative study involved secondary analysis of cross-sectional patient-level data collected by me as part of my service development and evaluation work with NHSGGC to address the antidepressant HEAT targets, from a purposive sample of 12 general practices.[245, 246] The data was primarily collected to provide a better understanding of antidepressant prescribing in general practice and support appropriate use of antidepressants within NHSGGC, and to test an academic detailing and reflective learning model for the treatment and management of depression, that built on a previously successful pharmacist led educational outreach prescribing initiative.[247, 248] However, the initial programme of work did not specify or state that a regression analysis would be undertaken to better aid an understanding of antidepressant use, using anonymised patient-level data.

While the regression analysis was considered to be service development and evaluation, therefore not requiring ethical approval as defined by the NHSGGC Research and Development team, it would require Caldicott Guardian approval.[249] I thought it was important to contact the West of Scotland Research Ethics Committee for clarity (Appendix A1.1). The ethics committee confirmed that this was correct, and Caldicott Guardian approval was required to permit the sharing of anonymised and publication of findings. Therefore Caldicott approval was sought from the lead GP within each of the 12 practices to use anonymised patient-level data for further analysis; 11 of 12 practice gave consent, and one declined.

For the qualitative study, the main issue with the one-to-one GP interview study was the potential to identify poor or substandard practice, although it was expected that this risk was low. It was planned that where poor or substandard practice was identified, information would be provided to update practice in line with current national and local guidelines. As I was employed by NHSGGC as a general practice clinical pharmacist, and the research was part of my professional role I was able to engage with senior clinical staff (e.g. HSCP clinical directors) and/or senior general practice clinicians too, if needed.

For both studies once participants agreed to participate, and prior to consenting, all participants had the opportunity to ask questions and have any concerns discussed prior to signing consent forms. All participants were informed that they were free to decline or withdraw from the study at any time without giving any reason. If participants change their mind regarding the use of patient-level data in the regression analysis then this data would be excluded from the study, or if they changed their mind during interviews the recording would be destroyed and their data would not be used in the study. As all participants were practicing registered GPs, it was expected that they would have full capacity to provide informed consent.

The systematic review of reviews used data from published studies and did not require ethical approval.

Researchers' conflict of interests: my supervisory team and I were unaware of any conflict of interest. I did not receive direct funding for the studies; however, this PhD is funded by educational bursaries from: NHS Scotland prize money; NHSGGC Learning and Educational Bursary Scheme; and NHSGGC Pharmacy Services Endowment Fund. This work is independent of the funders and does not necessarily represent their view.

4.3.2 Confidentiality and safe guarding of data

Patient-level data were extracted from general practice electronic systems and clinical notes for the cross-sectional study. Prior to removing data from the general practice to non-practice computers for further analysis, data were pseudonymised by removing identifiers: patient name and address, practice and staff names. For GP-level data from the qualitative study all recordings

and transcripts were anonymised by removing practitioner, practice, and patient identifiers.

Access to quantitative and qualitative data were limited to myself and my PhD supervisors. Electronic data was held on password protected computer. Practice and GP consent forms and paper copies of transcripts were stored in a locked filing cabinet.

Where clinically and ethically appropriate confidentiality may be required to be broken where substandard or poor practice significantly impacts on patient care. In such circumstances identified issues will be brought to the attention of NHSGGC Pharmacy Services, Central Prescribing Team.

All reports and outputs pertaining to these studies will preserve patient and practitioner anonymity. All quotes used in any report will be anonymised; pseudonyms will be employed.

Chapter 5

5. Patient factors associated with SSRI doses: a cross-sectional study

This study sought to address the first research question, what patient factors are associated with the prescribed daily dose of SSRIs for the treatment of depression, in adults, in primary care? The chapter presents the background, methods, results, summarises findings, discusses the strengths and limitations of this thesis' cross-sectional logistic regression analysis investigating potential patient-level variables associated with SSRI daily doses for the treatment of depression in general practice, as well as the findings within the context of the wider literature.

5.1 Background and aims

As outlined in more detail in Section 3.2 above, previous studies have mainly focused on practice-level factors associated with antidepressant prescribing. These studies have tended to use estimates of prescribed doses, by creating standardised prescribing ratios or average daily quantities, or used other prescribed medicines as proxy markers of morbidity, and not been able to link antidepressant prescriptions with patient characteristics and drug indication.[20, 21, 250] This important as long-term conditions such as diabetes, coronary heart disease, stroke, asthma, COPD are associated with a higher incidence and prevalence of depression.[222, 223, 251, 252] While it is also known that majority of antidepressants are prescribed to treat depression,[17, 31, 190] this is often missing from studies which use information from large databases such as the General Practitioner Research Database.[90, 190, 221, 239] SSRIs also account for the majority of antidepressants prescribed in the UK and elsewhere,[3, 4, 27, 31, 33, 201] and there has been an increase in the size of antidepressant doses used to treat depression.[17, 191, 201] Yet, SSRIs appear to have a flat dose-response curve; where standard doses are optimal doses.[209] Therefore, a better understanding of what patient-level factors are associated with the use of higher licensed SSRI doses for the treatment depression may help to develop

appropriate strategies to support appropriate SSRI prescribing and use. This study's aim was to investigate patient factors associated with SSRI prescribed daily dose for depression treatment in general practice.

5.2 Method

5.2.1 Research and ethical approval

Advice was sought from NHSGGC Research and Development team regarding whether Research and Development approval was required for this study involving secondary analysis of pseudonymised patient-level data from NHSGGC's Antidepressant HEAT target service review and evaluation work.[245, 246] The Research and Development team informed me that it was not required, however Caldicott Guardian approval would be required from each of the general practices.[253]

Ethical opinion was also sought from the West of Scotland Research Ethics Service regarding the secondary use of patient-level data for this study. The ethics service considered this study to be an audit followed by service evaluation not requiring ethics service approval. *'The patient data is only involved in the audit and audit does not require to be reviewed by an NHS research ethics committee. I would agree with the original advice you were given that research ethics review was not required as this was not a research project.'* and that *'The project is an audit using only data obtained as part of usual care but note the requirement for Caldicott Guardian approval to permit sharing or publication of anonymised data obtained from patient[s] under the care of NHS Greater Glasgow and Clyde.'* , Appendix A1.1.[254]

Practices were therefore were invited to allow anonymised patient-level data to be analysed, and give written consent for the data to be used (Appendix A1.2 and A1.3). Eleven of the 12 practices gave Caldicott Guardian approval and consent to use anonymised patient-level data; one medium prescribing practice declined approval to use anonymised data and were excluded.

5.2.2 Study design and setting

This cross-sectional study is reported in compliance with Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (See Appendix A1.4).[255]

A purposive stratified single cross-sectional study design was considered appropriate to identify inter-relationship between patient-level variables of interest, as informed by literature, and patients' prescribed daily doses of SSRIs to treat depression. Due to resource limitations, purposive stratified sampling was considered appropriate to capture the patient-level data from a range of general practices that were low to high prescribers of antidepressants by DDDs/1000 patients.

This cross-sectional study was a secondary analysis of routinely available patient-level data from a stratified sample of low to high volume antidepressant prescribing general practices in NHSGGC, involving 3518 individuals. The data were collected by myself as part of my service development and evaluation work within NHSGGC to address the antidepressant HEAT targets.[245, 246] The 269 NHSGGC practices were ranked low to high antidepressant prescribers, by DDDs/1000 patients from PRISMS for year to March 2009. Ranked practices were then categorised as low (practice 1 to 89: 8,076 to 25,657 DDDs/1000 patients), medium (practice 90 to 179: 25,666 to 34,872 DDDs/1000 patients) and high (practice 180 to 269: 34,886 to 65,409 DDDs/1000 patients) prescribing practices; practices were recruited from each category with varying characteristics known to influence antidepressant volumes: practice size and deprivation code. Other factors known to influence antidepressant prescribing, such as patient ethnicity, GPs being UK or non-UK trained and their country of birth, were not included due to unreliable data quality e.g. contractual obligations only requiring newly registered patients' ethnicity to be recorded.[20, 21, 256] As NHSGGC serves a largely urban area rurality was also not included.

Practices within each prescribing category, with a mixture of characteristics: low to high volume antidepressant prescribers; small to large practices serving populations in areas of low to high deprivation; as well as some being general practice training practices, were invited to participate in HEAT target service

evaluation work through a third party; namely their local Community Health and Care Partnership (CHCP)[xi] prescribing support team. In 2009, NHSGGC consisted of 10 CHCPs serving populations with varying levels of deprivation; as defined by Scottish Index of Multiple Deprivation (SIMD) code.[257] CHCP general practice prescribing support teams serving areas of low to high deprivation were asked to select and approach potential practices for participation in HEAT target service evaluation work. Six CHCPs supported practice recruitment and engagement with 12 practices agreeing to participate in the HEAT target work. Eleven practices gave Caldicott approval for anonymised data to be used in this study, and one medium prescribing practice declined and were excluded. This resulted in three low, three medium and five high volume antidepressant practices with SSRIs accounting for 63.7% to 72.4% of all antidepressant DDDs. The practices had similar proportions of female and male patients, with two to six GPs serving populations in areas of low to high deprivation. Six of the practices were training practices and there was a 4.7-fold difference between the lowest and highest prescribing practices by proportion of patients receiving SSRIs (Table 2).

All practices were 'paper-light', recording clinical information electronically for more than 5 years on individual practices' General Practice Administration System Scotland (GPASS) which was the most widely used general practice system in NHSGGC at this time. The patient demographics represented by the 11 study practices were similar to 47% (481/1014) of Scottish general practices: by urban setting, proportion of patients aged 15 to 74 years old, and patient-level SIMD deprivation quintiles. These 481 practices serve 58% (3 of 5.2 million people) of the Scottish population with 202 of these practices being in NHSGGC serving 1.2 million people.[258]

[xi] The 10 Community Health and Care Partnerships (CHCPs) evolved into the 6 Health and Social Care Partnerships (HSCPs) with health and social care integration and geographical partnerships being formed within local council areas.

Table 2. Cross-sectional study practice characteristics

Practice	*ADM volume DDDs/1000 patients (Category)	SSRI volume DDDs/1000 patients (%)†	Total Practice Population ≥18 years (female:male)	Number of GPs	‡SIMD Quintile	Training Practice	% Patients prescribed an SSRI (number of patients/practice population ≥18 years)
1	9,576 (L)	6,933 (72.4)	3,697 (1,072:2,625)	2	4	No	2.5% (94/3,697)
2	18,295 (L)	12,630 (69.0)	9,806 (5,327:4,479)	5	5	Yes	3.4% (337/9,806)
3	20,752 (L)	14,600 (70.4)	6,736 (3,601:3,135)	6	1	Yes	5.2% (353/6,736)
4	28,169 (M)	19,714 (70.0)	4,324 (2,262:2,062)	5	4	Yes	6.0% (261/4,324)
5	29,894 (M)	20,860 (69.8)	5,741 (2,964:2,777)	4	5	No	8.5% (487/5,741)
6	31,038 (M)	20,967 (67.6)	3,421 (1,657:1,764)	3	4	No	7.3% (250/3,421)
7	35,490 (H)	25,448 (71.7)	3,956 (2,005:1,951)	3	2	No	7.6% (299/3,956)
8	41,917 (H)	26,710 (63.7)	5,010 (2,493:2,517)	6	5	Yes	9.0% (451/5,010)
9	44,637 (H)	30,344 (68.0)	3,121 (1,653:1,468)	3	5	No	8.4% (262/3,121)
10	49,393 (H)	31,885 (64.6)	3,756 (1,888:1,868)	4	4	Yes	9.7% (365/3,756)
11	65,409 (H)	46,309 (70.8)	3,007 (1,550:1,457)	2	5	Yes	11.9% (359/3,007)

*From Prescribing Information Systems Scotland (PRISMS) data year to March 2009.
ADM: antidepressant medicines. DDDs: defined daily doses. Category: Ranked as L – Low, M – Medium and H – High prescribers from PRISMS. SSRI: selective serotonin re-uptake inhibitors. †% of total antidepressant DDDs/1000 patients. SIMD: Scottish Index of Multiple Deprivation, ‡categorise by practice postcode quintile 1 (least deprived) to 5 (most deprived).

5.2.3 Identification of patient-level data

A single cross-sectional data extraction was made for each practice between September 2009 and January 2011. Electronic data extraction tools specifically designed and piloted to identify all patients prescribed an SSRI within the previous 3 months, and patients who were prescribed the same SSRI for ≥2 years, from individual practices' GPASS were used.[17] Current UK and non-UK depression treatment guidelines recommend up to 2 years antidepressant treatment for those at higher risk of depression relapse, therefore this was considered an appropriate measure of long-term antidepressant use.[66, 67, 96, 181, 210] Patients were included if they were ≥18 years old and prescribed an SSRI to treat depression, including mixed depression anxiety.

The data extraction tools simultaneously gathered individuals' antidepressant prescription information, age, gender, smoking status and SIMD code derived from each patient's residential postcode.[257] Co-morbidities (Read Coded for diabetes, coronary heart disease, stroke, hypertension, asthma or COPD) were collected as these are associated with a higher incidence and prevalence of depression.[222, 223, 251, 252] Smoking status was of interest as it has been reported as having a bidirectional relationship with depression and may influence antidepressant response.[259] Co-morbidities and smoking status information was readily available, having been recorded and monitored as part of the general practice General Medical Services contract; Quality Outcomes Framework; details of Read Codes are provided in Appendix A1.5.[256]

I was aware of limitations with using depression Read Codes as a marker of antidepressant indication as there is no contractual obligation for GPs to code patients receiving treatment for depression. Read Codes are a standard hierarchical classification system for recording patient medical information in UK primary care.[220] Previous studies highlighted a lack of documented diagnosis,[90, 190] and audits in five NHSGGC practices demonstrated <50% of patients receiving antidepressant treatment for depression were coded for depression. Therefore the primary indication was identified using a combination of electronic GPASS Read Codes and written patient encounter information. For a small minority of patients electronic records of antidepressant indications were not available from GPASS therefore

individuals' clinical paper case notes were manually checked for antidepressant indication at the date of initiation by me before the data set was anonymised. Patients with no clear indication were recorded as indication unknown and excluded.

5.2.4 Data operationalisation and statistical analysis

Explanatory variables were included in a statistical model which I hypothesised from the literature would influence SSRI prescribed daily dose, and are known to be associated with depression and variations in general practice antidepressant prescribing.[20, 21, 26, 222, 223, 251, 252, 259, 260] These were individuals' age; gender; residential SIMD quintile; co-morbidity status; smoking status; being prescribed the same SSRI for ≥2 years; and their GP practice. It has been previously demonstrated that the presences of mental health disorders is strongly associated with the number of physical health disorders that people have.[222] Therefore co-morbidity was categorised into three options: having no co-morbidity (none); having one co-morbid condition; or having ≥2 co-morbidities. Severity of depressive illness at initial diagnosis was not included as a variable as this is poorly recorded, and may be subjective in nature as depression rating scales are rarely used to provide an objective measurement of severity by GPs in routine practice.[86, 87]

The outcome variable of interest was patients' SSRI prescribed daily dose, expressed as DDDs, as defined by WHO, see Table 3 below.[206] For example, a prescribed daily dose of 20mg or 30mg citalopram was recorded as 1 DDD or 1.5 DDDs, respectively. The statistical distribution of SSRI DDD data was decidedly 'non-normal', and was 'tooth-like' with substantial bimodal peaks observed at DDD equivalents of 1.0 and 2.0. As SSRIs demonstrate a flat dose-response curve for the treatment of depression with standard doses (1 DDD) representing a therapeutic dose, see sections 2.7 and 7.2.2.[66, 166, 167, 209] The outcome variable of prescribed daily dose was dichotomised as a binary outcome variable of ≤1 or >1 DDD i.e. those with a standard therapeutic dose versus those with a higher dose. Knowing that a DDD equal to 2 was not necessarily twice as effective as a DDD equal to 1, and that SSRI DDDs were not normally distributed and remained so after transformation, it was considered

more appropriate to adopt a logistic regression model in preference to an ordinal logistic model.[261]

Table 3. Serotonin re-uptake inhibitor defined daily doses

	Daily dose (mg)	Defined daily dose*
Escitalopram	10	1
Citalopram	20	1
Fluoxetine	20	1
Fluvoxamine	100	1
Paroxetine	20	1
Sertraline	50	1

*As defined by the World Health Organization.[206]

A multi-level model was considered to take account of clustering within practices, however practice-level variables were crude and the number of practices were relatively low limiting the meaningful use of the feature of clustering within practices in a statistical model. Very little work has been published to date on the minimum number of clusters required for a multi-level model, however an exploratory analysis conducted elsewhere suggested there should be at least 10 to 15 clusters,[262, 263] therefore with 11 practices the dataset was on the margins of what may be a robust approach. As the practices were not selected at random, and were a stratified selection, fitting practice as random effects variable was ruled out. It was hypothesised that the individual patient-level factors would be more explanatory of the variability in SSRI prescribing than practice-level factors, and that I could retain practice attended as a fixed effect patient-level variable in a pooled practice model, provided the heterogeneity of the coefficients of each explanatory variable was not dramatically different. To test this the logistic regression model was ran for each practice in turn, and tabulated variable coefficients with any statistical significance for: gender; age; co-morbidities; smoking status; SIMD code derived from patients' residential postcode; and use of the same SSRI for ≥2 years. It was found that practices did not dramatically differ, and I proceeded to use the statistical model with 'practice attended' as a patient-level fixed effect variable using the pooled patient data from all practices.

Exploratory analysis revealed a curvilinear relationship with age and prescribed daily dose, expressed as DDDs. Different transformations for age were

undertaken and although they improved model fit, the model failed to meet statistical assumptions. However, by truncating at ≤70 years, these assumptions were met and this upper age limit was retained in the model.

The approach taken was one of a full model fitting all predictor variables that were known to have an effect on overall antidepressant prescribing, but were hypothesised as being associated with different SSRI doses.[20, 21, 26, 222, 223, 251, 252, 259, 260] Backwards stepwise elimination of variables in turn of those which did not achieve a significance level of p=0.05 to explore what effect was achieved in gaining model parsimony i.e. the best model 'fit' with the fewest number of predictor variables, was then used. A low significance level of p=0.05 was pre-specified as a cut-off in eliminating variables in turn, as the dataset contained a large number of individuals enabling statistical significance to be more easily achieved. Variables greater or equal to p=0.05 if they improved model fit were retained. Data were analysed using Stata 11.2.

5.3 Results

5.3.1 SSRI prescribing variations

Inter-practice SSRI prescribing varied significantly; practice point prevalence ranged from 2.5% (94/3697) to 11.9% (359/3007) of the practice population ≥18 years old; median 7.3% (250/3421) (χ^2=2277.2, df=10, p<0.001). The SSRI point prevalence over all 11 practices was 6.3% (3518/52575) of which 67.3% (2369/3518) were female; 5.8% (3066/52575) of the total practice population received an SSRI for treatment of depression (Figure 12, Table 4).

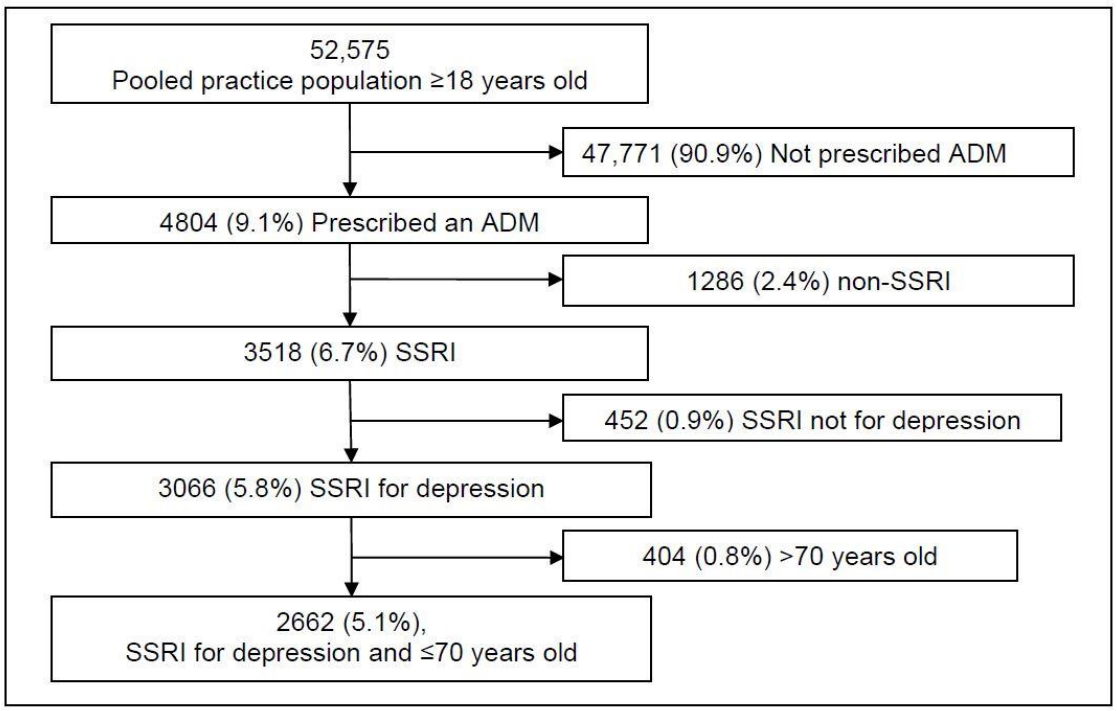


Figure 12. Pooled practice population prescribed antidepressants, excluding amitriptyline.

Note: As amitriptyline is predominantly used for neuropathic pain it was excluded from the search

Significantly higher SSRI doses were prescribed to ≤70 years old than those >70 years (mean ± SD), 1.43 ± 0.69 DDDs versus 1.12 ± 0.51 DDDs (Mann-Whitney U test p<0.001). There was no significant difference in SSRI prescribed daily dose by gender within the age groups.

Table 4. Antidepressant indication

	Number of patients prescribed an SSRI n=3518 (%)
Depression/Mixed depression anxiety	3066 (87.2)
Anxiety disorder	305 (8.7)
Bipolar	46 (1.3)
Schizoaffective	38 (1.1)
Personality disorder	10 (0.3)
Unknown	18 (0.5)
Other mental health	15 (0.4)
Other general medical	20 (0.6)

Other mental health: insomnia, eating disorders, etc
Other general medical: neuropathy, menopausal symptoms, irritable bowel syndrome, premature ejaculation, etc.

5.3.2 Regression analysis

97.5% (2596/2662) of those ≤70 years had complete data for all predictor variables, and were entered into a logistic regression model (Table 5). I hypothesised an age gender interaction term would be necessary as women live longer than their male counterparts and older age is associated with lower SSRI doses; however, the interaction term was not significant, did not improve model fit, and was left out. All the model assumptions held: there was no evidence of multi-collinearity (no variables were highly correlated >0.8), the link test was correctly specified (hatsq z=0.90; p=0.37), and Hosmer and Lemeshow's goodness of fit test failed to achieve significance (Chi-square (8) = 6.10; p=0.64). No outliers were excluded for having disproportionate leverage on the model.

Higher prescribed daily dose was significantly associated with the following variables in descending order of magnitude by odds ratios: individual practice attended, being prescribed the same SSRI for ≥2 years, and living in a more deprived area (Table 5). There were significant differences between doses for those prescribed SSRIs short-term versus those prescribed the same SSRI for ≥2 years (Table 6), with significant increases observed for all SSRIs except paroxetine and escitalopram.

Table 5. Patient demographics and independent variables

	n=2662	Unadjusted Odds Ratio (95% CI)	p-value
Mean Age ± SD (range) years	45 ± 13 (18 to 70)	1.00 (0 .99 to 1.01)	0.85
Male (%)	884 (33.2)	1	
Female (%)	1778 (66.8)	1.03 (0.86 to 1.23)	0.734
Deprivation (%)			
SIMD quintile 1(least deprived)	248 (9.3)	1	
SIMD quintile 2	322 (12.1)	1.17 (0.80 to 1.72)	0.41
SIMD quintile 3	167 (6.3)	1.67 (1.08 to 2.58)	0.021
SIMD quintile 4	522 (19.6)	1.38 (0.98 to 1.94)	0.068
SIMD quintile 5 (most deprived)	1364 (51.2)	1.55 (1.11 to 2.16)	0.009
SIMD unknown (not in model)	39 (1.5)		
†Co-morbidities (%)			
0	1728 (64.9)	1	
1	665 (25.0)	1.10 (0.90 to 1.33)	0.356
≥2	269 (10.1)	1.18 (0.90 to 1.54)	0.238
Current Smoking Status (%)			
Non-smoker	1581 (59.4)	1	
Smoker	1050 (39.4)	1.13 (0.95 to 1.34)	0.165
Smoking status unknown (not in model)	31 (1.2)		
SSRI use (%)			
ADM for <2y (%)	1909 (71.7)	1	
Same ADM for ≥2y	753 (28.3)	1.80 (1.49 to 2.17)	<0.001
Practice (% practice pop.)			
1	82 (2.2)	1	
2	265 (2.7)	1.98 (1.09 to 3.57)	0.024
3	242 (3.6)	1.26 (0.68 to 2.35)	0.461
4	191 (4.4)	3.26 (1.77 to 5.99)	<0.001
5	372 (6.5)	1.50 (0.84 to 2.69)	0.171
6	201 (5.9)	2.69 (1.47 to 4.94)	0.001
7	224 (5.7)	2.20 (1.21 to 4.01)	0.01
8	322 (6.4)	1.81 (1.01 to 3.24)	0.047
9	181 (5.8)	3.80 (2.06 to 7.01)	<0.001
10	302 (8.0)	2.32 (1.29 to 4.18)	0.005
11	280 (9.3)	3.54 (1.96 to 6.38)	<0.001

Odds ratio: unadjusted. CI: 95% confidence interval. SD: standard deviation. SIMD: Scottish Index of Multiple Deprivation. SSRI: selective serotonin re-uptake inhibitor. ADM: antidepressant medicine.

†Co-morbidities: Individuals had one or more of the following: asthma, COPD, cardiovascular disease, stroke, diabetes mellitus and/or hypertension.

Table 6. Mean daily doses: short-term, long-term (same SSRI ≥2 years) and difference in dose

	ADM <2 years (n=1909)		ADM ≥2 years (n=753)		Difference in mean dose (mg) 95% CI	Mann-Whitney U-test‡	All ADMs (n=2662)	
	Number of patients (%)†	Mean dose (SD) mg	Number of patients (%)†	Mean dose (SD) mg			Number of patients (%)	Mean dose (SD) mg
Citalopram	929 (34.9)	25.8 (12.2)	258 (9.7)	31.2 (14.8)	5.4 (3.6 to 7.2)	<0.001	1187 (44.6)	27.0 (13.0)
Fluoxetine	753 (28.3)	27.2 (12.0)	316 (11.9)	30.6 (14.0)	3.4 (1.6 to 5.2)	<0.001	1069 (40.2)	28.2 (12.7)
Sertraline	147 (5.5)	91.0 (43.7)	76 (2.9)	106.6 (49.2)	15.6 (2.3 to 28.8)	0.019	223 (8.4)	96.3 (46.1)
Paroxetine	35 (1.3)	28.0 (11.8)	67 (2.5)	29.4 (12.7)	1.4 (-3.6 to 6.4)	0.832	102 (3.8)	28.9 (12.3)
Escitalopram	44 (1.7)	15.2 (5.6)	35 (1.3)	15.4 (6.8)	0.2 (-2.6 to 3.0)	0.94	79 (3.0)	15.3 (6.1)
Fluvoxamine	1 (0.0)		1 (0.0)				2 (0.1)	
Total	1909 (71.7)†		753 (28.3)†				2662 (100%)	

Note: Total mean dose and difference in doses between short-term and long-term use presented as means and SD to aid clarity of actual differences groups.
ADMs: antidepressant medicines. SD: standard deviation.
† Percentage of total antidepressants prescribed to the 2662 patients.
‡ Dose distribution for ADM <2 years and ≥2 years compared using Mann-Whitney U-test.

5.4 Summary of cross-sectional study findings

The analysis found that higher SSRI doses for depression treatment were statistically significantly associated with the following variables in descending order of magnitude by odds ratios: individual practice attended, being prescribed the same SSRI for ≥2 years and living in a more deprived area.

While it was previously known that the total volume of antidepressant prescriptions and DDDs varied by practice attended and deprivation,[20, 21] and that there has been an increase in long-term use.[5] It was unknown that the magnitude of prescribed daily doses of SSRIs were also influenced by practice attended, long-term use and socioeconomic deprivation. Due to these findings, it was considered appropriate to explore GPs' perspectives and opinions on the findings of this regression analysis, as well as explore factors influencing GPs' use of antidepressants and their doses to treat depression in the subsequent qualitative study (Chapter 6).

5.5 Strengths and limitations

This is the first large study to my knowledge to explore patient-level factors and their associations with SSRI prescribed daily doses using routine practice data. The use of routine patient-level data – specifically individuals' SSRI dose and indication – enabled this study to overcome previous study limitations, such as missing diagnosis, lack of patient-level drug and daily dose information.[4, 5, 21, 189, 191, 218] By excluding non-depression and non-mental health SSRI use, it was possible to identify factors that were associated with individuals receiving higher than standard doses of SSRIs, specifically more than 20mg citalopram, fluoxetine, paroxetine, 10mg escitalopram, or 50mg sertraline for the treatment of depression.

Another strength was the size and completeness of the dataset with 98% of the 2662 patients receiving SSRIs in the 11 practices having complete data for all predictor variables. In part, this was due to hand searching of patients' paper clinical records where electronic codes were incomplete. This overcame the

lack of diagnostic information relating to depression highlighted in previous studies.[90, 190]

The cross-sectional nature of the regression analysis was a limitation, as it does not permit any analysis of dose progression with time, as doses may be increased, reduced or discontinued soon after data capture. However, other studies have shown that up to 50% of patients are continued on the same antidepressant long-term.[5, 17, 33, 190] Data capture for this study was staggered from September 2009 to January 2011, a period when new NICE, The Scottish Intercollegiate Guidelines Network, and updated British Association of Psychopharmacology depression treatment guidelines were issued. Therefore, it is possible that these may have influenced prescribing practice during this time. Although the antidepressant prescribing and dosing advice was no different to previous guidelines, the guidance did promote greater use of non-pharmacological approaches and the stepped care approach to depression treatment.[132, 264] I cannot exclude the possibility that data collection from practices at the end of the data collection period may have changed their practice in response to the guidance changes.

Another possible confounding factor which may have influenced the findings is whether patients took their medicines as prescribed. Only those who had an SSRI prescription issued in the three months prior to data capture were included. People issued the same SSRI for <2 years were more likely to have their prescription issued as a special request[xii], whereas people receiving the same SSRI for ≥2 years are more likely to receive a regular repeat prescription which is easier to request and access.[265] The use of special requests therefore, may in part, be why compliance with antidepressant treatment can be variable in the early months of treatment as opposed to longer term treatment, as the special request process may act as a barrier to access.[25, 218]

[xii] Special requests – are acute prescriptions created and issued by a GP without an appointment, such as a recently started new medicine, antidepressant course for a first episode of depression, or where potential concordance or safety issues require ongoing monitoring. Repeat prescriptions – are prescriptions that can be issued without the GP needing to review the patient, and are commonly used to ensure medicine supply for people with long-term conditions e.g. heart disease, diabetes, etc.

Depression severity may have influenced the use of higher doses, however it was inappropriate to include this as a variable, as a large proportion of GPs see rating scales as being intrusive and of limited value,[86, 87] and are rarely recorded in patients' clinical notes.[221, 245] In a similar vein, specialist mental health review of patients may have influenced the use of higher doses, but the majority of patients with depression are diagnosed and treated by their GP without seeing a psychiatrist or attending specialist mental health services.[266] Patient ethnicity is known to be associated with lower practice-level antidepressant,[228, 250, 267] and inclusion of ethnicity in my analysis would have provided further contextualisation; however, patient-level ethnicity data were unreliably and inconsistently recorded which precluded their inclusion in this study.

5.6 Comparison with literature

Data from the analysis indicated that 6.3% of the adult practice population were prescribed a SSRI which was lower than previous UK studies: 6.9% in a study that focused on SSRIs,[190] and 8.6% in a study that included all antidepressants.[17] National data from NHS Scotland and National Records for Scotland estimate that 12.9% (n=675,948)[xiii] of the population received more than one antidepressant prescription in 2010/11; half of whom (6.8%) received an SSRI.[188, 268] Some of these differences may be due to the different inclusion criteria such as receiving one or more antidepressant prescriptions within the previous 3 months in my study, versus the previous 12 month timeframe used in other studies.

The 87.2% of patients prescribed SSRIs for depression was slightly higher than the 85.4% reported in another general practice study,[199] however the proportion of females (67.3%) and males (32.7%) receiving treatment was consistent with other studies.[188, 218] The 28.3% of patients receiving the same antidepressant long-term (≥2 years) however was lower than previous estimates: 47.1% using the same definition of long-term use;[17] 40.6 to 51.4%[5] and 33 to 55%[190] using different definitions of long-term use. In part, some of these observed

[xiii] Mid-year population estimate 5,246,000, from National Records of Scotland 2011.[268]

differences may be due to the GPs in this study's practices having a greater interest in depression management, and possibly providing more dynamic care such as proactively reviewing and stopping treatment more frequently than other practices that have more patients prescribed the same drug long-term.[199]

In line with previous studies assessing practice-level variables, greater individual patient-level socioeconomic deprivation had a small but significant association with higher SSRI doses, Table 5.[20, 21, 27, 33]

In contrast to other practice-level studies, prescribed daily dose was not associated with co-morbidity.[21, 224] This difference may indicate however, that practices with a higher proportion of patients with long-term illness treat more patients with antidepressants rather than prescribing higher doses to fewer patients. Some researchers suspect that smoking may influence antidepressant response,[259] however the regression analysis did not identify an association with SSRI dose and smoking status. The average SSRI doses for individual drugs in this study was up to 25% higher for <2 years use, and up to 42% higher for those prescribed the same SSRI for ≥2 years, when compared to previous cross-sectional studies.[17, 99, 235-237]

Chapter 6

6. Exploring factors influencing GP's antidepressant prescribing: a qualitative study

This study sought to address the second research question, what influences prescribers' use of specific antidepressants and doses for the treatment of depression, in adults, in primary care? The chapter presents the background, methods, results, summarises findings, discusses the strengths and limitations of this thesis' qualitative study as well as the findings within the context of the wider literature.

6.1 Background

As outlined in more detail in Section 3.2 above, previous studies have mainly focused on examining quantitative factors associated with antidepressant prescribing at patient, GP and population levels, as well as the influence of policy and clinical guidelines.[5, 20, 21, 196, 228] Some studies have explored patient and GP experiences and perceptions regarding the use and rise in antidepressant prescribing, as well as the barriers and enablers to stopping antidepressants.[8, 25, 179, 232] However, only a few studies have examined quantitative factors associated with antidepressant prescribing and doses,[17, 99, 191] and no studies have been identified that have explored GPs' views and explanations regarding prescribing and doses used to treat depression. This qualitative study attempts to fill this gap in the literature by exploring GPs' explanations and perceptions of their decision making in relation to antidepressant prescribing and the doses prescribed to treat depression. This qualitative study also made use of the findings from the cross-sectional study (Section 5.3) as a way of exploring GPs' explanations and perceptions.

6.2 Study aims and setting

The primary aim was to explore factors influencing GPs' use of antidepressants and their doses to treat depression. Secondary aims were to explore GP views and explanations of the effects of: 1) The MHRA citalopram and escitalopram QT prolongation safety warning on prescribing practice; 2) The new local NHSGGC depression guideline and formulary on influencing prescribing behaviour; as well as capturing their thoughts and perspectives on: 3) This thesis' cross-sectional study findings and factors associated with the use of higher SSRI doses for the treatment of depression.

While it is known that geographical and regional factors are associated with variations in antidepressant prescribing (Section 3.2), it was considered appropriate to conduct this study in a single health board area due to variations in the implementation, delivery and content of policies, prescribing guidelines and drug safety warnings between health boards.[196] NHSGGC was also considered appropriate due to the large number of general practices and potential GP participants; 260 practices with 1047 registered GP partners in 2014, serving 1.2 million people across a varied urban area as outlined in Section 4.2 above.

6.3 Rationale for study design and method

Quantitative methods can be limited in providing explanation or depth of clarity on issues, therefore qualitative methods were considered appropriate and used to enable an in-depth understanding of GPs' perspectives and rationale for prescribing, and factors influencing GPs' use of antidepressants and their doses.

Although there are a range of qualitative and survey methods which may be appropriate in developing an understanding of GPs' perspectives and views, there are strengths, limitations and pragmatic issues associated with their use.[269, 270] Surveys and questionnaires were assessed as being inappropriate in addressing the aims of this study, as these would be less effective at capturing individuals' decision-making processes; would not allow an opportunity to correct possible misunderstandings relating to the questions;

would not allow probing or provide opportunities to delve deeper into an individual's explanation; and could allow respondents to restrict, limit or ignore open ended questions that required further explanation.[271]

An ethnographic approach of embedding oneself within one or two practices over a long period of time might permit direct observation of GP and patient interactions and prescribing actions, however this approach would only allow me to observe a limited number of such interactions, and may introduce the 'Hawthorne effect' whereby my presence may influence the prescribers actions.[272] Observing a limited number of interactions would be unlikely to cover the range of decisions that a GP might make when faced with a wide range of patients, for example those being newly introduced to antidepressants compared to those who have taken them long-term. This observational approach would also need to be accompanied by interviews to understand the rationale behind the observed behaviour. Another limitation is the timely capture of GPs-lived experiences and actions while caring for people with common mental health problems; as depression is an episodic illness with variable recurrence during a patient's life-time.[66] If a phenomenological approach was used, a major challenge would be how best to follow the patient-prescriber journey, and the development of their relationship over a number of years as patients potentially move from 'novice' to 'expert' patient.[25] Ethnographical and phenomenological approaches were therefore considered to be impractical within the time limitations and resources available for this study.

Focus groups were considered, but were assessed as being inappropriate for a combination of reasons. Group interactions, focus group discussions and dynamics can create a group response to the topic under discussion, which may result in loss of the unique individual perspectives. This may also lead to the loss of more controversial aspects of practice and care due to standardising or normalising responses to match peers, or allow dominant voices to dictate and direct discussions and exclude others' opinions from being heard.[273] While some of these challenges can be overcome and managed through probing and allowing and enabling one participant to respond at a time, the data may still provide a group perspective due to group interactions and dynamics, as well as

the potential for moderators to influence or direct discussions.[273] Other practicalities that limited the feasibility of focus groups were that these would be difficult to organise, especially within working hours and there was no funding for incentives for participants to attend a focus group, or pay for premises and hospitality for the group.[274] I knew from previous experience as a general practice prescribing support pharmacist that a lack of incentivisation would be a significant barrier to focus group participation for busy practicing GPs, and it would be easier to engage GPs within their own practice, within routine working hours.

It was therefore considered that one-to-one, face-to-face interviews conducted in each GP's office, was the most pragmatic and optimal method for capturing in-depth GP perspectives. In order to capture their practical experience and opinions of what influences their antidepressant prescribing and doses used to treat depression across the range of patients that they see.

6.3.2 Sampling rationale and strategy

There are a number of sampling methods that could be used for this study, such as: randomised, convenience, snowball, theoretical and purposive. They all have strengths and limitations which may help and/or hinder me as a researcher in addressing this study's aims.

Randomised sampling, for example, would capture the frequency of responses while helping to reduce the risk of selection bias, and give a range of views that would be more representative of the sampled population, such as for all GPs working within the 260 practices in NHSGGC for this study.[244] However, randomised samples may not capture the views and opinions of more controversial or outlier voices that provide greater variety of opinions and perspectives. Despite that, this study considered it appropriate to explore low, medium and high prescribers' views working in a range of small, medium and large surgeries, serving populations who lived in areas with low, medium and high socioeconomic deprivation, as these factors have been shown to be associated with variations in prescribing.[20, 21, 27]

Convenience and snowball sampling, via GP colleagues that I have worked with over the years within NHSGGC, was also considered but excluded. While

I believed my GP colleagues and work associates would have been open and free in truly giving their perspectives and views, my good working relationships and previous practice based antidepressant work may have influenced their responses.[245] Snowball, also known as chain-referral sampling, is commonly used to engage 'hidden' populations, where participants suggest colleagues or peers who may be willing participate.[275] This was excluded as a potential sampling method as it is associated with a high risk of bias, and participants may identify practitioners with similar prescribing habits and attitudes, and because GPs are not 'hidden' populations that may be difficult to identify and engage with.

Theoretical sampling, is a core principle of grounded theory and necessary for any grounded theory study. Grounded theory is inductive; theory is generated from data.[270, 276, 277] Theoretical sampling is not bounded by a priori participant selection, it is iterative and entails jointly collecting and analysing data to decide what data to collect next based on emerging categories and themes, enabling the theoretical sample to evolve and develop as the analytical process evolves.[276, 277] It is necessary however, for grounded theory researchers to start somewhere with data collection and therefore they require a pre-defined participant or sample of participants to collect data from. Thus, it is necessary to start with a convenience or purposive sample prior to identifying a theoretical sample that maximises the similarities and differences within the data.[244, 277] After considering the inherent contradictions within theoretical sampling, starting with a predefined sample, and the pros and cons of other sampling methods, it was considered to be more appropriate to pursue a purposive sampling strategy that was informed by findings from previous quantitative studies and national reports.[20, 21, 27]

Therefore I aimed to recruit a purposive sample of GPs from across NHSGGC using a sampling frame based on the following practice characteristics: volume of antidepressants prescribed, as it is not possible to accurately quantify GP-level prescribing from PRISMS or PIS; number of GP partners; practice population deprivation score; GP genders; and a proportion of GP partners working in the same practice (Table 7). From my prior experience working with GPs, it was anticipated that interviews would last for between 20 to 40 minutes.

The concept of saturation was used to help inform this study's estimated sample size, in conjunction with the topic and scope, in order to gather sufficient depth of information.[278, 279] Previous literature however, presents a confusing and mixed picture where some studies have demonstrated that 5 to 6 interviews produce the majority of new information, and little additional information was gain as the sample approached 20 interviews and saturation. Whereas others indicate that 12 to 40 interviews may be required,[280] yet others have demonstrated that 'code saturation' was reached after 9 interviews, but 16 to 24 were required to reach 'meaning saturation' where a by a 'richly textured understanding of issues' was achieved.[281] Therefore it was estimated that approximately 30 GPs would need to be recruited.[278, 281] It was assumed that practice dynamics and culture may also influence prescribing behaviour, whilst at the same time some GP partners could display very different prescribing habits,[231] it was considered appropriate to capture data from two or more GPs working in the same practice, to allow the exploration of practice culture and dynamics associated with prescribing and depression management.[278] It was estimated that a total 3 to 4 pairs of GPs (6 to 8 GPs) working within the same practice would need to be recruited.

Table 7. Purposive sampling frame

Practice/GP Characteristic	**Number of GPs**		
Antidepressant volumes in DDD/1000 patients	Low: 8 to 12	Medium: 8 to 12	High: 8 to 12
Number of GP partners	Small (single handed): 8 to 12	Medium (2-3 GPs): 8 to12	Large (≥4 GPs): 8 to 12
Deprivation level	Low: 8 to 12	Medium: 8 to 12	High: 8 to 12
Gender	Female 15	Male 15	
Partners working in same medium to large practice	6 to 8		

DDD: defined daily doses.

Potential participants were identified by obtaining antidepressant prescribing data for the 260 NHSGGC general practices from the PRISMS for the year to March 2014, as previously described (Section 5.2.2). The 260 practices were

first ranked from lowest to highest antidepressant prescribers, and were then categorised as low (practice 1 to 86:12,333 to 35,356 DDDs/1000 patients), medium (practice 87 to 172: 35,436 to 46,048 DDDs/1000 patients) and high (practice 173 to 260: 46,048 to 84,742 DDDs/1000 patients) prescribers. The number, names and genders of GPs working within the 260 practices were then identified from Public Health Scotland's GP workforce and practice population information, and matched with the PRISMS data above.[258] Practices were then subcategorised as small (single handed GP), medium (2-3 GPs) and large (≥4 GPs) by the number of GPs contracted to individual practices, as recorded in April 2014.[258] Finally, practices' SIMD derived from each practice's postcode was used as a proxy marker of the practice patient population's socioeconomic deprivation; as general practices are located within the same geographical area that the majority of their patients live within. Practices were ranked by SIMD quintile,[282] and categorised as being in areas of low, medium and high deprivation.

6.3.3 Recruitment

From August 2014 to December 2015, GPs matching the sampling frame (Table 8) were initially contacted by letter in groups of 30 to 40. The letter included: 1) Cover letter, that briefly outlined the study and highlighted that higher doses of SSRIs were routinely being prescribed for the treatment of depression (Appendix A2.1.1).[17, 191] 2) Participant study information (A2.1.2), and 3) Invitation and expression of interest form which could be emailed to me or faxed to a secure location (A2.1.3). Potential participants that did not submit an expression of interest form or respond, were then contacted by administrative staff from the NHSGGC Pharmacy and Prescribing Support Unit team by telephone within 2 weeks to enquire if the GP would like to participate or not. This process was repeated until recruitment was complete.

Potential participants showing an interest, either by returning the 'expression of interest form' or verbally to the administrative staff, were then contacted by myself within 7 days to arrange interviews at their offices' at a time convenient to them. Prior to interviews starting the interview, I discussed the study and sought participant's consent for inclusion in the study (Appendix A2.1.4). GPs were not incentivised to participate in any way.

In total 188 GPs were initially contacted by letter during the study period. A total of 28 GPs who were currently practicing in general practice were recruited to participate in the study, Table 8.

Table 8. Individual GP and practice characteristics

Individual GP Characteristics (n=28)			
Female (%)			14 (50)
Median age (range)			43 (33 to 60)
Years since qualified as doctor, median (range)			19 (10 to 37)
Years as a GP median (range)			12 (2 to 33)
Number of GPs with psychiatry training as part GP training rotation (%)			19 (68)
Number of GPs with extra psychiatric training, as locum or psychiatry training (%)			4 (14)
Individual practice characteristics (n=20)			
Antidepressant volumes in DDD/1000 patients, (n, GPs)	Low = 9 (10)	Medium = 4 (6)	High = 7 (12)
Number of GP partners, (n, GPs)	Small (single handed) = 1 (1)	Medium (2-3 GPs) = 10 (13)	Large (≥4 GPs) = 9 (14)
Deprivation (n, GPs)	Low = 6 (6)	Medium = 5 (7)	High = 9 (15)
GP partners working in same practice (n, GPs)	15 (7)		
Training practice (n, GPs)	Yes = 10 (16)	No = 10 (12)	

DDD: defined daily doses.

6.3.4 Data collection

One-to one, face-to-face, semi-structured interviews were carried out by myself, at the GP's office. Interviews lasted between 15 and 55 minutes with most lasting approximately 30 minutes. Although an initial topic guide (Appendix A2.2) was developed and informed from previous literature (Sections 2.4 to 2.7, and 3.2). The interview process was iterative;[283] allowing early interviews and subsequent interviews to inform the refinement of subsequent topic guides, and enable the inclusion of emergent themes expressed as GPs' views and experiences at interview (See Appendix A2.2). Interview guide topics included: experience and training as a GP, and prior to becoming a GP; how training and experience influenced their antidepressant prescribing; what factors influenced

their prescribing; diagnosis of depression, and decision to prescribe; aims of antidepressant treatment, and assessing and quantifying improvement; and effects of the formulary, guidelines and antidepressant safety warnings. Interviewees were also asked how their antidepressant prescribing compared to their GP colleagues and peers. The topic guide then covered class and individual drug effects: time to effect; therapeutic doses; combination antidepressant use; and co-prescribing with B-Zs (Appendix A2.2). In the final quarter of the interview, the guide was used to seek GPs views and opinions on the findings of the logistic regression analysis by focusing attention on factors associated with higher SSRI doses: practice patients attended and same antidepressant for ≥2 years. Finally, as part of my reflexive process participants were asked if my role as a NHSGGC prescribing support pharmacist had influenced their responses. Interviews were audio-recorded and transcribed verbatim.

Reflexivity is important and an essential component of qualitative research; from study inception to final write up. Reflexivity is concerned with paying attention to how the data is constructed and my role in its construction.[269] As a researcher I am aware that consciously, subconsciously and/or inadvertently I can and do influence the data during the study process. From my experience of working with GPs and other medics for more than 20 years, I was acutely aware that my behaviours and actions may affect study recruitment, and engagement during the interview. I consciously tried to optimise the potential for GP engagement by interviewing GPs in their own practice, at a time that was convenient to them, and being flexible in my approach e.g. if they had an emergency to deal with or had forgot about our agreed appointment, we would re-arrange the interview. While being conscious to allow interviewees to freely give and explain their responses, the interview was also flexible enough to allow ebb and flow, as topics spontaneously arose, or where it was necessary to probe further with follow up questions or seek clarification through echoing and summation, or a change of focus to explore topics not yet covered. This was achieved through actively matching, but not mimicking, the behaviour-type of the participant while allowing time for the interviewee to speak, such as: matching the pace of discussion; being passive enough to allow interviewees to

express themselves; re-focusing the interview when the interviewee drifts too far from the subject of the interview; or gently probing more reserved participants to articulate their perspectives.[284, 285]

Unconsciously however, my experience as a clinical pharmacist, who has worked in patient-facing roles with multiple GPs in a number of practices for more than two decades, and my specialist interest in mental health and psychotropic prescribing may have influenced data collection. I may have unconsciously probed further than other researchers may have in relation to dose-response effects. On the other hand, due to my knowledge of general practice, the healthcare system, and challenges of delivering patient care, I may not have probed or asked for clarifications when specific issues or topics were discussed, due to a perceived commonality of understanding of routine practice. While this may have been the case, it was also important to clarify and ask participants to comment if they considered my role as health board pharmacist had influenced their responses.

My personal and professional experiences may have unconsciously enabled me to visualise the challenges and empathise with GPs around the challenges of identifying, managing and treating common mental health problems in general practice. These include: the confines of 10 minute appointments; 'door handle disclosures' – as patients are leaving the consultation; and poor patient attendance for agreed and arranged follow up reviews. All which may, or may not, be against a backdrop of managing complex comorbidities and social issues. Nonetheless, being consciously aware and reflecting on my experiences and my position within the data, may have better enabled me to actively take a meta-position within the analysis and during the reporting of this study; to contextualise and articulate the study findings and interplay of identified themes.

6.3.5 Analysis

The range of approaches to analysing qualitative data are diverse but can be broadly separated into four groups: quasi-statistical approaches such as content analysis; the use of frameworks or matrices such as a framework approach and thematic analysis; interpretative approaches that include

interpretative phenomenological analysis and grounded theory; and sociolinguistic approaches such as discourse analysis and conversation analysis.[286, 287]

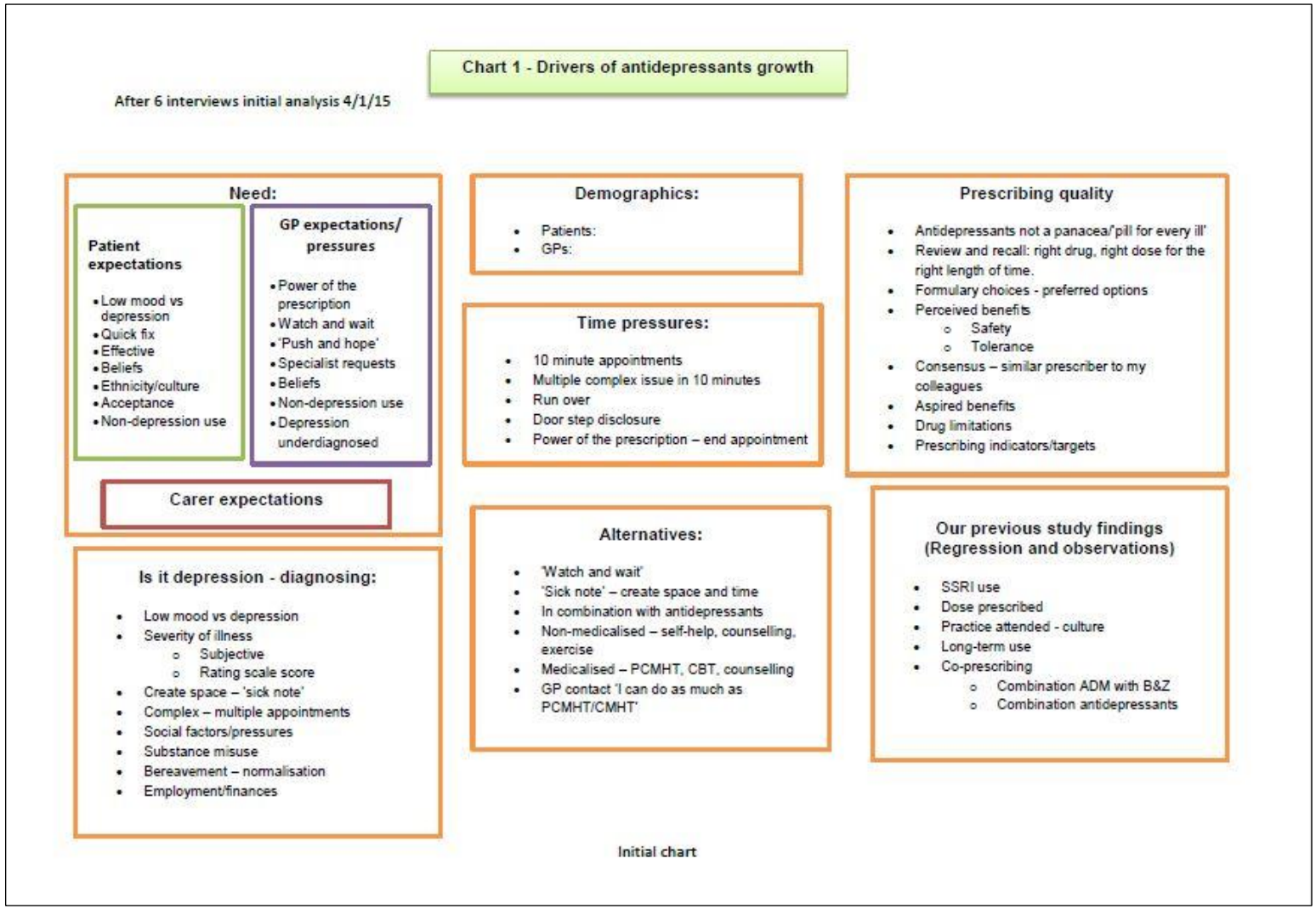
Content analysis, which commonly focuses on the frequency of words, phrase and/or themes within the text,[287] was considered to be of limited value as the research question called for a more inductive approach to exploring the depth, breadth and essence of GPs views rather than a deductive or reductionist approach. By that, I mean that I considered that content analysis would limit the analysis; limiting the emergence of new themes and theories, as well as hindering the development of an understanding of the complexities and nuances in the treatment and management of depression. As the interviews were part of a formal process to elicit and gather data, conversation analysis was considered to be an inappropriate approach as the discussion was not 'naturally occurring' but formalised within the GP's offices.[287] Discourse analysis was also considered inappropriate, as I, as the researcher was eliciting GPs views and perspectives on prescribing and depression management. Whereas, if the research question focused on developing an understanding of GP-patient interactions in relation to depression management, treatment and antidepressant use by the patient, analysis of the use of persuasive and dissuasive language (linguistic repertoire and rhetorical strategies) would have been of possible use.

Grounded theory was also considered to be inappropriate, as already outlined above, however I sought to draw on the constant comparative and disconfirmation elements of grounded theory methodology through an inductive and continuous process of checking and comparing interview data; within and between transcripts, from the start to the finish of this study.[288] From my perspective it was an analytical imperative that my analytical process was auditable, transparent and rigorous, as well as enabling my supervisors to easily view and assess my analytical process. This study's research objectives were also set in advance of data collection and where focused on antidepressant prescribing and depression treatment and not a potentially highly heterogeneous or poorly defined phenomena. Therefore, I considered

Framework analysis at the time to be the most suitable method of analysis.[287-292]

The Framework approach involved five stages: 1) Familiarisation by immersion in the raw data: listening to audio recordings; reading and checking transcripts for accuracy; and studying interview notes to list and identify key and recurrent themes. 2) Identify a thematic framework. This involved open coding, by summarising the content of short sections of text, interview transcripts in this study, to develop the initial base codes (Appendix A2.3.1). This created a large number of 'fuzzy' categories which were then refined by progressive focusing, where open coding base codes were then grouped, categorised or assimilated as codes and nodes to identify and develop an initial thematic frame (Appendix A2.3.2). 3) Indexing. Data were then systematically applied to the thematic frame. This however was not simply a cataloguing process, but a working analytical framework that involved constant comparison and refining of the thematic frame as new themes emerged, as well as summarising (reducing) data without losing the original meaning (Appendix A2.3.3). 4) Charting. Summarised data were then rearranged and grouped under key subjects, as part of a fluid and dynamic process involving abstraction and synthesis. This stage of the analysis was initially carried out with summarised data from the first group of interviews (Figure 13), and evolved and developed as more interview data were captured and analysed. See Appendix A2.3.4 for more detail and examples. 5) Mapping and interpretation, involved using the charts to help define, develop and refine the broad themes and patterns both within and across interviews (Appendix A2.3.4). These five stages of analysis did not adopt or follow a linear process, but were dynamic, flexible, inductive and guided by the data.[290-292] NVivo 11 was used to store and organise data.

Figure 13. Example of early chart, after six interviews: Drivers of antidepressant prescribing growth



Data analysis was inductive and continuous, and began from the start of data collection. The constant comparative technique was used while adopting Framework analysis, as already outlined. Rigour was assured through the integration of a constant comparative approach to the analysis, and a supervisor examining 10 selected manuscripts and applying established codes to check interpretation. Respondent validation, also known as 'member checking' or 'cross checking', was also considered in relation to new emergent themes and topic guide development, in order to gauge respondents' reactions to emerging findings and refine explanations.[293, 294] This involved checking the new emergent themes with interviewees during subsequent interviews when similar concepts and perspectives were discussed by the participant. Likewise coding and meaning saturation was also considered, and while some have attempted to pseudo-quantify saturation and there is debate regarding its appropriate application and use,[279, 280, 295] I applied the pragmatic qualitative methodological approach, *"as the point in data collection and analysis when new incoming data produced little or no new information to address the research question."*[279, 280] Therefore terminating data collection and analysis at this point.

I have used the term 'rigour' in this qualitative study, as I have had to communicate my findings to doctors and other health care professionals who are predominantly trained in using and analysing quantitative data. However due to differences in epistemological and ontological assumptions underpinning qualitative and quantitative methods,[296, 297] qualitative researchers tend not to report validity or reliability, but prefer to use the term trustworthiness. High-quality research would be considered as being 'trustworthy', when it encompasses credibility (internal validity), dependability (reliability), confirmability (objectivity), and transferability (generalisability).[298] I have however, strived to deliver trustworthiness by incorporating, embedding and applying constant comparison, framework analysis, respondent validation, and supervisory coding checks within the data analysis, as well as actively considering my place within and throughout this study (reflexivity) from its inception to final write up. All which aimed to deliver credibility, dependability and confirmability.

Transferability, on the other hand, was and is a more challenging concept as part of the study – current practice – fitted better with a 'naturalistic' stance, where *'generalisation [is] a function of people's knowledge based on their experiences; empowers the readers and democratises generalisation; provides sufficient context for reader to judge applicability of study findings to their world.'*.[298] Whereas GPs' perspectives regarding the findings of the logistic regression analysis fitted better with a 'theoretical' stance where *'…concepts developed [were] based on data can [or may] be applied elsewhere.'*.[298] From a pragmatic point of view only the individual who is reading the study report can decide on the transferability of this study's findings to their individual experience and practice; no two people have exactly the same experiences, so their world views must differ; they may have a shared experience but differing degrees of shared beliefs and views.[243]

Finally, from this process, an understanding of the factors influencing GPs decision-making regarding the use of antidepressants and their doses emerged, and were conceptualised into an overarching explanatory model of factors influencing prescribing; balancing treatment and decision to prescribe (Appendix A2.3.5), and antidepressant growth in relation to the management of depression (Appendix A2.3.6).

6.3.6 Research, ethical approval and reporting

Ethical and research advice were sought from the NHSGGC Research and Development team. I was informed by the NHSGGC Academic Research Co-ordinator that, *'Staff studies are deemed low risk and as such are exempt from ethics review'*,[299] however the study would require completion of the Integrated Research Ethics Application System forms which would require to be reviewed by the Research and Development team.[300]

The University of Stirling requires ethical approval for all research studies undertaken by staff and students at the University. Therefore, approval was sought from the School of Nursing Midwifery and Health Research Ethics Committee. This study was approved by the School Research Ethics Committee; 21st April 2014 by email and followed up by letter 22nd May 2014, see Appendix A2.4.

Sponsorship and indemnity were also considered. NHSGGC would usually provide sponsorship as my employer, as the study was continuing health board work to support the appropriate use of antidepressants. However, NHSGGC considered it inappropriate to act as sponsor for this study as it was also being used for a postgraduate degree, therefore the University of Stirling agreed to sponsor this study, see Appendix A2.5.

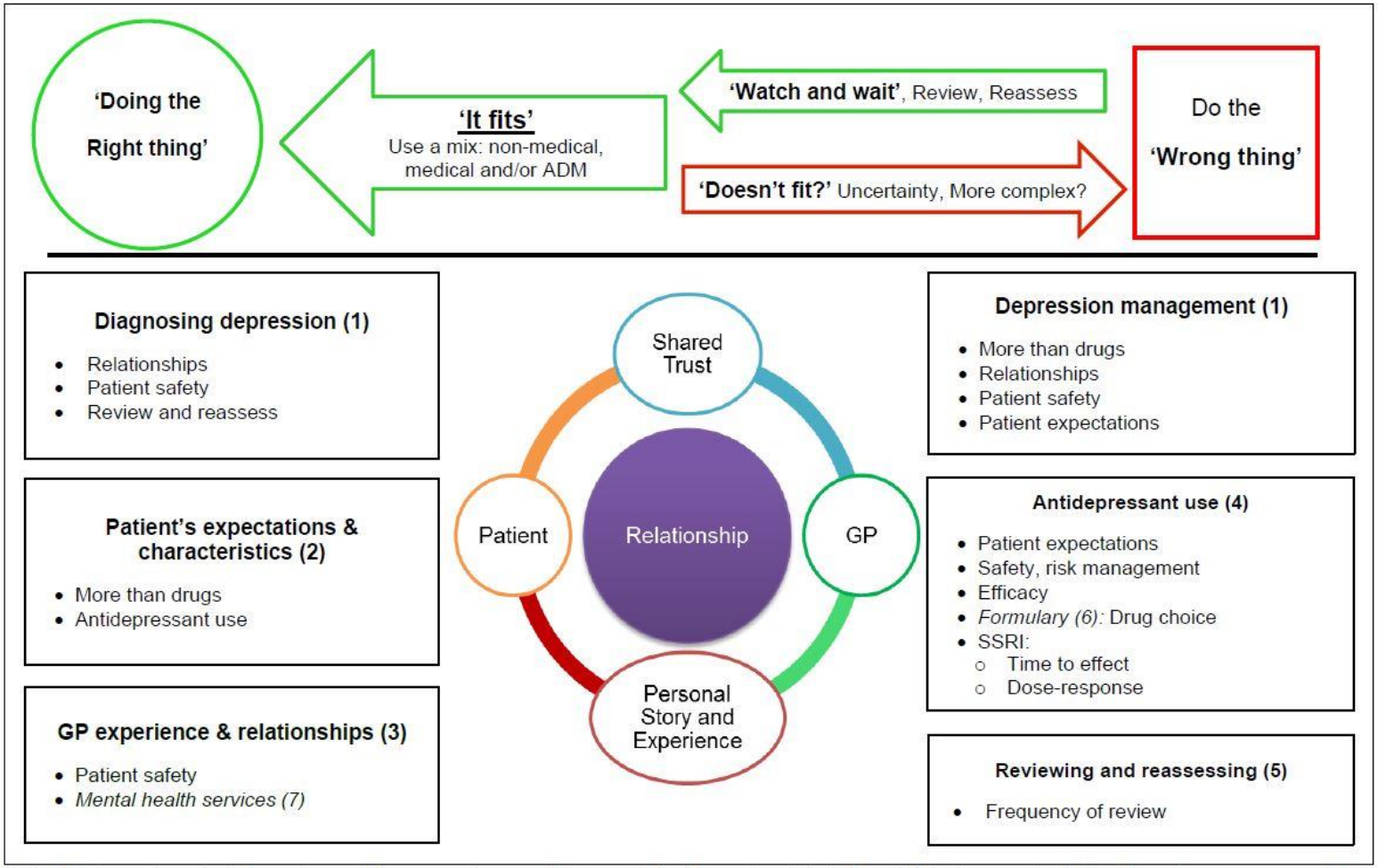
Finally, this study is reported in line the Standards for Reporting Qualitative Research recommendations, see Appendix A2.6.[301]

6.4 Results

6.4.1 Overview

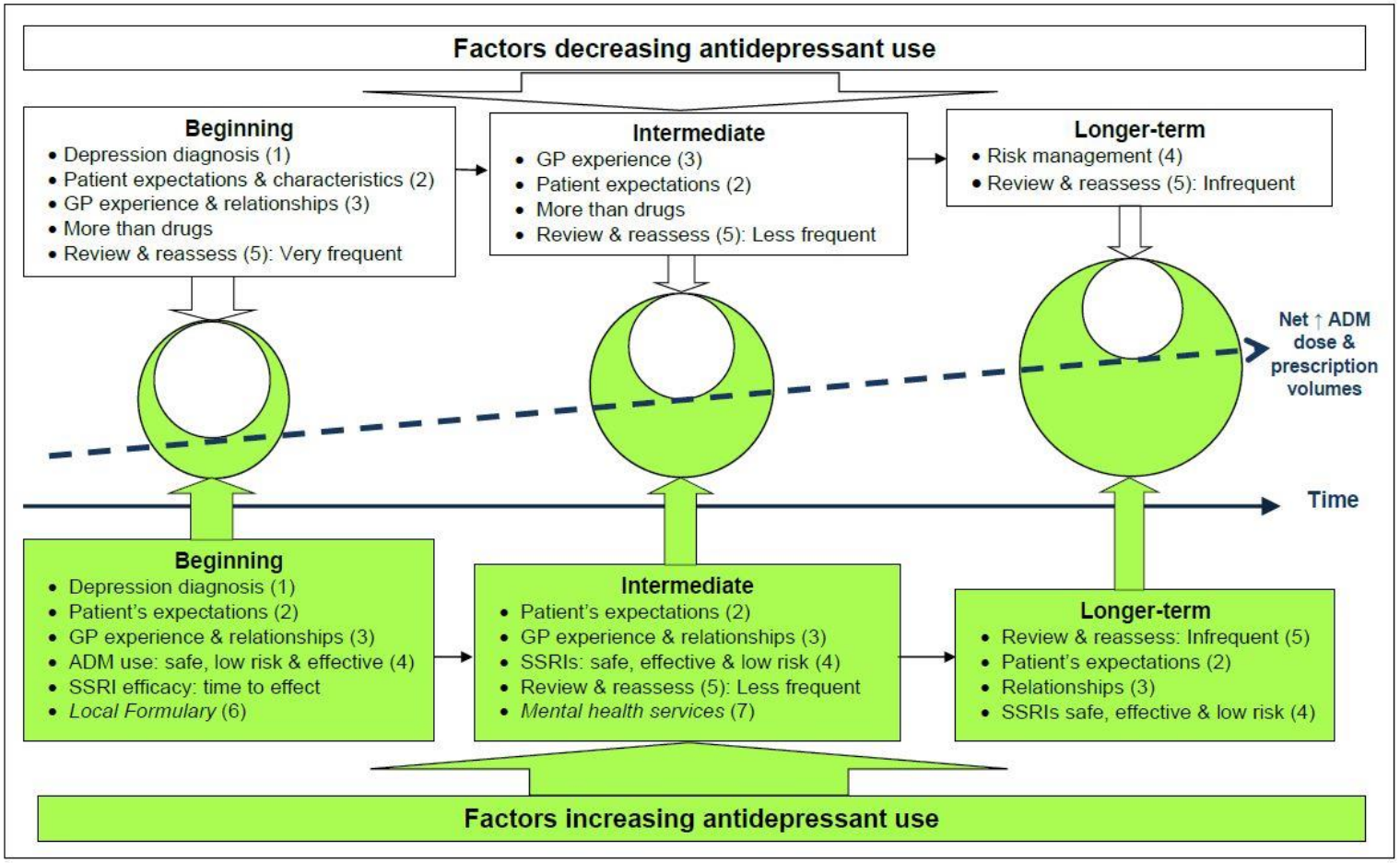
Analysis revealed that depression treatment involved two key overarching concepts of ‘doing the right thing’ and achieving the ‘right care fit’ for individuals. This involved medicalised and non-medicalised patient-centred approaches with antidepressants being only one facet of treatment, while striving to balance and optimise treatment options, as summarised in Figure 14. However, factors influencing antidepressant prescribing and prescribed doses varied over time from first presentation and the beginning of treatment, to antidepressant initiation and longer-term treatment. Seven interwoven factors influenced antidepressant prescribing, and are represented by the following emergent themes, five of which can be described as strongly influential: 1) Depression diagnosis and management; 2) Patients’ expectations and characteristics; 3) GPs’ experience and relationships; 4) Antidepressant use: safety, risk management and efficacy; 5) Reviewing and reassessing. Two of the seven themes can be described as moderately influential, 6) Local prescribing resources, and 7) Mental health services. The magnitude of influence exerted by the emergent factors and their influence on increasing and decreasing antidepressant prescribing during the treatment journey, see Figure 15. This is a dynamic process however, that varies with the individual patient, GP, context and time. The factors are not fixed in a specific order, progression or linear process, but vary in magnitude and influence during the patient’s journey.

Figure 14. Balancing treatment and management: factors and sub-factors



Note: Factors strongly influencing antidepressant prescribing are in bold, moderately influential factors are in italics (Numbers correspond to emergent factors). Sub-factors are listed and match the subheadings within the main text.

Figure 15. Factors increasing and decreasing antidepressant prescribing for the management of depression



Note: This is a dynamic process that varies with the individual patient, GP and time; the listed order is not fixed, but variable. Factors influencing antidepressant prescribing listed, moderately influential factors are in italics (Numbers correspond to factors). Sub-factors are listed and match the subheadings within the main text (not numbered). ADM: antidepressant. SSRI: selective serotonin re-uptake inhibitor.

6.4.2 Depression diagnosis and management (Factor 1)

6.4.2.1 Diagnosing depression

Across the sample diagnosing depression was rarely seen as a simple task or process. This was due to a variety of issues and complex interactions involving: normal life events; relationship problems; social and environmental issues; patients' expectations of happiness; duration of symptoms; mixed anxiety and depressive symptoms; comorbidities; and the risk of medicalising normal and '*appropriate misery' (D21,18p3)* due to life events. However, time well spent in this initial presentation period – regularly reviewing patients – was seen as an important part of the biopsychosocial assessment. Some practitioners routinely used depression rating scales to quantify depression severity or as a tool to support discussions with patients, whereas others found rating scales hampered assessment, or were not used as they lacked a social domain. Patient information was used to ascertain and balance how well signs, symptoms and subjective assessment fitted with standardised concepts of clinical depression and severity to achieve the best treatment 'fit' (Figure 14).

…the bottom line for GPs is that we want to help, we want to offer something that we think will help. D12,8

You also want to look at the person as a whole and find out where they are in their life. You have to assess the actual severity of the situation before determining what kind of treatment would be appropriate for them. Then, we would go down the route of discussing what sort of therapies we could offer them. D25,6

In general, GPs rarely prescribed antidepressants at the first presentation, unless patients had a recurrent depressive episode where antidepressants were previously effective. This is because a large proportion of patients presented in crisis and were experiencing an acute reaction to life events or stressors. GPs in my study viewed it as more important to listen to patients and discuss issues in the first instance, especially for mild to moderate forms of depression where patients needed someone to talk to, not prescribe. Allowing a period of 'watch and wait' where depressive symptoms would remit.

…for a lot of people with a mild to moderate depressive illness, is to say, "you might not need anything here. You might just need, someone to talk to you about it and some support and things might improve on their own". D12,96

Although for some patients, there was an expectation about receiving something.

They think they're coming here [pause] for me to do something for them [empathetically said]. And that, they almost feel as if there needs to be a physical display of that, like the prescription or whatever. D2,14

For more severe cases, and for patients that GPs knew well, they would consider prescribing at the first presentation if symptoms were sufficiently severe to warrant an antidepressant. However, this was not routine practice. Referral to specialist CMHTs was also considered for people with more severe symptoms.

6.4.2.2 More than drugs

Treatment involved more than drugs. As already identified, GPs considered listening, talking and allowing patients time for spontaneous remission as an important core part of appropriate care, treatment and management. For all severities of depression, and where patients preferred not to take antidepressants for moderate to more severe depression due to stigma or personal choice, GPs embraced, supported and used multiple options to manage and treat signs and symptoms in line with the patient's preferences. This included a varied array of medical and non-medicalised approaches: creating space for patients by using sickness certification; exercise and exercise referrals to local council gyms; counselling; signposting to information sources e.g. Links-workers to address money worries; bibliotherapy in libraries; online cognitive behavioural therapy e.g. Moodgym; talking therapies via NHS and non-NHS providers in combination with or without antidepressants. A multifactorial interwoven approach was thus created in achieving the 'right care

fit' and 'doing the right thing', with drug treatment being only one of many therapeutic approaches.

I explain to them that, "You have to look at this [responding to an antidepressant] in conjunction with other things." So, it's always going to be a multifactorial approach. It's never going to be just one thing [an antidepressant]. D28,28.

... [I] would discuss things like about lifestyle measures, about cut back on alcohol and trying to improve their general wellbeing with a good diet, but also exercise is obviously shown to be helpful with mental health problems, and also just as an aid to stress and relaxation. D20, 12

There's usually things to discuss and a lot of that with patients is about education of lifestyle things that can make a difference, be it alcohol, exercise, interrelationships. These kind of things. Often, it's not a magic bullet with an antidepressant. It's part of your treatment. It's part of the other things you're trying. D24,8.

6.4.3 Patients' expectations and characteristics (Factor 2)

Study data indicated that GPs' prescribing was not overtly influenced by patients' expectations of receiving an antidepressant. The need for a clear benefit to the patient was still the main influence, assessed on the basis of knowing the patient's history, comorbidities and social context. However, it was acknowledged that time pressures could play a role, as it was difficult to discuss and encourage the use of non-antidepressant alternatives if clinics were running late.

I think most of my colleagues here wouldn't prescribe unless they felt somebody was going to get benefit from them. We all kind of have roughly the same sense of what's bad and what's good. D4,24

Many GPs felt that some patients were looking for 'a quick fix', and that this was rooted in wider societal expectations that problems could and should be solved medically. However, it was usually those with milder symptoms that had greater expectations of 'a quick fix'. As they presented in crisis there was an

expectation to do something to solve the problem; a physical display with a prescription, which was sometimes driven by family members more than patients. For some the 'quick fix' was short-term antidepressant use, which stopped within a couple of months of starting, while others did not expect 'a quick fix' and wanted to avoid antidepressants altogether, regardless of the patient's socioeconomic status.

They think they're coming here [pause] for me to do something for them. [empathetically said, resigned]. And that, they almost feel as if there needs to be a physical display of that, and in like the prescription or whatever. I think the people that, [think] that they wouldn't get something to take home from the consultation, is the people that probably would need the antidepressants and don't have the insight to see that they're actually quite ill. So those are almost the people that don't expect treatment, whereas the people that are milder, that are here, and seeking help, I think feel that they do expect more. D2,14

I probably have the wrong words, but it tends to be the people who want drugs that I don't think need it, tend to either be an acute reaction to something, a bereavement or something. A normal [emphasis] episode of low mood that would be expected, or people who are rightly depressed... but not to the level where I think they necessarily need so much intervention, but want a pill to... inverted commas "fix it" or the quick fix. I don't think they are then looking at the underlying problems or the way they're dealing with stress, or the way their expectations.... and then... or what they're... how they feel about their lives. D19,24

I think, they think talking to someone is not going to help, even though they want to come in and talk to me. [Interviewer: Right.] I think people want a quick fix as well. [Right.] And they see an antidepressant as a quick fix. D22,37-41

I think there's an expectation generally, that if there is a problem perhaps you know there is a pill for it. I think that is an expectation that's held by a lot of people. Other people are very resistant to the idea of taking antidepressants. D18,6

The data also presented a mixed picture for the influence of deprivation on patients expectations, and the GPs' decisions to prescribe or not.

...you know working in an affluent area, ...particularly those middle class and above people, have partly made a decision before they come sometimes as to what they want. And it is difficult to sway them from that if you... feel as though that is not really what they need. So if they do have social problems and you feel as though those are the things they need to address... if they want the antidepressant, then that's their agenda. Then perhaps maybe in the other areas you can sometimes discuss and say "you need to deal with this or you need to deal with that." ... But, but definitely I think there's a difference. In less affluent areas people are probably in some ways more open to maybe you suggesting an antidepressant isn't the way to go. D12,6

It depends where you work. I've worked in deprived areas. This is a very affluent area. I think people come here, probably, not necessarily wanting antidepressants but maybe you have to persuade them that this might actually be good for them. Where I'd worked before, people were so desperate and there were so little options for them that [big breath..] they probably think, "Well, let's give it a go." And they're probably more amiable to that because there isn't anything else for them, and they're probably more accepting of the fact that "The doctor has given me a tablet. I must take it." Which round here they're probably, you know, doing research on the internet, they're asking me questions, they're... D4,10

6.4.4 GPs' experiences and relationships (Factor 3)

Experiential learning significantly influenced how GPs prescribed antidepressants. This cumulative knowledge was gained through a mixture of formal training, such as general practice training schemes and acute psychiatric experience, and informal reflective practice - seeing improvements in one patient and repeating the same intervention with others. However, with time and greater experience prescribers formulated their own ideas about depression management, becoming more *'idiosyncratic'* to achieve the 'best care fit' such as using mirtazapine rather than fluoxetine, where insomnia was a significant issue, or sertraline instead of citalopram for patients with cardiac disease.

I think initially absolutely with guidelines and I guess, as I alluded to before, the more experienced I've got, the more idiosyncratic I've got. It tends to be how a patient's presenting, so it might be side-effects or likely side-effects or beneficial side-effects that may guide me on where I would go [with treatment]. D24,20

National and local guidelines were considered by GPs to weakly influence antidepressant prescribing, with some specialist resources being helpful in specific situations e.g. switching drugs. However, local prescribing resources, namely the formulary and prescribing support teams, did influence drug choices and cost-effective prescribing decisions.

We've got our in-house pharmacist, and it's fantastic, 'cause we sit down and talk about these things... For example, with venlafaxine slow release people, we've changed all of them [to lower cost ordinary release], and we resisted pressure from secondary care and patients as well. So that's definitely a positive influence. Because we're not pharmacists, and we don't know nearly as much about pharmacology as pharmacists do. D26,129

Most GPs indicated they prescribed within formulary guidance whereas psychiatrists and other specialists tended to prescribe third- or fourth-line agents which were outwith formulary guidance. This sometimes caused friction, especially with children and adolescents where the evidence is weaker;

there were potentially greater safety concerns and risks; and shared care structures were lacking or not considered robust enough, thus providing a 'poor care fit' and raising potential medico-legal issues.

The other issue is prescribing antidepressants in young people. We won't prescribe antidepressants that are unlicensed in young people. We won't prescribe them in people under the age of 18 because there is no shared-care protocol. Unfortunately, without the support of shared-care protocol we don't feel really we have the specialist knowledge to be prescribing it much for [children and adolescents]. D25,29 We've been asked to prescribe sertraline and fluoxetine, I think, in people around about age 15. Both of which we've refused. We've refused all of them. The issue then is that they feel that once they've initiated it we should take over the prescription. But because there's no shared-care protocol it still leaves us fairly vulnerable. So, we have still decided as a partnership that we won't be involved in that…D25,31

However, these frictions were partly overcome where there was good communication, supportive structures and good relationships.

Pharmaceutical companies were considered not to influence prescribing as GPs avoided seeing company representatives for a variety of reasons e.g. anger about 'me-too' drugs, promotion of active isomers of cheaper older drugs sold at a premium price. However, GPs acknowledged that companies had subtle influences on depression management.

Well... escitalopram really pissed me off, I hate that sort of carry on, it was like loratadine and desloratadine, I just hate that! I mean "me-too" drugs that happen to appear just as patents are running out and are another way of creaming money out of the unsuspecting public,… D21,70

…there was the Defeat Depression campaign and that was the Royal College. But the Royal College and GPs really got into tow I think with pharma in a big way, and I think actually that was probably fairly influential but,… pharma were probably being very very clever there, and more subtle than usual. I would say…people get quite well

develop antibodies to pharma now. So they actually probably have to work harder to convince me… But they are more subtle, and they have subtle links. D18,23

In general the media was considered not to influence prescribing, but some GPs were aware of previous media articles regarding fluoxetine and adolescent suicide, which had changed prescribing habits. The media was thought to influence patients' attitudes and expectations regarding depression treatment, although this was often presented in a confused ambiguous manner.

I think that the media give quite a muddled view on things. They all seem to be reporting the celebrities who are getting treatment or counselling for this, that and the other. And, then, on the other hand, they bash GPs for overprescribing antidepressants like sweeties. D3,20

6.4.5 Antidepressant use (Factor 4)

GPs indicated that a range of medicines related factors influenced their use of specific antidepressants, from patient characteristics to safety concerns and adverse drug effects. While all antidepressants were seen as being effective, opinion varied over how long it took for them to show their antidepressant effects, and what the optimal doses were.

6.4.5.1 Safety, risk management and efficacy: drug choice

Across the sampling frame prescribing was influenced by GP's prior clinical experience, severity of patient's depressive symptoms and needs, along with age and comorbidities. Treatment options were agreed through GP-patient discussions.

You aim to certainly do it [prescribe] in partnership with the patient. At the end of the day, if you don't do it in partnership with them and you prescribed it, then they won't take it anyway, so you do it in partnership with the patient. …based on advice, guidelines. I think there is an element of doing what you believe is the right thing from your own experience. D8,22

SSRIs were seen as being effective, well tolerated and a safe choice, especially when compared to TCAs. Consideration was also given to the slight

differences between SSRIs with fluoxetine seen by some as more stimulating and appropriate for depression, whereas sertraline and citalopram were considered more appropriate for mixed depression anxiety symptoms and better tolerated. The MHRA safety warning regarding citalopram and escitalopram causing dose dependent QT interval prolongation, which is associated with ventricular tachycardia and sudden cardiac death,[198] had influenced prescribers who were now using less citalopram and more sertraline.

They're safer. So, no one in their right mind now is going to give an MAOI if you're a GP. There's no good reason to start a tricyclic rather than an SSRI unless you'd been through a few of them [antidepressants] already. You know, there's far less risk from a GP's point of view in terms of overdosing, in terms of side effects from the medication. D22,33

Mirtazapine's side effects were considered beneficial for some patients, with weight gain being positive for underweight patients while the sedative effects alleviated insomnia and anxiety symptoms for some. Low dose mirtazapine was being used in preference to more traditional low dose trazodone, or as a safer non-addictive alternative to avoid B-Zs.

...well I know that it's a funny drug [mirtazapine], because it's supposed to be only sedating at low dose, because it has the antihistamine effect. We use it a lot at 15mg just for the sedating effects, as a non-addictive sleeping pill, really. D26,39

Opinion was split when using mirtazapine to treat depression - some quickly increased to therapeutic doses while others maintained people on 15mg subtherapeutic doses. In part this may have been influenced by CMHTs and Addictions Teams use of low dose mirtazapine as a single agent or in combination with other antidepressants. A small minority of GPs acknowledged that they rarely added another antidepressant to augment current treatment, e.g. adding mirtazapine to an SSRI, and considered their practice to be influenced by CMHTs as only a minority of these GPs had extensive psychiatric training. Others, however, questioned the appropriateness of combining antidepressants without specialist input and considered it as the specialist's

domain, as with other psychotropics e.g. antipsychotic augmentation with quetiapine. Most were comfortable initiating low dose amitriptyline for neuropathic pain for patients already receiving an antidepressant for depression.

Well that's one of the places I have been influenced by secondary care. Because a lot of the psychiatrists say, we're going to add this to augment the effect of this. It's usually mirtazapine and citalopram together. And I actually do think that works, I'm not quite sure the biochemistry behind that. But... erm, I now do that sometimes myself. It's often for the poor sleepers. D26,65

6.4.5.2 SSRI efficacy: time to effect and dose-response

All GPs reported that they prescribed standard therapeutic SSRI doses: 20mg daily for citalopram, fluoxetine and paroxetine, or 50mg daily for sertraline. Half considered that SSRIs were effective within 2 to 4 weeks, with some indicating that some patients respond well within the first 2 weeks of treatment. The remaining half considered efficacy was achieved within 6 to 8 weeks. When SSRIs taken at therapeutic doses were ineffective or partially effective, a large proportion of GPs would wait 8-12 weeks before increasing the dose or changing the antidepressant. Most of these prescribers were female and had completed GP psychiatric or extra psychiatry training but did not differ in other characteristics to GPs that increased or changed sooner. In part, persevering with one antidepressant for a longer period may have been due to concerns about giving people an adequate trial, and fears of running out of pharmacological treatment options.

Keep them on... probably quite some time, 2 or 3 months, and if they weren't responding, then change. D17, 50

From experience, a minority of GPs thought that standard SSRI doses provided maximum efficacy, with higher doses lacking greater benefits, so rarely increased or 'pushed doses' up. In contrast the majority considered higher SSRI doses were more efficacious with sertraline being routinely increased.

There were no differences in characteristics (GP age, gender or practice deprivation, antidepressant prescribing volumes and deprivation) between the two groups, with both acknowledging that psychiatrists routinely 'pushed the dose' of SSRIs. However when dose-response effects were discussed, as part of the MHRA advice restricting citalopram to lower doses, most GPs observed that a few patients' depressive symptoms had worsened after reduction while the majority of patients remained well controlled on lower citalopram doses.

…there seemed to be historically the idea was to sort of 'push the dose up' and certain psychiatrists always seemed to kind of push the dose up with antidepressants. D13,100

As we know the response to higher doses doesn't grow, you know, parallel to the increasing dose. So, if we get a good response to the first dose... doubling the dose to, a higher dose doesn't always make a big difference. That's our clinical experience. D6,44

Some prescribers acknowledged being drawn into responding to a patient's distress by 'doing something' although they were aware the intervention may have limited or negligible benefits. Some considered this to be less than an ideal care 'fit' even though it provided patients with hope, demonstrated that patients had been listened to, and that all options were being tried.

…when you've got a patient, a desperate patient in front of you wanting something to be done, it's, the temptation is to crank up the dose. Again, one of my colleagues will go up to much higher doses of fluoxetine than, than perhaps the rest of us would. D3,60

6.4.6 SSRI dose: perspectives on the cross-sectional study findings

GPs' opinions were sought regarding the observations from previous studies that higher than standard SSRI doses were routinely being prescribed.[17, 191, 201] Their opinions were also sought on the regression analysis' findings that higher than standard SSRI doses for the treatment of depression were associated with the practice the patient attended, long-term use (receiving the same antidepressant for ≥2 years), see Section 5.3.2.

GPs considered that practice factors associated with higher SSRI doses may be due to more aggressive prescribers 'pushing the dose', but was in part due to prescriber's experience, what worked with previous patients and/or if GPs had psychiatry training. Although GPs admitted to being more comfortable prescribing antidepressants and patients were more comfortable taking antidepressants, most practitioners considered that their prescribing was similar to their colleagues. Only two GPs considered that they prescribed more, one due to being female and seeing more female patients and the other because he prescribed lots of everything.

A few GPs highlighted differences in management styles between them and their colleagues relating to: frequency of review and follow up, use of alternatives, and again that a minority were happier prescribing antidepressant combinations for depression, whereas the majority were not.

I think there's two of us in the practice seeing more people who have got psychological problems. I would then however suspect that others might prescribe more antidepressants per head if you know what I mean. Whereas I would be more interested in trying alternatives to antidepressants. D18,26

Long-term SSRI use was considered to be due to a combination of factors: greater depression severity with more refractory symptoms; and SSRI dose escalation over the years in response to patients experiencing crises and seeking help, as previous dose increases were considered effective. However, these higher doses may not have been reviewed and reduced at a later date, and then further increased with subsequent crises, with colleagues within the practice not feeling comfortable reducing and/or stopping medication because they had not increased the dose. As patients presented in crisis, and not when they are well, there were challenges in ensuring proactive routine antidepressant reviews and opportunities to appropriately reduce prescribing. GPs did however acknowledge that most patients who were proactively reviewed due to the MHRA citalopram warnings were able to reduce or stop citalopram without any significant problems.

Patient and GP fears of relapse due to reducing or stopping antidepressants – causing more harm than good – were also discussed by some prescribers.

This was especially a concern for patients with chronic depression, creating challenges for restarting, optimising and stabilising individuals.

I suppose if you've got somebody that goes through crisis and they're on a drug anyway for a long time, every time they have a crisis the dose might be bumped up and then not reduced. So, I wonder if there's an element of just not reducing the drug when it's appropriate... and patients psychologically seem to be quite dependent on these drugs as well. So, they might want that increased dose too. D10,93

6.4.7 Reviewing and reassessing (Factor 5)

All GPs indicated that they would routinely review patients more frequently at the start of treatment, and after starting an antidepressant, as this was seen as an important part of the biopsychosocial assessment. The frequency of follow up reviews however, varied depending on patient needs and risk factors such as thoughts of deliberate self-harm and/or suicide, and as the course of treatment continued the frequency of follow up reviews reduced.

Two weeks. So if ever I see someone with depression or anxiety, whether I start them on meds or not, it's a two week review. And it's every two weeks until things are significantly better, and then we increase it to monthly, and then two monthly. D27,104

…but I might want to review them sooner. Just to sort of assess their progress in terms of say suicidal thoughts or agitation or anxiety. D11,86

While GPs acknowledged that the longer patients received antidepressants the less frequent reviews became, they also reported that a combination of factors hindered follow up reviews. One challenge was that patients only presented in crisis and did not attend when proactively recalled and asked to attend for review.

…then you might not see them again until there's another crisis, though. And then you are not seeing them at a time when they have been well for a while. D16,64

I think another factor is that patients often end up on antidepressants long-term and we do try and bring them in to review them, but even when we invite them in they don't always come, which can be a problem. And I think that obviously indicates a reluctance by them to probably discontinue or reduce their medication D15,2

Time was also considered a challenge for arranging and organising face-to-face follow up reviews, although GPs would routinely use phone reviews to enable them to review more patients within a limited time. However, proactively reviewing all patients receiving long-term antidepressant treatment was seen as *'…a daunting prospect.'. (D9,101)*

I think one thing that we've been quite proactive to do here is increasing telephone consults. So, we recognise that a telephone consult on average would be half the time of our face-to-face consult. Now that means that you don't get as much from a telephone consult as you do face-to-face in a depressed patient. But, I think if somebody is very well, actually, you do get almost as much if you speak to them on the phone, so we try and do lots of telephone consults for our reviews on antidepressants as long as the patient's stable. D24,64

Continuity of care was also considered an issue for patients who attended and were seen by multiple GPs; one GP may be uncertain for example why a patient's dose was increased and how long the increase was to continue for. This type of uncertainty was also reflected in resistance and fear of reducing doses and/or stopping antidepressants from a prescriber and patient perspective, especially when an antidepressant has been prescribed for a long time.

…there's little chance of getting them off unless the patient wants to. And if you even try and discuss it with them, you meet complete resistance... to reducing the dose or coming off. So, only when they're ready to come off will they come off. They rarely come in and discuss it with you. D9,34

…there's a huge resistance, usually, on their [patient's] part, to bring it down, because of their fear of relapse. So I tend to find the folks that are on higher doses have had really tough times. It's got better, and they're happy where they're at, they're willing to just keep going on that. D27,164

6.4.8 'Doing the right thing' and 'the right care fit'

The analysis revealed that depression treatment involved two key overarching ethical and professional imperatives of 'doing the right thing' for individuals by striving to achieve the 'right care fit'. This involved medicalised and non-

medicalised patient-centred approaches with antidepressants being just one facet of treatment and care (Figure 16).

I think it's important in a pressed ten-minute consultation... that, you, deal with these issues as they should be dealt with... and don't see prescribing a pill as a panacea. I think you have to be... the patient may come in looking for a pill. That may be what they want, but it may, absolutely, not be the most appropriate line of action for them. I think you have to be careful with that. D23,4

...guidelines are great, but an individual in front of you, it's a value judgement and I think that's where there's a wee bit of the art of what is right for that person, and you hope you are making the right decision. Even if the guidelines tell you to do something you sometimes get the feeling it is not right for that person. D12,14

...you do it in partnership with the patient. And it's erm... You make your recommendations, I think, based on advice, guidelines. I think there is an element of doing what you believe is the right thing from your own experience. D8,22

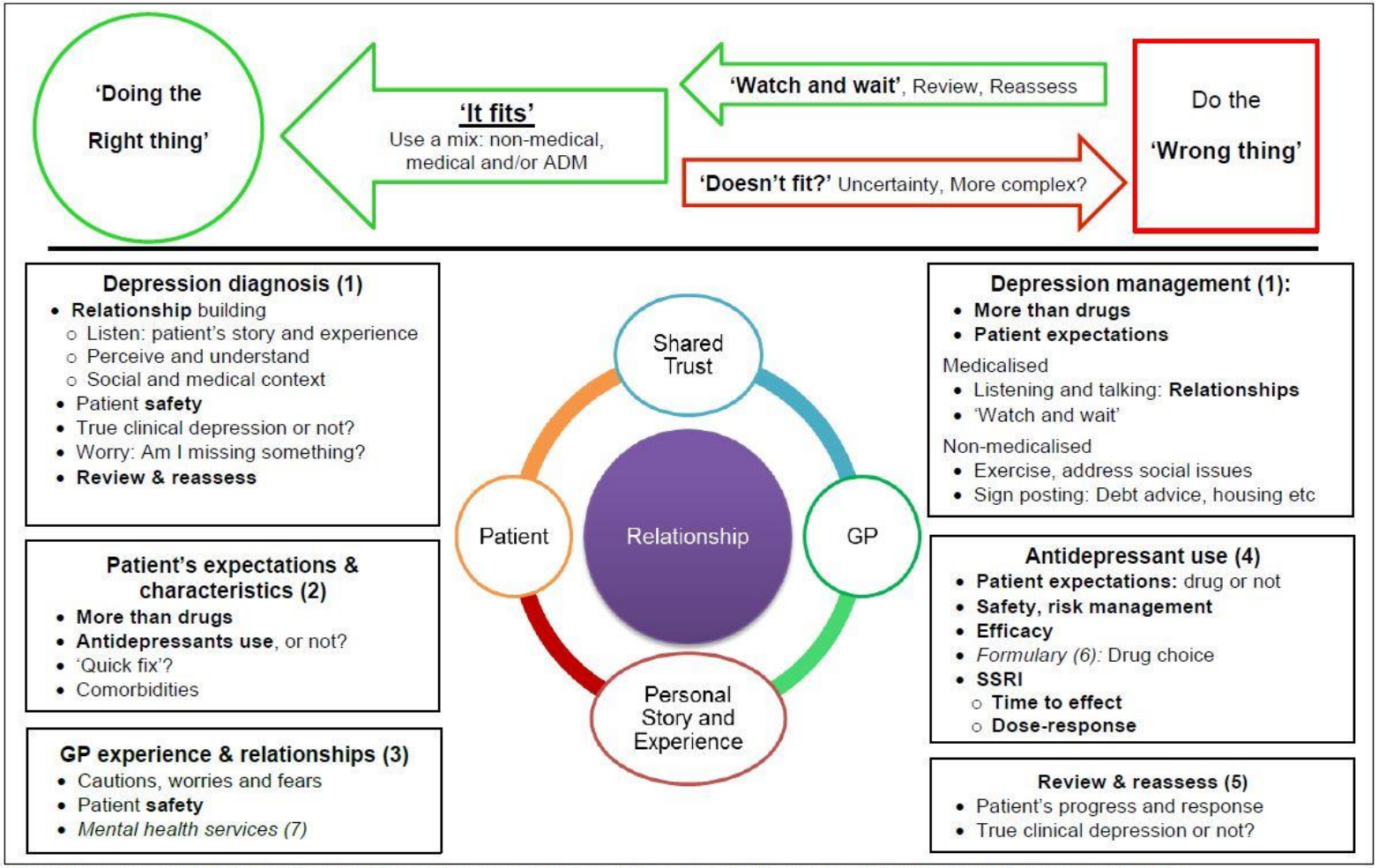
I explain to them that, "You have to look at this [responding to an antidepressant] in conjunction with other things." So, it's always going to be a multifactorial approach. It's never going to be just one thing [an antidepressant]. D28,28.

When faced with distressed patients showing symptoms of moderate to severe depression GPs were confident prescribing SSRIs which they considered as safe and effective medicines, and ethically and professionally appropriate.

...I think most people have come to the same conclusion, whether it's... I don't know how strongly they are. I think most of my colleagues here wouldn't prescribe unless they felt somebody was going to get benefit from them D4,24

Well, the SSRIs I would always use first line in depression just because they're safer. Whereas, the tricyclics I would keep for [breath in...] further down the line or if they had other co-morbidities. So if it was somebody with huge amount of sleep disturbance or had chronic pain [emphasis] as well, then I would probably, possibly think about a tricyclic. In terms of side-effects, you know the SSRIs is better tolerated 'cause tricyclics can cause a lot of side-effects. D5,76

Figure 16. Balancing treatment and management options, revisited



Note: Factors and sub-factors influencing antidepressant prescribing are in bold, moderately influential factors are in italics. Numbers in brackets correspond to emergent factors.

Many GPs were unaware that higher SSRI doses lacked greater efficacy and onset of action occurred within 1-2 weeks, preferring to wait 8-12 weeks before increasing or switching.

See them back just to make sure they are okay, and then you know that hopefully the plan is, "over the next 6 to 8 weeks you will have more good days than you had bad days", and then at 8 weeks then you look at whether or not going to increase it or going to switch it. D16,74

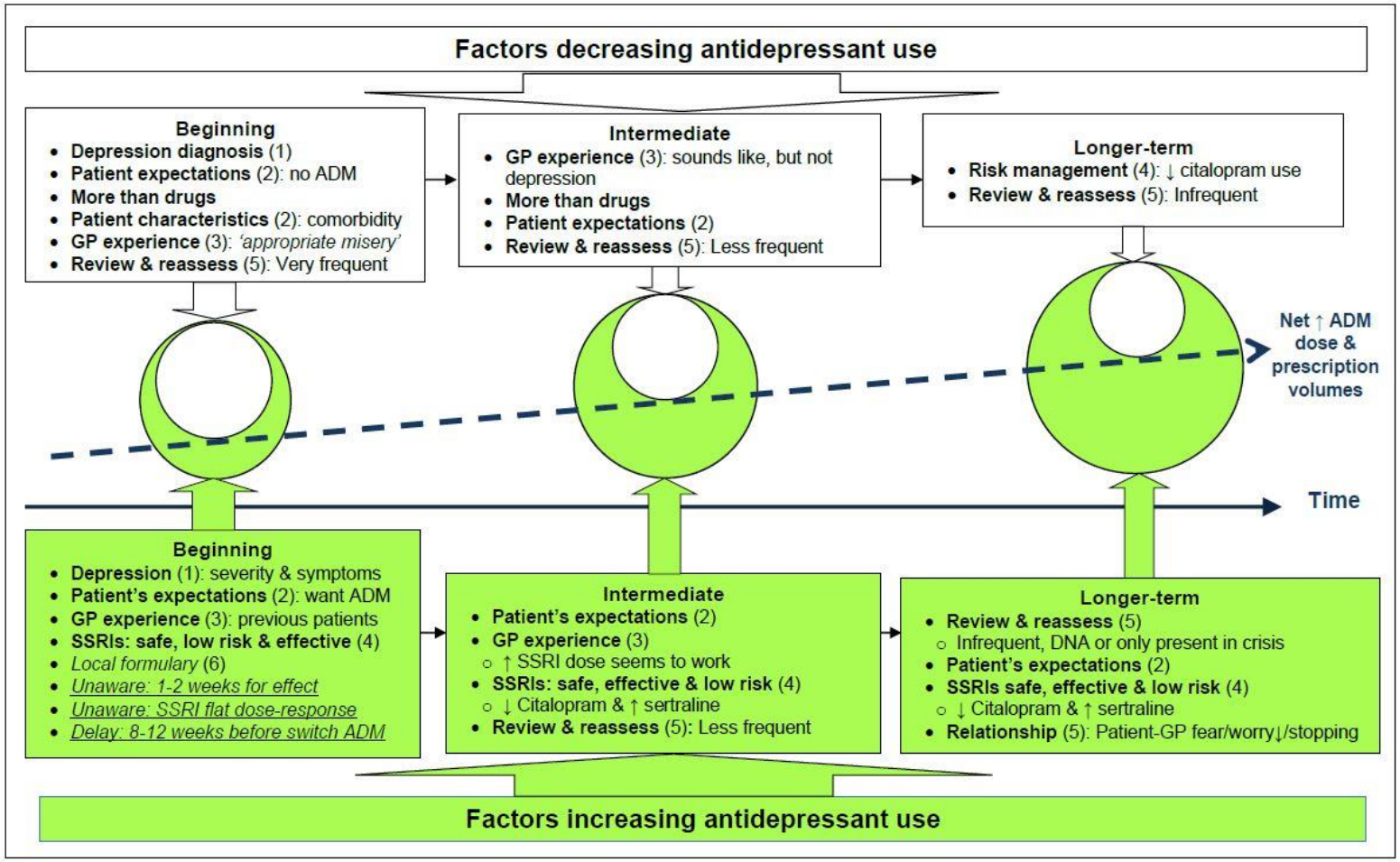
Factors influencing antidepressant prescribing and doses varied over time from first presentation, to antidepressant initiation and longer-term treatment. The ongoing pressures to maintain prescribing (e.g. patient wishes, fear of depression recurrence), few perceived continuation problems (e.g. lack of safety concerns) and the lack of proactive medication reviews (e.g. patients only present in crisis) contributed to further antidepressant prescribing growth over time. All of which may combine to further drive antidepressant prescribing growth over time, especially as SSRI account for the majority of antidepressant prescriptions in the UK and elsewhere (Figure 17).

…there's a huge resistance, usually, on their [patient's] part, to bring it down, because of their fear of relapse. So I tend to find the folks that are on higher doses have had really tough times. It's got better, and they're happy where they're at, they're willing to just keep going on that. D27,164

… not reviewed, erm... enough. They don't have the reviews... once... there is always that risk, you know, you review them in the early stages. Once they're stable they might come six months later, see someone and feel that they are worse. The dose is increased and then the dose is on repeats [regular prescription]… before you realise it's two years, three years and so on,… But, we're probably failing at that, at reviewing patients on long-term antidepressant medication. And err... Probably, what happens... well, I can think from a clinical point of view, what happens is that these patients are on antidepressants for months or a year or more and then they come with a new crisis. At that time someone decides they need a higher dose. The dose is stepped up and is left there indefinitely... D6,60.

The patients have a lot of expectations around antidepressants. They think that higher doses are better and they also think that switching antidepressants has a general a good effect or they feel, "Well, this has helped but I'm back to the way I was, can I have another one?" D6,62

Figure 17. Factors increasing and decreasing antidepressant prescribing for the treatment of depression, revisited



Note: Factors strongly influencing antidepressant prescribing are in bold. GP practice not matching evidence in italics and underlined.
ADM: antidepressant. DNA: do not attend for review. esp. especially. SSRI selective serotonin re-uptake inhibitor. ↑ increase ↓ decrease.

6.5 Summary of qualitative study findings

GPs' treatment of depression involved ethical and professional imperatives of 'doing the right thing' for individuals by striving to achieve the 'right care fit'. This involved use of both medicalised and non-medicalised treatment approaches with antidepressants being only one facet of patient-centred care, and appropriately initiating antidepressants where there was a clear need.

Factors influencing antidepressant prescribing and doses varied over time from first presentation, to antidepressant initiation and longer-term treatment. However, after patients were established on antidepressants and with increasing treatment duration, there were fewer and fewer factors over time which provided counterbalances to reduce prescribing and use, thus explaining the phenomenon sustaining and driving net growth in antidepressant prescribing and use over time.

Lastly, many GPs were unaware that higher SSRI doses lacked greater efficacy or that onset of action occurred within 1-2 weeks; preferring to wait 8-12 weeks before increasing the dose or switching to another antidepressant. Ongoing pressures to maintain prescribing (e.g. patient wishes, GP and patient fear of depression recurrence), few perceived continuation problems (e.g. lack of safety concerns) and lack of proactive medication review (e.g. patients only present in crisis), all combined to further drive antidepressant prescribing growth over time.

6.6 Strengths and limitations

This study's main strengths were the sampling frame and capturing local GPs' perspectives on the regression analysis findings. The study also captured perspectives from GPs working in the same practice, in order to explore practice culture and practitioners' perspectives of their colleagues' behaviour. Whilst the majority considered that they were similar in their prescribing habits to their colleagues; others identified that that some colleagues had a different approach to prescribing which may account for intra-practice variations in prescribing.[231]

The interviews were arranged at a time that was convenient for the GPs to participate, and express their views within their own offices. I took a flexible approach to engaging practitioners on their terms, such that when GPs were called to an emergency or had double booked, we would rearrange the appointment. These actions may have helped to build rapport and trust prior to the interview. Another strength was that during the study period there were no changes to the local formulary, prescribing support team activities or local depression guidelines. British Association of Psychopharmacology issued new guidelines for depression treatment in May 2015,[66] however this was assessed as having negligible effects on GPs' responses, as most acknowledged guidance was a weak influencing factor on their prescribing.

On the other hand, as GPs were not incentivised to participate, I suspect that participants may have been more interested in mental health and psychotropic prescribing, and/or were more willing to openly share their experience of treating people with mental health issues. Some potential participants acknowledged that a lack of time and work pressures prohibited study participation when contacted by telephone. This bias is inherent in all research where participants are invited to take part; however, the study sample was representative of the health board, for practice size, proportion of female GPs and training practice status. Slightly more GPs from higher prescribing practices and practices serving areas of higher deprivation agreed to participate. In part, this may have been due to 62% of NHSGGC practices serving higher areas of deprivation and the inclusion of GPs working in the same practice.

After the initial interviews and analysis, emergent themes were discussed as part of subsequent interviews, however these themes were not overtly checked for trustworthiness with future interviewees. The variety and availability of medicalised and non-medicalised support services did vary within the health board area which may have influenced prescribing, however GPs acknowledged that these were only one aspect of patient care and support, and such variation in support services commonly occur in other urban regions.

Some may criticise this study for not stating that 'coding' or 'meaning saturation' was reached, and while significant debate and uncertainty remains regarding the definition, application and reporting of saturation in relation to qualitative methodologies,[279, 280, 295] I considered the pragmatic qualitative methodological approach to be more applicable to this study's methods and reporting. Likewise, some may criticise framework analysis as lacking the theoretical underpinnings of other qualitative approaches such as grounded theory, while others argue that it is too flexible as an analytic approach.[291] However, the use of charting and mapping demonstrates the methodological transparency that was applied to this study to ensure there was a rigorous, consistent and congruent approach to data analysis and identification of themes.

6.7 Comparison with literature

In the qualitative study, GPs considered that higher SSRI doses were due to a combination of factors: some prescribers being more aggressive at '…*push[ing] the dose up…' D13,100* or '…*crank[ing] up the dose' D3,60* than others; greater illness severity and/or complexity; dose escalation during crises that were never reduced due to a lack of proactive review; and patient and GP fears of relapse when considering reducing or stopping treatment. All of which link with more recent studies highlighting variations in prescribing between individual GPs working in the same practice,[231] healthcare system failures,[195] and barriers to reviewing and reducing antidepressants.[178, 179, 232]

Safety and risk management were recurring features in the qualitative study. In line with previous studies, GPs were confident using SSRIs due to perceived and actual safety benefits when compared with other antidepressants.[8, 302] However, GPs indicated that national safety warnings had influenced SSRI prescribing practice, reducing citalopram use and increasing sertraline use. This shift in practice is now being observed in national prescribing studies,[196] and may further drive up overall antidepressant DDD volumes as sertraline has traditionally been prescribed at higher doses (larger DDDs) than citalopram.[17, 234, 235] Conversely, GPs preferred to prescribe low dose mirtazapine or trazodone for anxiety and/or insomnia instead of riskier B-Zs. However as with

B&Zs, tolerance quickly develops to the sedating effects of mirtazapine and trazodone.[130, 303]

In line with other studies, GP's experience and training, and individual patient characteristics influenced drug choice and use.[21, 304, 305] Some of the GPs in the thesis study indicated that prescribing became more *"idiosyncratic" D24,20*, using learned experience and habits to achieve the 'best care fit' for individuals. In contrast to my study, other studies did not consider the role of specialist services affecting GPs' treatment decisions, whether that consisted of shared experience and good working relationships, or conversely, a lack of robust support structures and fractured care.[306] In part, some of these idiosyncrasies and experiences may contribute to variations in antidepressant prescribing as one GP partner within a practice can skew drug use and prescribing figures.[231] Experience was also identified as a barrier to the use of evidence-based medicine in practice in one systematic review,[307] while another review indicated that evidence-based mental health guidelines had zero to minimal effects on practice, due to a range of barriers.[308] This may partially explain my study's GPs' perspectives that guidelines were a weak influence on practice. It is therefore important that policy makers develop implementation strategies that consider and plan how to overcome such barriers; one solution might be educational outreach as that has been shown to have a significant and sustainable impact on prescribing practice.[197, 247]

The qualitative finding that GPs' preference for waiting as long as 8-12 weeks before increasing or switching antidepressants links with a previous quantitative study demonstrating an 8 week lag in drug optimisation.[239] Together these identify a new potential factor which may influence early antidepressant discontinuation, possibly linking with perceived inertia and service dissatisfaction.[25, 309] But more importantly, such actions inadvertently prolong peoples' misery, as it is known that antidepressants exert their greatest effects within the first 2 weeks of treatment.[97, 310] Therefore, if there are no effects after 3-4 weeks this should stimulate prescribers to review the diagnosis, and if appropriate optimise treatment; changing the drug if they are using an SSRI, or increase the dose if they are using a TCA or SNRI.[166, 167, 311-313]

Prescribers also indicated that antidepressants were only one of many treatment modalities, and that the GPs themselves had a therapeutic function as listener, counsellor and facilitator,[24, 25, 314] as well as creating space through use of sickness certificates.[315] As with other studies, GPs rarely saw depression diagnosis and management as a simple task or process. This was due to the complex interplay of social, environmental and comorbidity issues, as well as individuals' expectations of happiness and unvoiced agendas.[8, 22] Yet, GPs did not readily take the perceived easy option to prescribe antidepressants, preferring instead to 'watch and wait', however they would consider prescribing earlier if depressive symptoms were more severe and/or they knew the patient well.[24, 304] Finally, unlike other studies which identified patients' expectations of antidepressants as being a 'quick fix',[8, 25] GPs in this study were clear in viewing this phenomenon as not being unique to depression treatment, but reflecting wider societal expectations.[176]

Lastly, a lack of awareness of drug limitations and time to effect. This may in part be due to the majority of national depression treatment guidelines lacking clarity regarding dose-response effects and limitations of different classes of antidepressants. Only a few guidelines acknowledge dose limitations,[66, 183] whereas the majority advise all antidepressant doses should be increased where patient's response is 'poor or lacking'.[67, 96, 181] The lack of clarity and consistency between guidelines however, may be due to most systematic reviews and meta-analyses focusing on antidepressant efficacy without assessing dose-response effects.[10, 15, 95, 145] Reviews that have assessed dose-response effects, present conflicting and contradictory evidence with some stating that SSRIs demonstrate a flat dose-response effect for efficacy,[166, 167, 209] while others demonstrate that SSRIs exert dose-response effects with higher doses being more effective for the treatment of depression.[316-318] Therefore, my next step in this thesis was to systematically review previous reviews assessing SSRI dose-response effects for the treatment of depression.

Chapter 7

7. Systematic review of reviews: a meta-narrative synthesis

This review sought to address the third research question, are higher SSRI doses more effective than lower doses for the treatment of depression, in adults, in primary care? The chapter presents the background, methods, results, summarises findings, discusses the strengths and limitations of the systematic review of reviews, as well as the findings within the context of the wider literature.

7.1 Background and aims

As already acknowledged above (Section 2.7 and 3.1). SSRIs are the most commonly prescribed antidepressants across the world, accounting for more than 50% of all antidepressant prescriptions.[3, 27, 32, 33] The majority of which are prescribed in primary care for the treatment of depression.[17, 31] Over recent years there has been an increase in the routine use of higher than standard licensed SSRI doses for depression treatment in primary care.[17, 191, 201]

Historically general practitioners have been criticised for prescribing subtherapeutic doses of TCAs for the treatment of depression, whereas SSRIs have traditionally been prescribed at therapeutic doses.[30, 99] SSRIs exert their effects via serotonin re-uptake inhibition, and demonstrate a hyperbolic relationship between dose and transporter occupancy and plasma concentration with SSRI initiation doses: 20mg citalopram, fluoxetine, paroxetine; 50mg sertraline; and 10mg escitalopram, daily providing optimal receptor occupancy and serotonin effects.[319] Conversely, TCAs and SNRIs demonstrate changes in serotonin, noradrenaline and dopamine activity and effects as doses are increased, with higher doses demonstrating greater efficacy (Section 2.7).[68, 168, 202] Therefore, theoretically the rationale for increasing SSRI doses for poor/non-responders does not appear to support the use of higher doses.

Over the years numerous reviews have assessed antidepressant efficacy,[10, 95] however few have assessed dose-response effects. Those that have demonstrate a mixed picture, some indicate higher than standard initiating doses are more efficacious,[316, 317] while others refute this,[166, 320] demonstrate mixed effects,[321] or remain ambiguous.[322] In part some of these differences in findings may be due to newer analytical methods being more comprehensive and robust however newer reviews also demonstrate mixed findings.[167, 316, 317, 320] Although, some agree that higher doses are associated with more ADEs.[166, 167, 317, 321, 322]

This ambiguity, regarding SSRI dose-response and efficacy, feeds into national depression treatment guidelines where a few highlight the possible limitations of increasing SSRI doses,[66, 210] while the majority do not, and promote the general message to increase the dose for poor and non-responders regardless of drug class or individual drug being prescribed.[67, 181, 182] Therefore 'push the dose' prescribing has become a routine approach, and while in part this may be due to the doses used in clinical trials and different prescribing cultures i.e. higher SSRI doses more commonly prescribed in North American trials compared with European studies,[211, 212] it may also be in response to some patients' expectations of higher doses being more effective.[22] However, it remains unclear if increasing SSRIs doses provides greater efficacy for the treatment of depression. Therefore this systematic literature review of reviews aimed to assess and clarify the relationship between SSRI dose for efficacy (response and/or remission), acceptability (early treatment discontinuation – dropouts) and tolerability (reported ADEs), and critically evaluate the methods previously used to examine SSRI dose-response effects for the treatment of depression for adults.

7.2 Method

7.2.1 Study design

This systematic literature review of reviews aimed to assess and clarify the relationship between SSRI dose-response for efficacy, acceptability (early treatment discontinuation – drop outs) and tolerability (reported ADEs), and critically evaluate the methods previously used to examine SSRI dose-response effects for the treatment of depression for adults.

As a diverse range of review methodologies were used to assess SSRI dose-response effects in previous reviews, a meta-narrative synthesis approach was used.

7.2.2 Search strategy, and criteria of eligibility and inclusion

Recommendations from the Cochrane Handbook for Systematic Reviews of Interventions informed the design of this systematic review.[323] The predefined inclusion criteria for this systematic review and synthesis are presented according to PICOS (Population, Intervention, Comparator, Outcomes, Study design) criteria, Table 9.

This systematic review was initially started to scope and develop the rationale for a registered protocol for a systematic review and meta-analysis which is now redundant: PROSPERO registration number CRD42018091797. See Appendix A3.1 for the protocol for this review of reviews.

Table 9. PICOS inclusion criteria

Population	• Adult human ≥18 years old • Major depressive disorder
Intervention	• Monotherapy • Selective serotonin re-uptake inhibitors (SSRI): escitalopram, citalopram, fluoxetine, fluvoxamine, paroxetine and sertraline
Comparison	• Placebo • SSRI
Outcome	Antidepressant response • Efficacy: reduction in depression signs and symptoms • Acceptability: early treatment discontinuation • Tolerability: any reported adverse drug effects
Study design	• Dose-response • Review • Narrative review • Systematic review • Meta-analysis • Meta-regression • Network meta-analysis

7.2.2.1 Population

Literature reviews for adults ≥18 years old with depression. Depression was used as the common summary term that includes: major depressive disorder, unipolar depression, depressive disorder, endogenous depression and organic depression. Diagnostic criteria and severity of depression were not defined as primary studies were not being assessed. A broad age range was considered appropriate due to the common trend of aging populations across Westernised Societies, and significant number of older adults (≥65 years) receiving antidepressants in the UK and elsewhere: 14% to 19% of people prescribed antidepressants in the US;[35, 324] 17% to 22% of adults in England;[33] significant numbers in Scotland, with 13% (404/3,066) of people ≥70 years receiving SSRIs for the treatment of depression in this thesis' regression analysis, see Figure 12.[27]

Reviews were excluded that involved children and adolescents aged <18 years with depression, as this cohort are not routinely treated in primary care by

general practitioners and demonstrate variable antidepressant response rates possibly due to differences in neural development.[325] Reviews including older people with dementia were excluded as antidepressants are known to be of questionable benefit for depressive symptoms in this cohort [326]. Additional exclusions included: treatment resistant depression, depression during pregnancy, perinatal or postnatal, bipolar, concomitant psychiatric disorders, people who use drugs, concomitant opioid replacement therapy and/or co-morbidity.

7.2.2.2 Interventions and comparators

Reviews assessing SSRI monotherapy for the treatment of depression for all licensed SSRIs were included: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline. The SSRI zimelidine was not included as it has been withdrawn from the market as Guillain-Barré syndrome was associated with its use.[93] Antidepressants outwith the SSRI class with novel serotonin or mixed receptor effects were excluded: vortioxetine a direct modulator of serotonergic receptor activity and inhibitor of serotonin re-uptake; vilazodone with mixed SSRI and buspirone-like activity; the SNRIs venlafaxine and duloxetine; the TCA clomipramine.[100, 327, 328]

Reviews examining concomitant combination treatments: using two or more antidepressants; psychotropic and non-psychotropic medicine augmentation strategies; antidepressant with psychotherapies; and switching antidepressant studies were excluded as these strategies can be more effective than monotherapy and may be reserved for treatment resistant depression.[66, 329] The majority of national guidelines [66, 67, 96, 181, 210] and drug licenses recommend standard starting doses,[100] which are routinely prescribed in practice,[17, 99, 235-237] and represent standardised DDD as defined by the WHO.[206] It was therefore considered appropriate to assess baseline standardised comparator dose effects against placebo and higher SSRI doses (Table 10), however due to the range of methodologies and reporting methods it was not possible to summarise the magnitude of effects using standardised DDDs.

Table 10. Serotonin re-uptake inhibitor defined daily doses

	Daily dose (mg)	Defined daily dose*
Escitalopram	10	1
Citalopram	20	1
Fluoxetine	20	1
Fluvoxamine	50	0.5
Paroxetine	20	1
Sertraline	50	1

*As defined by the World Health Organization.[206]

7.2.2.3 Outcomes

These were defined as dose-response effects for efficacy, acceptability and/or tolerability. Efficacy was defined as a response to antidepressant treatment achieving a reduction in signs and symptoms of depression, and/or remission. Acceptability was defined as treatment discontinuation, where patients terminate treatment early for any reason and did not complete the study (dropouts). Whereas tolerability was defined as patients experiencing ADEs that were reported in studies including death, suicidality, and effects relating to major organ systems: cardiovascular i.e., arrhythmias, QTc prolongation, etc.; central nervous system i.e., headache, anxiety, insomnia, hypersomnia, etc.; dermatological; endocrine; ear; eye; gastrointestinal; genital urinary and reproductive; haematological; musculoskeletal; respiratory; and other non-categorical ADEs.

7.2.2.4 Study design and setting

Reviews assessing dose-response effects for orally administered SSRIs to human adults for the treatment of moderate to severe depression were included. Data from the following review study designs were included: pooled data, systematic literature, narrative, meta-analysis, meta-regression and/or network meta-analysis. Reviews including data from primary and secondary care were included as, although currently the majority of antidepressants are prescribed in primary care to treat depression, a large proportion of the initial randomised controlled trials that inform the reviews were based in secondary care inpatient and/or outpatient settings, not general practice. The duration of treatment was not defined in order to capture information regarding short and

long-term use and potential dose-response effects at different periods of depression treatment.

7.2.2.5 Information sources and literature search

The following electronic databases were searched: Embase, Medline, PsycINFO, Scopus and Cochrane Collaboration library. Reference lists of national and international depression treatment guidelines were searched by hand to identify previous reviews.[66, 96, 181, 210, 330] Reference lists of editorials, commentaries and letters identified from the electronic database searches were also searched for previous reviews. Reviews and/or meta-analysis for all licensed SSRIs: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline, as monotherapy for the treatment of major depressive disorder were searched for. Key search terms included: “systematic review”, “meta-analysis”, “dose-response relationship”, “dose-response”, “antidepressant$”, “antidepressive agent$”, “citalopram”, “escitalopram”, “fluoxetine”, “fluvoxamine”, “paroxetine”, “sertraline”, “serotonin uptake inhibitor$”, “serotonin reuptake inhibitor$”, “SSRI”, “depression”, “depressive disorder”, “depressive disorder major”, “unipolar depression”, “major depressive disorder”, and “human”. See Appendix A3.2.

The terms “systematic review$”, “meta-analysis”, “dose-response”, were combined using the “OR” rather than the “AND” term, as this increased the search sensitivity while reducing specificity, e.g. Embase using “OR” term identified 9414 rather than 1633 articles, see Appendix A3.2.1 to A3.2.3.

Fluoxetine studies were first published in the mid 1970’s and it is the SSRI that has been available on the market for the longest period.[71] Therefore, 1975 was used as the start date until the end of December 2021. Reviews were limited to English language.

7.2.3 Literature inclusion process and data extraction

Article titles and abstracts were screened for inclusion. Subsequently, potentially relevant full-text articles from the literature search were then screened for inclusion, using a structured process and standard terms supporting inclusion and exclusion. Studies that did not meet the criteria outlined above were excluded.

The following data were extracted for each review article using a standardised data collection form specifically designed for this systematic review (Appendix 3.3). Review characteristics (e.g. lead author; type of review; protocol driven review; patient-level data or not; type of depression being treated; review setting primary or secondary care, etc.), antidepressant and comparator information (e.g. SSRI used; fixed or flexible dose study; placebo controlled; dose standardisation technique; treatment duration; etc.), and dose-response effects (e.g. efficacy, dropouts and ADEs) were recorded.

7.2.4 Risk of bias assessment

Each review article was assessed according to the Risk of Bias in Systematic Reviews (ROBIS) tool,[331] in line with Cochrane recommendations.[323] Reviews were assessed by myself using ROBIS and checked by one of my supervisors. The ROBIS tool has been specifically developed and designed to assess reviews within health care settings: interventions, diagnosis, prognosis and etiology. The tool is completed in three phases: 1) assessment of relevance, 2) identify concerns with the review process and 3) judge risk of bias. Phase 2 covers four domains: study eligibility criteria; identification and selection of studies; data collection and study appraisal; and synthesis of findings. Phase 3 assesses overall risk of bias (low, high, unclear) from interpretation of review findings, and considers limitations identified in any of the phase 2 domains.[331]

There is no consensus on how best to assess and address overlap (i.e. duplication), where primary studies are included more than once across two or more reviews which may bias findings, and although a range of methods have been applied such as only including meta-analysis or reviews assessed as being at low risk of bias these may lead to loss of information.[332-334] In order to avoid loss of information, and to demonstrate the diversity of reviews that met inclusion criteria, sub-analysis assessing the corrected covered area (CCA) for reviews assessed as being at low risk of bias was carried out; A citation matrix and pairwise CCA were calculated and tabulated as per Cochrane.[334, 335] Grading as previously defined by Pieper et al. was applied.[334] Similarly there is no consensus regarding sensitivity analysis and how best to assess sensitivity of findings, therefore findings from the CCA analysis were analysed to identify discordant review findings and assess differences.[333]

Likewise there is no consensus on how best to assess and present data on the quality of primary studies.[333] Therefore, for reviews assessed as being at lower risk of bias, the methodological quality of the primary studies was determined using the review authors' original assessment of risk of bias by domains. Primary studies were classified as having low risk of bias if none of the domains were rated as high risk of bias and three or less were rated as unclear risk; moderate if one was rated as high risk of bias or none were rated as high risk of bias but four or more were rated as unclear risk, and all other cases were assumed to relate to a high risk of bias.[336] Overall primary study quality, across the reviews at low risk of bias, was then identified by applying the most frequent quality assessment rating e.g. 3 reviews rated a primary study as high, high and low risk of bias the study was recorded as high, for primary studies included in 2 reviews that did not agree on rating the lower assessment rating was applied e.g. high and moderate recorded as high risk of bias.

7.2.5 Data analysis, synthesis, and ethics

In view of the heterogeneity of primary reviews, due mainly to methodological diversity: narrative, meta-analysis, network meta-analysis, meta-regression, it was considered appropriate to use a meta-narrative synthesis approach.[337] Tables were used to summarise the population, interventions, and outcomes of interest. The updated Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow chart was used to outline study selection process used to identify reviews which met the inclusion criteria.[338]

This systematic meta-narrative synthesis is reported in compliance with PRISMA and RAMESES (Realist And MEta-narrative Evidence Syntheses: Evolving Standards), Appendix A3.4 and A3.5 respectively.[337, 338]

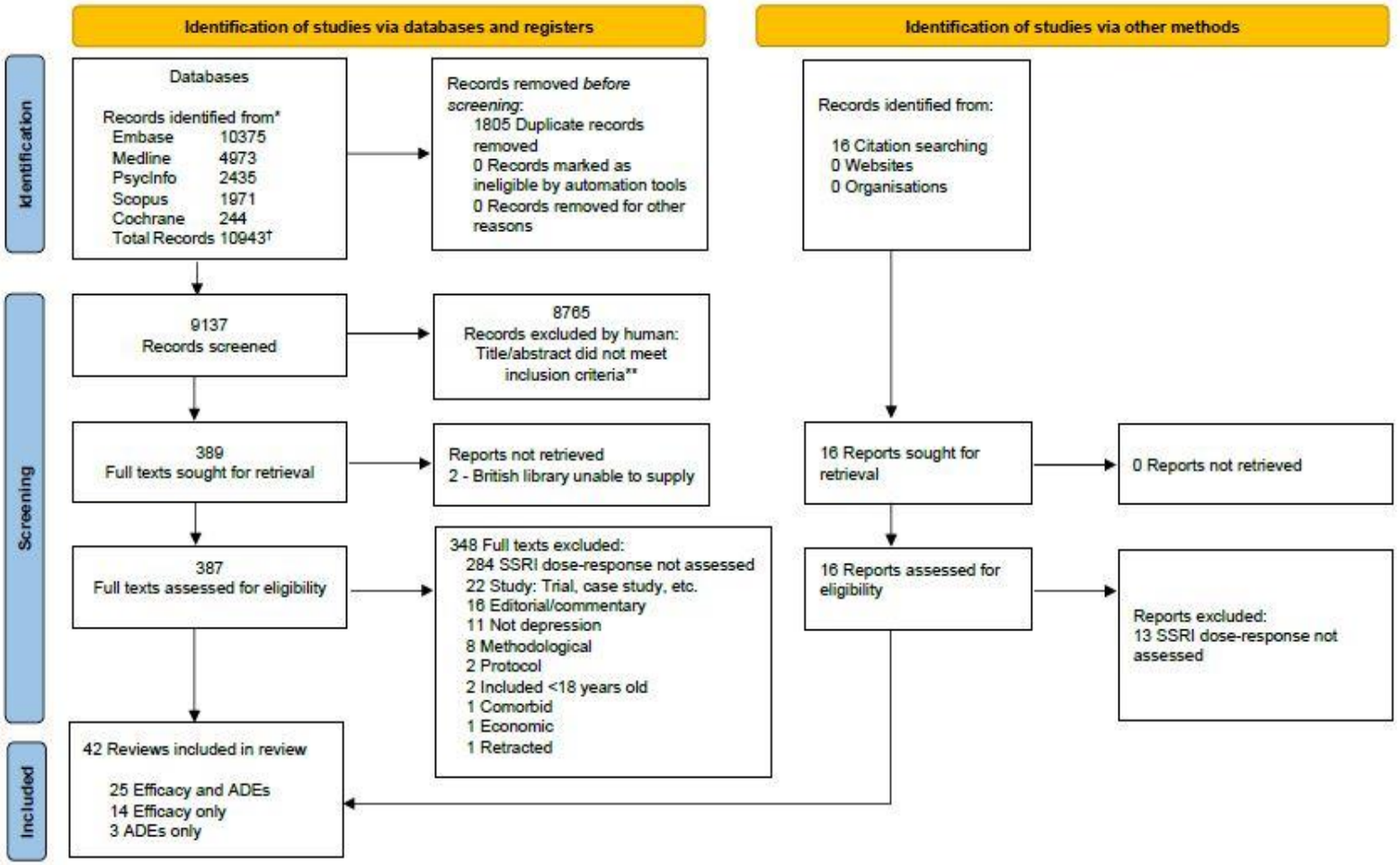
This systematic review did not require ethical approval.

7.3 Results

7.3.1 SSRI dose-response effects

In total 9137 records were identified from electronic search, hand searching reference lists and grey literature. Full-text reports (N=387) were assessed for eligibility, and 42 reviews based upon published and unpublished reviews matched the inclusion criteria: 25 assessed SSRI efficacy, ADEs and dropouts; 14 efficacy only; and 3 ADEs and dropouts only (Figure 18). The year of publication ranged from 1988 to 2021. A range of review methodologies were used: 60% (N=25) meta-analyses of which 14 were systematic, 7 non-systematic and 4 used pooled study data; 40% (N=17) narrative reviews of which a minority (N=3) reported that they had systematically identified primary studies, whereas 8 had included a mix of primary and secondary studies (meta-analysis and/or narrative reviews), Table 11. Of the 42 reviews identified, 83% (N=35) included data from studies for 12 weeks or less; the acute phase of depression treatment, whereas 5 did not define the treatment period and 2 lacked greater detail. Four reviews considered the continuation phase and relapse prevention, but did not report on dose-response effects during the continuation phase.[339-342] The care setting also varied; 17% (N=7) of reviews stated that they included data from studies conducted in primary care (general practice and/or outpatient clinics), 28% (N=11) for both primary and secondary care, whereas 56% (N=24) of reviews did not define the care setting.

Figure 18. Review identification, inclusion and exclusion



* Number of records identified from each database (rather than the total number across all databases). ** No automated tools used. As per PRISMA 2020 guideline.

† Total records identified: Combined Embase, Medline and PsychInfo 8728 records, plus Scopus plus Cochrane

Table 11. Efficacy, dropouts (acceptability) and adverse effects (tolerability)

Study	Primary, Studies (N=)	Review design	Efficacy & Dose	Dropouts & ADEs	Dose Standardisation	Study duration (range)	Risk of bias in the review
Braun 2020 [343]	33	Syst. M-A. Net-M-A	↔ SSRI grouped ↔ cit, escit, fluox, fluvox par, sert	↑ SSRI grouped	Low, Med, High.	6 wks (2-12 wks)	Low
Cheng 2020 [344]	115	Model-Based M-A	↔ cit, escit, fluox, fluvox par, sert	n-a	Fluox Equiv	4-12wks	Low
Dold 2017 [345]	5	Syst. M-A. M-R	↔ fluox, par, sert	↑ fluox	Fluox, par 20mg/d, sert 50mg/d, v higher doses	5 wks (3-8 wks)	Low
Furukawa 2019 [167]	66	Syst. M-A	↑ SSRI grouped (to 40mg/d). ↑ cit (to 30mg/d), ↔ escit, fluox, par, ∩ sert.	↑	Fluox Equiv	8 wks (4-12wks)	Low
Furukawa 2020 [313]	108	Syst. M-A	↔ SSRI grouped ↔ cit, escit, fluox, par, sert	↑ flexible dose	Fluox Equiv	7 wks (4-12 wks)	Low
Benkert 1996 [346]	7 (+7 Revs)	Narr.	↔ cit, fluox, fluv, par, sert	n-a	Actual doses from other reviews	Not defined	Unclear
Dunner 1992 [339]	Pooled (n=460)	Pooled SKB data	↔ Par	n-a	Par. dose	Acute ≤6 wks Long-term 52 wks	Unclear
Gutsmiedl 2020 [347]	44	Syst. M-A. M-R	↔ SSRIs & non-SSRI grouped	n-a	Fluox Equiv	9 wks (4-26 wks)	Unclear
Hamza 2021 [348]	60	M-A	SSRI grouped (↑ to 40mg/d) ↑ cit (to 30mg/d), par, sert (to 75mg/d), ↔ escit, fluox,	n-a	Fluox Equiv. Individual drug effects reported as fluox equiv not actual drug dose.	8 wks (4-12wks)	Unclear
Khan 2003 [349]	36	FDA subs M-A	↔ SSRIs & non-SSRI grouped	↑	SSRI study doses used	6-8wks	Unclear
Klemp 2011 [350]	26	Syst. M-R.	↔ par	n-a	Par dose	8 wks (6-56 wks)	Unclear
Montgomery 1995 [340]	1	Narr.	↔ sert	↑	Sert dose	Acute 6-8 wks Long-term 44 wks	Unclear

Note: Reviews are ranked by assessed risk of bias, then alphabetically by author.
Drug-response effects: ↑ increased, ↔ flat, ∩ curvy linear, ? unclear. ADEs: adverse drug effects. mg/d: milligrams/day. DDD: defined daily doses. FDA: Federal Drug Agency. Fluox Equiv: fluoxetine dose equivalents. Ind.: Industry. Imip Equiv: imipramine dose equivalents. M-A: meta-analysis. M-R: meta-regression. n-a: not assessed. PDD: prescribed daily dose. SKB SmithKleineBeecham. SSRI: selective serotonin re-uptake inhibitor (cit: citalopram, escit: escitalopram, fluox: fluoxetine, fluv: fluvoxamine, par: paroxetine, sert: sertraline). Syst: systematic review. Wks: weeks.

Table 11. Continued. Efficacy, dropouts (acceptability) and adverse effects (tolerability)

Study	Primary studies (N=)	Review design	Efficacy & Dose	Dropouts & ADEs	Dose Standardisation	Study duration	Risk of bias in the review
Murdoch 2005 [351]	Pooled (n=1307)	Pooled Lundbeck Forrest	n-a	↑ escital	Escit dose	Not defined	Unclear
Preskorn 1995 [352]	3	Narr.	↔ sert	↑	Sert dose	≤8 wks	Unclear
Purgato 2015 [353]	173	Syst. M-R.	↔ fluox	n-a	Mean doses poorly reported: min and max doses to DDDs then PDD/DDD. Grouped: ≤20mg/d or 20-80mg/d	Majority ≤6 wks	Unclear
Safer 2016 [320]	33	Narr.	↔ SSRI & non-SSRI grouped ↔ cit, escit, fluox, fluv, par, sert	↑	SSRI dose	8-28 wks	Unclear
Tan 1999 [341]	2 (+1 Revs)	Narr.	? cit	↑	Cit dose	6 wks (3-24 wks)	Unclear
Vaswani 2003 [354]	3 (+5 Revs)	Narr.	↑ cit (to 40mg/d), ↔ fluox, fluv, par, sert	↑	Not defined	Not defined	Unclear
Adli 2005 [166]	12	Syst. Narr.	↑ fluv. ↔ cit, fluox, par, sert	↑	SSRI dose	4-8 wks	High
Altamura 1988 [355]	2	Narr.	↔ fluox	↑	Fluox dose	6 wks	High
Baker 2003 [322]	4	Syst. M-A.	? fluox, par, sert	↑	Low, Medium, High. No clear definition	≤8 wks	High
Barbui 2002 [356]	103	Syst. M-A.	↑ fluox	↑	20-30mg/d, >30mg/d. Dose range 20-40mg/d & >40mg/d	≤9 wks	High
Beasley 1990 [357]	Pooled (n=669)	Pooled.	↔ fluox	↑	Fluox dose	≤8 wks	High
Beasley 1993 [358]	3	Narr.	n-a	fluox: ↑ anxiety, agitation, insomnia., drowsiness, asthenia.	Not defined	6 wks	High
Berney 2005 [359]	14 (+4 Revs)	Narr.	↔ cit, escit, fluox, par, sert. ? fluv	↑ fluox, dropout[a]	SSRI dose	6-8 wks	High
Bollini 1999 [321]	33	Syst. M-A.	∩ SSRI & non-SSRI grouped	↑	Imip Equiv	6 wks (4-24 wks)	High

Note: Reviews are ranked by assessed risk of bias, then alphabetically by author.
Drug-response effects: ↑ increased, ↔ flat, ∩ curvy linear, ? unclear. ADEs: adverse drug effects. mg/d: milligrams/day. DDD: defined daily doses. FDA: Federal Drug Agency. Fluox Equiv: fluoxetine dose equivalents. Ind.: Industry. Imip Equiv: imipramine dose equivalents. M-A: meta-analysis. M-R: meta-regression. n-a: not assessed. PDD: prescribed daily dose. SKB SmithKleineBeecham. SSRI: selective serotonin re-uptake inhibitor (cit: citalopram, escit: escitalopram, fluox: fluoxetine, fluv: fluvoxamine, par: paroxetine, sert: sertraline). Syst: systematic review. Wks: weeks.

Table 11. Continued. Efficacy, dropouts (acceptability) and adverse effects (tolerability)

Study	Primary studies (N=)	Review design	Efficacy & Dose	Dropouts & ADEs	Dose Standardisation	Study duration	Risk of bias in the review
Caley 2002 [360]	5 (+7 Revs)	Narr.	↑ cit, ∩ fluv, ↔ fluox, sert ?par	↑	SSRI dose	4-6 wks	High
Corruble 2000 [209]	10 (+6 Revs)	Syst. Narr.	↔ SSRI grouped	n-a	SSRI dose	4-8 wks	High
Hansen 2009 [361]	74	Syst. M-A. M-R	↑ SSRIs & non-SSRI grouped	n-a	Yes: licensed dose range e.g. fluox <45mg/d low >45mg/d high	7 wks (6-24 wks)	High
Hieronymus 2016 [316]	11	M-A. Ind. Data.	↑ cit, par, sert	n-a	Patient-level doses	≤6 wks	High
Holper 2020 [312]	153	Net-M-A	↑ escital, fluox, ↔ cit, par	↑ (≤70y) ↑↑ (>70y)	Fluox Equiv	4-12 wks	High
Jakubovski 2016 [317]	40	Syst. M-A.	↑ SSRIs grouped	↑	Imip Equiv	6 wks (4-24 wks)	High
Jenner 1992 [362]	Pooled (n=4668)	Pooled. SKB data.	↔ par	↑	Par. dose	6 wks (≤2 yr)	High
Lam 2006 [363]	3	M-A. Lundbeck data.	↔ escital	n-a	Escit dose	8 wks	High
Lane 1995 [62]	4 (+2 Revs)	Narr.	↔ cit, fluox, par, sert	↑	Not defined	Not defined	High
Montgomery 1994 [364]	9	M-A. Not Syst.	↔ cit	n-a	Cit dose	4-6 wks	High
Montgomery 1995 [342]	2 (+2 Revs)	Narr.	↔ Cit	n-a	Cit dose	≤24 wks	High
Oliva [365]	Not defined	Syst. M-A	n-a	↑ N&V cit, escital	Low v high dose	6-12 wks	High
Papakostas 2010 [318]	9	Syst. M-A.	↑ SSRIs grouped	↑	Usual (10mg/d escit, 20mg/d cit, fluox, par, 50mg/d sert, fluv), intermediate, double (2x usual) & higher.	6 wks	High
Parker 2000 [366]	1 (+1 Revs)	Narr.	↑ cit	↑	Cit dose	4-6 wks	High
Rifkin 1997 [367]	4	Narr.	↔ fluox, par, sert	n-a	SSRI dose	Not defined	High
Ruhe 2006 [368]	8	Syst. Narr.	↔ fluox, par, sert	↑	SSRI dose	8 wks (3-12 wks)	High

Note: Reviews are ranked by assessed risk of bias, then alphabetically by author.
Drug-response effects: ↑ increased, ↔ flat, ∩ curvy linear, ? unclear. ADEs: adverse drug effects. mg/d: milligrams/day. DDD: defined daily doses. FDA: Federal Drug Agency. Fluox Equiv: fluoxetine dose equivalents. Ind.: Industry. Imip Equiv: imipramine dose equivalents. M-A: meta-analysis. M-R: meta-regression. n-a: not assessed. PDD: prescribed daily dose. SKB SmithKleineBeecham. SSRI: selective serotonin re-uptake inhibitor (cit: citalopram, escit: escitalopram, fluox: fluoxetine, fluv: fluvoxamine, par: paroxetine, sert: sertraline). Syst: systematic review. Wks: weeks.

7.3.2 Efficacy

The majority of reviews, 93% (N=39), assessed SSRI dose-response effects for the treatment of depression Table 11. The majority (N=26) indicated that the SSRI class of antidepressant demonstrated flat dose-response effects for the acute phase of treatment of depression; higher than standard initiation doses did not provide greater efficacy. [62, 166, 209, 313, 320, 339, 340, 342-347, 349, 350, 352-355, 357, 359, 362-364, 367, 368] A minority (N=8) demonstrated that higher doses were more efficacious,[167, 316-318, 348, 356, 361, 366] while others (N=3) demonstrated mixed effects,[312, 321, 360] or remained ambiguous.[322, 341]

At an individual SSRI-level the majority of reviews also demonstrated flat dose-response effects for efficacy; standard daily starting doses were the optimal doses: 20mg citalopram, 10mg escitalopram, 20mg fluoxetine, 20mg paroxetine and 50mg sertraline (Table 12).[62, 166, 167, 313, 320, 339, 340, 342-346, 350, 352, 354-357, 359, 360, 362-364, 367, 368] A minority of reviews however, indicated that some SSRIs did have linear dose-response effects with higher doses being more effective. For example, escitalopram;[312] citalopram e.g. up to 30mg daily;[167, 316, 348, 360, 366] fluoxetine;[312, 356] fluvoxamine;[166] paroxetine;[316, 348] and sertraline.[316] Other reviews indicated mixed curvy linear efficacy with increasing doses for fluvoxamine [360] and sertraline.[167, 348] All curvy-linear efficacy responses were characterised by there being an initial increase, then peak and decline in efficacy with increasing dose.

Blood plasma concentrations of fluoxetine, fluvoxamine and paroxetine, were assessed in association with depression treatment response rates. It was found that there was no correlation with blood plasma concentrations and individual's response to treatment regardless of the severity of depression.[354, 357]

Six reviews compared the efficacy of fixed dose with flexible dose regimens for poor and non-responders: two narrative reviews [359, 368] and four meta-analyses.[312, 313, 345, 349] All demonstrated that use of flexible dose titration for poor and/or non-responders did not provide greater efficacy.

Table 12. Efficacy dose-response effects by individual SSRI

Study	Design	Cital.	Escital.	Fluox.	Fluvox.	Parox.	Sert.	Risk of bias in the review
Braun 2020 [343]	Syst. M-A	↔	↔	↔	↔	↔	↔	Low
Cheng 2020 [344]	Model-Based M-A	↔	↔	↔	↔	↔	↔	Low
Furukawa 2019 [167]	Syst. M-A	↑	↔	↔		↔	∩	Low
Furukawa 2020 [313]	Syst. M-A	↔	↔	↔		↔	↔	Low
Dold 2017 [345]	Syst. M-A			↔		↔	↔	Low
Benkert 1996 [346]	Narr.	↔		↔	↔	↔	↔	Unclear
Safer 2016 [320]	Narr.	↔	↔	↔	↔	↔	↔	Unclear
Hamza 2021 [348]	M-A	↑	↔	↔		↑	↑	Unclear
Vaswani 2003 [354]	Narr.	↑		↔	↔	↔	↔	Unclear
Tan 1999 [341]	Narr.	?						Unclear
Purgato 2015 [353]	Syst, M-R			↔				Unclear
Dunner 1992 [339]	Pooled.					↔		Unclear
Klemp 2011 [350]	Syst. M-R					↔		Unclear
Montgomery 1995 [340]	Narr.						↔	Unclear
Preskorn 1995 [352]	Narr.						↔	Unclear
Adli 2005 [166]	Narr.	↔		↔	↑	↔	↔	High
Berney 2005 [359]	Narr.	↔	↔	↔	?	↔	↔	High
Holper 2020 [312]	Net-M-A	↔	↑	↑		↔		High
Lane 1995 [62]	Narr.	↔		↔		↔	↔	High
Montgomery 1994 [364]	M-A	↔						High
Montgomery 1995 [342]	Narr.	↔						High
Caley 2002 [360]	Narr.	↑		↔	∩	?	↔	High
Lam 2006 [363]	M-A		↔					High
Altamura 1988 [355]	Narr.			↔				High
Beasley 1990 [357]	Pooled			↔				High
Rifkin 1997[367]	Narr.			↔		↔	↔	High
Ruhe 2006 [368]	Syst. Narr			↔		↔	↔	High
Jenner 1992 [362]	Pooled						↔	High
Hieronymus 2016 [316]	M-A	↑				↑	↑	High
Barbui 2002 [356]	Syst. M-A			↑				High
Parker 2000 [366]	Narr.	↑						High
Baker 2003 [322]	Syst. M-A			?		?	?	High

Design: M-A: meta-analysis. M-R: meta-regression. Narr: narrative. Net-M-A: network meta-analysis. Syst: systematic. Antidepressants: Cital: citalopram, Escital: escitalopram. Fluox: fluoxetine. Fluvox: fluvoxamine. Parox: paroxetine. Sert: sertraline. Drug-response effects: ↑ increased, ↔ flat, ∩ curvy linear. ? unclear.

Note: Reviews were ranked by most common finding for efficacy and dose-response; alphabetically starting with citalopram.

7.3.3 Acceptability and tolerability

Of the 42 reviews, 28 (67%) assessed and reported the dose-response effects related to acceptability (early treatment discontinuation – dropouts) and tolerability (reported ADEs). All reviews demonstrated that dropouts and ADEs increased with increasing dose, Table 11.

At a class and individual SSRI-level ADEs that were associated with dose-response effects were, but not limited to: nausea, sexual dysfunction, fatigue, anxiety, insomnia.[62, 166, 167, 313, 320-322, 340, 341, 343, 351, 352, 354-360, 362, 365, 366] A network meta-analysis identified escitalopram as potentially providing the best balance between efficacy and tolerability.[312] However this study considered that escitalopram doses up to 27mg daily may be more effective, and all SSRIs demonstrated a poor risk-benefit ratio for older adults (>70 years old) due to adverse effects exceeding potential efficacy.

The four reviews comparing flexible upward dose titration versus maintenance for poor and/or non-responders, also demonstrated that higher doses were associated with poor acceptability and tolerability.[312, 313, 345, 349, 359, 368]

7.3.4 Risk of bias

The assessment revealed that the minority (12% N=5) of reviews were at low risk of bias, see

Figure 19 and Appendix A3.6 for risk of bias table.[167, 313, 343-345] Four of which demonstrated a flat dose-response effect for efficacy, and a positive dose-response effect for ADEs and dropouts for all SSRIs.[313, 343-345] One review however, indicated that citalopram demonstrated efficacy dose-response to 30mg daily, and sertraline curvy-linear effects peaking at approximately 75mg.[167] Thirteen (31%) reviews were assessed as having an unclear risk of bias, whereas the majority (57%) had a high risk of bias that was mainly associated with a range of methodological issues.

Overlap assessment of primary studies across the five reviews at low risk of bias was very high, with a CCA of 26%.[167, 313, 343-345] Pairwise overlap assessment indicated that one review demonstrated slight overlap (≤5%), whereas the Cheng et al. 2020, Furukawa et al. 2019 and 2020 demonstrated high to very high overlap (Figure 20). However, Furukawa et al. (2019)[167] findings that optimal daily dose range is between 20 mg and 40 mg fluoxetine equivalents, and citalopram to 30mg daily, was at odds with the majority of reviews that demonstrate that 20mg fluoxetine equivalents were optimal dose at a class and individual drug level.[313, 343-345]

Finally, of the 160 primary studies included in the five reviews overall risk of bias was rated as low 34 (21%), moderate 120 (75%) and high 6 (4%), see Appendix A3.8 for risk of bias table. Eleven (7%) of the primary studies where identified as inlcuding patients with mild depression; as defined in current guidelines e.g. Hamilton Depression 17 rating scale score <17.[67] However after exclusion of the reviews includings mildly depressed populations,[167, 313, 343, 344] lower doses continued to demonstrate non-inferiority to higher doses.[345]

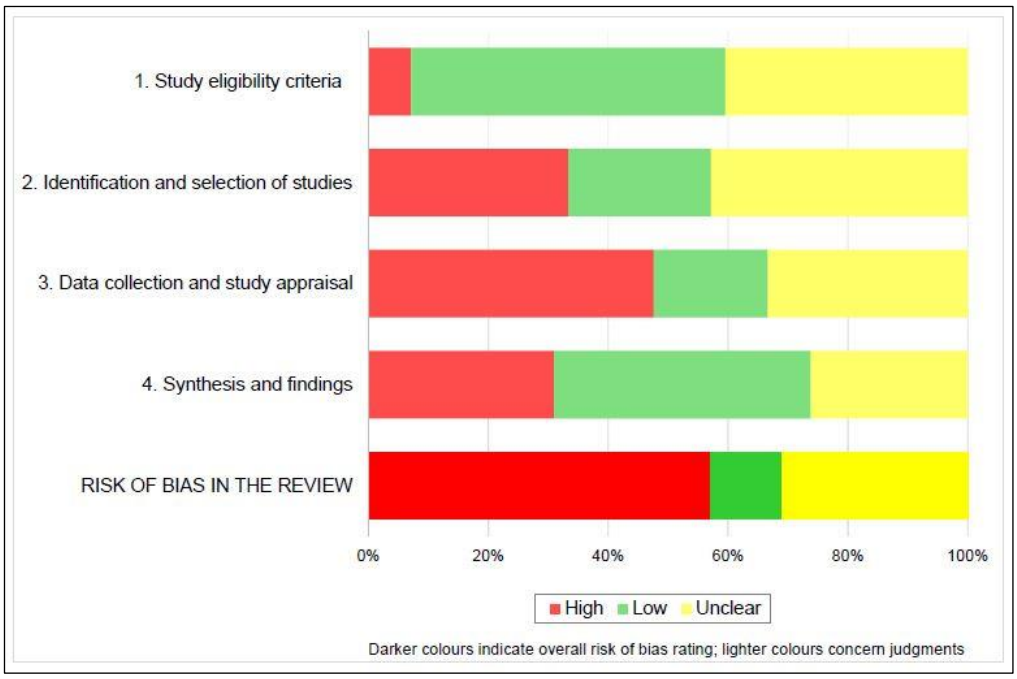


Figure 19. ROBIS assessment of all reviews meeting inclusion criteria (N=42)

	Braun 2020	Cheng 2020	Dold 2017	Furukawa 2019
Cheng 2020	11%			
Dold 2017	0%	0%		
Furukawa 2019	27%	35%	0%	
Furukawa 2020	16%	59%	0%	45%

Figure 20. Corrected covered area pairwise matrix of primary studies citations

Pairwise analysis of review citations assessed as being at low risk of bias. Overlap categorisation: 0-5% - slight (white), 6-10% - moderate (green), 11-15% - high (yellow), >15% - very high (red).

7.3.5 Critical evaluation of previous reviews

The majority of reviews meeting inclusion criteria agreed that SSRIs demonstrate a flat dose-response effect for efficacy, and poorer acceptability and tolerability with higher doses in the treatment of depression. There remains however, a range of methodological issues that may explain some of the conflicting findings. Firstly, inclusion of flexible dose studies. Only a few reviews exclusively include and/or report the effects of fixed dose studies,[166, 167, 209, 320, 322, 340, 349, 352, 355, 359, 362, 367] while the majority include flexible dose studies. One of the weaknesses of including flexible dose studies is that it requires clinicians to make a judgement early in treatment to increase the dose, which creates additional placebo effects that may be associated with the dose change, sometimes after several weeks of treatment.[368] This may make drug response hard or impossible to distinguish from spontaneous remission, as 50% of patients with clinical depression spontaneously remit within 12 weeks.[369] Another issue is that increasing doses may fit with patient's expectations regarding dose-effects,[22] leading patients to receive higher than necessary doses, potentially influencing the results of reviews using patient-level data from flexible dose studies.[316, 339, 362] Flexible dose studies may also select dose tolerant patients who are able to complete these studies,[370] limiting generalisability and applicability to the wider population who are commonly prescribed SSRIs and exposing them to avoidable adverse effects. Newer studies have started to examine and compare the differences in effects between fixed dose and flexible dose studies, and report that there are no identifiable differences in efficacy with dose titration or fixed doses studies but patients experience more ADEs and dropouts with higher doses in both groups.[312, 313, 345]

Secondly, dose standardisation and drug grouping techniques such as 'imipramine dose equivalents', 'fluoxetine dose equivalents' and other techniques. These standardise individual drugs from different classes with different doses, or dose ranges, against the TCA imipramine or SSRI fluoxetine.[167, 312, 313, 317, 318, 321, 344, 347, 348] This may seem like a good idea, however, using such grouping methods inadvertently over simplifies antidepressant pharmacology, potentially missing differences between and

within drug classes. It does not take account of, or even consider that these groupings maybe inappropriate due to different antidepressant's mechanisms of action. Unlike SSRIs, that are highly specific for inhibiting serotonin transporter reuptake and increasing pre-synaptic serotonin levels. TCAs, SNRIs and other non-SSRI antidepressants have mixed serotonin and non-serotonin (noradrenaline, dopamine, melatonin, muscarinic) effects which influence their dose-response efficacy and ADE profiles e.g. venlafaxine, duloxetine, etc (see Section 2.7).[68, 161, 168, 202, 204, 205, 319] Therefore grouping drugs with different dose-response characteristics may provide questionable findings. Nonetheless, a few of these reviews have also presented their findings for individual SSRIs which aids clarity and may help to better inform practitioners.[167, 312, 313, 344, 348]

Another issue with 'imipramine dose equivalents' is that this strategy uses irregular dose groupings: imipramine daily doses of <100mg, 100-199mg, 200-250mg and >250mg.[317, 321, 371] Introducing these groupings reduces sensitivity to detect differences in dose-response, and gives greater weight to those patients that can tolerate higher doses. These 'imipramine dose equivalents' are also based on arbitrary SSRI doses which cannot routinely be prescribed in clinical practice: 45mg citalopram, 125mg sertraline, fluoxetine 33.3mg etc. Whereas, other dose standardisation techniques have different limitations, for example, Braun et al. have compared non-equivalent low, potentially subtherapeutic SSRI daily doses, with higher potentially more therapeutic doses of the same compound e.g. citalopram ≤10mg (equivalent to 5mg escitalopram) versus escitalopram ≤9mg (equivalent to 18mg citalopram).[343] Citalopram is racemic 50:50 mixture of active s-enantiomer (escitalopram) and inactive r-enantiomer, such that 2mg of citalopram contains 1mg of S-citalopram (escitalopram) and 1mg of R-citalopram, see Section 2.4.3.[159, 161, 163] Conversely, Braun et al. also categorised a wide range of doses as 'high' which also may affect their findings e.g. citalopram ≥40mg with fluoxetine ≥80mg.[343] More positively however, others have focused their systematic review's aims on individual SSRIs, using the actual drug dose therefore removing inter- and intra-class variations.[166, 209, 316, 320, 339-342, 344, 350, 351, 355, 357, 359, 360, 362-364, 366-368]

Few reviews focus on primary care i.e. general/family practice and outpatients.[350, 352, 355, 357, 358, 361] While some combine primary and secondary care inpatient studies,[167, 312, 313, 342, 347, 348, 353, 356, 359, 360, 362, 363] the majority lack clarity regarding primary study-settings.[62, 166, 209, 316-318, 320-322, 339-341, 343, 345, 346, 349, 351, 354, 364-368] This is problematic as the majority of SSRIs are prescribed for the treatment of depression in primary care and findings from secondary care inpatient populations may not be generalisable to primary care populations, as demonstrated by Cheng et al.[344] Other methodological issues include: inclusion of mild depression studies;[167, 209, 313, 344, 348] non-placebo controlled studies;[167, 322, 348, 356] narrative reviews which may lack a systematic approach;[62, 320, 340-342, 346, 351, 352, 354, 355, 358-360, 366-368] use of 'data on file', missing search strategies and references preventing others from replicating the review;[339, 348, 349, 362, 363] assessing and reporting on efficacy but not adverse effects or dropout rates;[209, 316, 320, 339, 342, 344, 346-350, 353, 361, 363, 364, 367, 368] and assessing response without reporting remission effects. However, even after considering the potential limitations of previous reviews, this systematic review of reviews and meta-narrative synthesis demonstrates that in general there is an overall consensus that SSRIs demonstrate a flat dose-response effect for efficacy, and poorer acceptability and tolerability as SSRI doses are increased for the treatment of depression.

7.4 Summary of findings

Ambiguity regarding SSRI dose-response and optimal dosing for the treatment of depression, has been a major challenge for prescribers in general practice, and guideline developers. This systematic review of reviews has identified and clarified that all individual SSRIs, except for fluvoxamine, demonstrate a ceiling effect for efficacy, and poorer acceptability and tolerability as SSRI doses were increased during the acute phase (up to 12 weeks) of depression treatment for adults. Dose-response efficacy however remain unclear for fluvoxamine.

The prescribing of higher than recommended standard initiation SSRI doses was associated with higher rates of early treatment discontinuation (poorer acceptability) and a higher incidence of ADEs (poorer tolerability) such as, but not limited to, nausea, sexual dysfunction, anxiety, insomnia.

Comparison of fixed standard initiation dose and flexible dose regimens for poor and non-responders demonstrated that dose titration above standard starting doses did not provide greater efficacy, but was associated with poorer acceptability and tolerability.

7.5 Strengths and limitations

A major strength of this review was the inclusion and assessment of a range of meta-analyses and narrative reviews that met the inclusion criteria, and demonstrated the breadth and depth of review literature assessing SSRI dose-response effects. To my knowledge, and my supervisory team's knowledge, this is the first review of reviews to investigate SSRI drug-response effects.

Although the literature search aimed to be as comprehensive as possible and included a range of reviews using different methodologies, it is possible, as with all systematic reviews, that an important review may have been missed. However, searching a range of key electronic databases and hand searching reference lists from guidelines and other sources helped to reduce the risk of missing relevant reviews. It could have been beneficial to include reviews in languages other than English, however there was no funding for this study. While some may consider this as limiting generalisability of findings, the

majority of reviews that were assessed as being at low risk of bias included non-English language primary studies therefore overcoming language limitations.[167, 313, 343-345]

Other potential limitations are that data from individual published and unpublished randomised controlled studies may not have been included in the initial review. The reporting quality of many of the older reviews was assessed as being poor with a high risk of bias; primarily due to data collection and study appraisal issues, see Appendix A3.6. Overlap of primary studies within the reviews may be considered as limitation, and while there are no clear guidelines on how best to address this issue,[332] the analysis of reviews at low risk of bias indicated a high to very high overlap; Furukawa et al 2019 finding that the SSRI class and citalopram dose response up to 20mg and 40mg,[167] being at odds with reviews assessing similar data sets and those with no overlap.[313, 344, 345] Similarly the quality of primary studies is a potential limitation, however the majority were considered to be at low to moderate risk of bias (Appendix A3.8). Furthermore, there was a high degree of heterogeneity between the 42 reviews due to methodological diversity and the progressive development of systematic review methodologies since 1988. Despite this, the review of reviews found that there was a general consensus between older and newer reviews that SSRIs demonstrated flat dose-response effects for the treatment of depression, and larger doses were associated with more ADEs, even when reviews assessed as having a higher risk of bias were excluded. Due to similar results being observed across and within the reviews, including data from primary and secondary care settings, the findings appear to be generalisable to routine general practice, and are considered as being relatively robust.

7.6 Comparison with literature

As already acknowledged, to my knowledge, this is the first review of reviews to investigate SSRI dose-response effects. However the findings are congruent with previous studies which indicate that serotonin re-uptake receptors are highly saturated when standard SSRI doses are administered; exhibiting ceiling

effects for efficacy at standard initiation doses: 20mg citalopram, fluoxetine, paroxetine; 50mg sertraline; and 10mg escitalopram, providing optimal receptor occupancy and serotonin effects.[319] In contrast, TCAs, SNRI and other non-SSRI antidepressants demonstrate multiple receptor effects (serotonin, noradrenaline, dopamine) with increasing doses that influence their efficacy.[68, 202]

At an individual SSRI-level, reviews carried out in the early 1990s indicated that citalopram, fluoxetine, paroxetine and sertraline demonstrated flat-dose response effects for efficacy with standard initiation doses providing optimal efficacy.[339, 340, 342, 352, 357, 362] While the British Association of Psychopharmacology and Australian and New Zealand Royal College of Psychiatry guidelines do highlight SSRI dose limitations for the treatment of depression,[66, 210] the majority of national guidelines in the USA, Canada and UK fail to highlight SSRIs' dose-efficacy limitations,[67, 181, 182] which may be contributing to the routine prescribing of higher SSRI doses.[99, 201, 235]

Chapter 8

8. Discussion

8.1 Summary

The overarching aim of this thesis was to address current gaps in knowledge, as identified from literature and clinical practice, by exploring and examining SSRI dose-response effects and the drivers of the rise in prescribed doses. A single methodology was considered to be limited in developing a better understanding, therefore this thesis took a three-pronged approach: 1) Investigating patient factors associated with the prescribed daily dose of SSRIs, 2) Exploring factors influencing GP's use of antidepressants and their doses, and 3) Systematically identifying and reviewing previous reviews to assess and clarify the relationship between SSRI dose efficacy, acceptability (early treatment discontinuation – drop outs) and tolerability (reported ADEs), for the treatment of major depressive disorder for adults, for the treatment of major depressive disorder for adults.

Firstly the cross-sectional study found that higher prescribed SSRI doses for the treatment of depression were significantly associated with, in descending order of magnitude, individual practice attended, being prescribed the same SSRI for ≥2 years and living in a more deprived area.

Secondly, the qualitative study then found that GPs' treatment of depression involved ethical and professional imperatives of 'doing the right thing' for individuals by striving to achieve the 'right care fit'. This involved use of both medicalised and non-medicalised treatment approaches with antidepressants being only one facet of patient-centred care. Factors influencing antidepressant prescribing and doses varied over time from first presentation, to antidepressant initiation and longer-term treatment. However, many GPs were unaware that higher SSRI doses lacked greater efficacy or that onset of action occurred within 1-2 weeks; preferring to wait 8-12 weeks before increasing the dose or switching to another antidepressant. Ongoing pressures to maintain prescribing (e.g. patient wishes, GP and patient fear of depression recurrence),

few perceived continuation problems (e.g. lack of safety concerns) and lack of proactive medication review (e.g. patients only present in crisis), all combined to further drive antidepressant prescribing growth over time.

Lastly the systematic review of reviews identified 42 reviews assessing SSRI dose-response effects for efficacy, acceptability and/or tolerability. The majority of reviews indicated that SSRIs demonstrate a ceiling effect for efficacy, and poorer acceptability and tolerability as SSRI doses were increased during the acute phase (up to 12 weeks) of depression treatment for adults. Standard daily doses of 20mg citalopram, fluoxetine, paroxetine, 50mg sertraline and escitalopram provided the optimal balance between efficacy and dose-related adverse events such as early treatment discontinuation (poorer acceptability) and a higher incidence of ADEs (poorer tolerability).

8.2 Thesis strengths and limitations

The main strength of this thesis was that it explored and examined SSRI doses from three different perspectives. The use of patient-level data from routine practice, and GPs' experiences and opinions relating to current practice enabled a greater understanding of how antidepressants are being used in routine practice. The systematic review of reviews, on the other hand, identified that higher doses lacked greater efficacy but were associated with more ADEs.

Another strength was that the thesis analysed patient and GP data from one large urban health board with the same pharmacy prescribing support team, prescribing initiatives, medicines formulary, and local depression guidelines.[196] Some may consider that the use of data from one region may not be generalisable to other areas such as rural practices, however the cohort of practices in the regression analysis were similar to 47% (n=481) of general practices in Scotland that serve 55% (3 million people) of the population. In addition, the sampling frame that guided participant inclusion in the qualitative study ensured that the views of a wide variety of GPs' experiences were captured. Seeking local GP perspectives on the regression study findings (Section 5.3), allowed GPs to use their unique insight in considering local and national contextual issues contributing to the use of higher SSRI doses. Therefore the findings may be of interest to others working in urban areas with

similar populations, while key elements or common aspects of prescribing and patient care may be ubiquitous to practice regardless of setting or population.

Yet another strength of this thesis was that the study sequence was influenced by the findings with the cross-sectional study informing the qualitative study's topic guide. Whereas, if the studies were completed in the reverse order the long-term prescribing effects on dose may not have been considered or identified. Likewise the review of reviews was influenced by a combination of factors: 1) the quantitative finding that higher doses were associated with long-term use, 2) the qualitative finding that GPs were unaware that higher doses of SSRIs lacked greater efficacy and 3) my conscious reflection, 'do SSRIs truly demonstrate dose-related efficacy or not?' Some may consider that the review of reviews assessing acute (up to 12 weeks) response as being at odds with long-term use, however the majority of evidence for antidepressant efficacy and ADEs for the treatment of depression comes from acute studies, not long-term studies; >500 acute (≤12 weeks) studies versus <40 for up to 2 years, and these long-term studies do not assess dose-response effects.[95, 145, 372-374]

The main limitation of this thesis, however was a lack of patient perspectives. Although patient inclusion was considered at the start of the thesis development process, it was considered more appropriate to focus on routine clinical data to understand what SSRI doses were being used and patient-level factors associated with their use. It was also considered more appropriate to seek GP perspectives on antidepressant use, as GPs are commonly seen as the 'gatekeepers' that authorise and allow access to NHS care and are responsible for the majority of antidepressant prescribing in the UK.[27, 33, 375] Then the review of review was considered necessary to clarify dose-response effects, and consider these findings in the context of current practice. However, if resources and time would have allowed, a study seeking patients' perspectives would have been the next step in this sequence of inter-related studies. Nonetheless, future studies should consider exploring patient perspectives, expectations and experiences regarding SSRI doses from first starting antidepressants to longer-term use, as patient perspectives may change with time.[25]

One concern I must address is my role as a researcher and also as a NHSGGC primary care pharmacist. This may have influenced both my ability to access patient-level data, GPs and also what the GPs revealed to me in their interviews. Firstly, my professional role enabled me to more easily access patient-level data and receive practice approval to further analyse NHSGGC's HEAT target service development and evaluation data, while minimising the need to repeat data collection and the need for extra resources.[245, 246] The fact that one practice declined to participate demonstrates that there were no obligations for practices to take part. It is however unclear how much the administrative support from the NHSGGC Pharmacy and Prescribing Support Unit may have encouraged or discouraged some GPs from participating in the qualitative study. Another potential limitation and/or area for bias was myself as the researcher and pharmacist. On inquiry, as part of the interview schedule (Appendix A2.2), the majority of GPs stated that it did not influence their answers, while a minority were unsure, or thought that it may have influenced their use of language and technical terms, and one considered that it may have influenced their responses. Nonetheless, the use of mirroring to support relationship building and interviews may have helped to put some GPs at ease by creating a supportive atmosphere and enabling them to freely give their opinions.

So whether it has or not I don't know. D7,147

Only in that I'll maybe have given you slightly more technical responses than if you had been a lay person. Because I know that you'll understand it. D27,184

Possibly... I don't know, [laughter] I didn't think about it, I don't know the answer to that. I think it is good because you are neutral, you know like it is not doing it through a drug company. D14,124. [Int: I try to be neutral, definitely. D14,125]. *You know, so, but you are also quite supportive when somebody is speaking to you, so you're kind of nodding and everything like that. D14,126*

8.3 Implications for practice, policy, education and research

This thesis has implications for practice within and outwith the UK, as SSRIs account for more than half the antidepressants prescribed in North America, Europe and Australasia.[3, 27, 31, 192, 201, 376] As long-term prescribing increases and is associated with greater use of higher SSRI doses, antidepressant volumes may possibly increase further.[5, 191, 376]

From practical experience of working in primary care for more than 20 years; working closely with GPs, psychiatrists and clinical pharmacists, as well as addressing and enabling general practices to tackle areas of challenging prescribing e.g. long-term B-Z review and reductions, optimising treatment for people with heart failure, etc.[17, 125, 377, 378] I know that the findings of this thesis may create a number of challenges for practitioners and policy makers. However, some of the studies may have a broader range of implications than others, Table 13.

Table 13. Key findings and implications

Study	Key finding	Practice	Policy	Education	Research
Review of review	Dose limitations • Flat dose-response: efficacy • Higher doses: ADEs	√	√	√	√
Qualitative study	Lack of proactive review	√	√	√	√
	Delayed treatment • 8 to 12 weeks wait	√	√	√	√
	Pressures to maintain prescribing	√	√	√	
Regression analysis	Higher doses associated with				
	• Practice attended	√	√	√	
	• Long-term SSRI use	√	√		√

√ May have implications for. Note: Studies have been ranked by the number of areas to which the findings may be potentially applicable to.

8.3.1 Practice implications

8.3.1.1 Dose limitations – '20's plenty and 50's enough'

The systematic review of reviews indicated that standard daily doses of SSRIs: 20mg citalopram/fluoxetine/paroxetine, 10mg escitalopram, and 50mg sertraline, provide optimal antidepressant effects for the acute phase treatment of depression. Higher doses were associated with more ADEs and dropouts. Therefore, '20's plenty' for citalopram/fluoxetine/paroxetine and '50's enough' for sertraline to provide optimal antidepressant effects while minimising the risks of ADEs such as anxiety, insomnia, sexual dysfunction, etc.[379]

Firstly, and most importantly, the rationale for increasing and 'pushing' SSRI doses for poor and non-responders, as promoted by current guidelines,[66, 67, 96, 181] is not supported by current literature, Section 7.3.2. Even at the neurological cellular-level the rationale for *'…crank[ing] up…' D3,160,* doses is of questionable value. SSRIs are highly selective for inhibiting serotonin transporter reuptake with low affinity for other receptors.[203-205] Standard SSRI doses provide 76-85% serotonin transporter occupancy, and demonstrate a hyperbolic saturable relationship between dose and transporter occupancy (Figure 4).[203-205] Therefore, as serotonin reuptake transporter receptors are already highly occupied, there is little or no space for more drug to exert its effects on that receptor site. Thus 'pushing the dose' will deliver negligible or very small antidepressant effects that are of questionable value and/or benefit to patients. TCAs and SNRIs on the other hand, affect different receptors and transmitters at different doses to deliver serotonin, noradrenaline, dopamine and histamine effects.[112, 168, 202, 203] Furthermore, the qualitative study findings that low dose mirtazapine use is common, present the opposite challenge; getting prescribers to use optimal doses of mirtazapine.[167, 303]

Secondly, the use of higher than standard licensed doses causes and exposes patients to avoidable ADEs, such as a greater risk of QTc prolongation, falls, hip fracture, emotional blunting, cognitive dysfunction, and SSRI induced anxiety and insomnia.[380-384] Some of these ADEs may be mistaken for depressive symptoms that require more follow up appointments, are treated with a higher SSRI dose, that may even lead to acute and/or long-term use of

sedating antidepressants, B-Z drugs and/or antipsychotics and unnecessary polypharmacy.[129, 130, 260]

Thirdly, the use of higher SSRI doses is associated with a greater risk of withdrawal symptoms.[385] This may result in patients continuing long-term treatment, as both the patient and/or prescriber see these withdrawals as being a recurrence of depressive symptoms and restart or increase the SSRI dose while continuing treatment indefinitely.[195, 386, 387]

8.3.1.2 Lack of proactive review

The overarching challenge for current and future practice is continuing support and management for people with depression which is a relapsing and remitting disorder. Pragmatically, as ongoing pressures exist to maintain prescribing and long-term prescribing increases,[5, 376] while the frequency of review decreases with antidepressant duration,[200] and 50% of people now receive long-term antidepressant prescriptions, [5, 17, 33, 190] more consideration should be given to managing depression as a long-term condition like diabetes and cardiac disease. This would create proactive opportunities to review and optimise care to match individuals' needs whether that be pharmacological, non-pharmacological, non-medicalised or a combination of these.[17, 388]

At the same time, proactive reviews would allow practitioners and patients to discuss, plan and agree appropriate strategies to continue long-term treatment, or reduce and stop antidepressants at the end of a course of treatment; overcoming some of the barriers recently identified by prescribers and patients.[178, 195, 232] Some prescribers would see this as an opportunity to take a holistic approach to care, as the majority of people with depression also have multiple morbidities.[222] This group of people are also likely to receive polypharmacy, some of which may worsen depressive symptoms e.g. beta-blockers, benzodiazepines, etc., while antidepressants can cause cognitive dysfunction, falls and gastric bleeds.[100, 127, 240, 389, 390] This holistic approach allows a review of the patient and their medicines in full, that meets old and new policy commitments,[391-394] but more importantly identifies patients that are suitable for medication reductions and where appropriate support safe and appropriate long-term antidepressant use.

Other prescribers may see this proactive approach as creating another round of chronic disease management clinics, promoting more 'silo' medicine and single disease state models of care, adding to their current practice pressure and staffing issues that limit general practice space and capacity to deliver services.[395-398] Despite these challenges, GPs can, and do, in the short-term, create space to actively review patients and deliver changes in practice where there are safety concerns e.g. MHRA citalopram/escitalopram QTc warning, or where there are funded local initiatives.[17, 196]

However, there is a need for a long-term solution, that creates time to proactively review patients and their antidepressants – not when individuals are experiencing a crisis and expecting *'…something to be done… D3,60'*. Possibly by using an integrated multidisciplinary approach through new ways of working, as this can be effective in sharing workloads and drawing on other professionals skills to address challenging areas of prescribing and free GP time and capacity.[125, 265]

8.3.1.3 Delayed treatment

An 8-12 week delay in drug optimisation potentially slows patient recovery, and when doses and/or drugs are changed at 8-12 weeks following initiation it might be harder to identify and separate true antidepressant response from spontaneous remission. This is particularly relevant since 50% of patients experiencing an episode of clinical depression spontaneously remit within 12 weeks, as part of the natural course of their depressive episode and do not experience further episodes.[369, 399] This 8-12 week delay in optimising treatment may potentially result in inappropriate dose increases and drug changes that are ineffective and lead to patients with milder or no symptoms continuing antidepressants that are ineffective.[66] In order to appropriately optimise antidepressant use in the acute phase of treatment, it is important that prescribers are more aware that the greatest response occurs within the first 2 weeks of treatment.[97, 98]

8.3.1.4 Pressures to maintain prescribing

As identified in the qualitative study, the pressures to continue treatment are significant. The fear of relapse and the fear of causing more harm than good

are major factors. Prescribers however, have indicated that it is *'...easier to start [psychotropic medicines] than to stop [them],'*,[179] and that *'...we're [prescribers] probably not good enough, at the moment, is sort of the long-term managing and the coming-off part.'*.[232] Others have highlighted that there are also perceived and actual barriers to reducing the pressures to prescribe, such as some healthcare professionals lacking confidence, knowledge and skills to support and enable proactive antidepressant review and discontinuation, as well as patients getting lost in 'the system'.[178, 195] It has even been estimated that 30% to 50% of people receiving long-term antidepressant treatment lack a clear indication, and may be receiving inappropriate treatment.[386]

It is possible however, to challenge and overcome these barriers by: regularly reviewing the need for continued antidepressant treatment updating policy to reflect current evidence; educating prescribers and patients, and engaging in new ways of working, to try and ensure more appropriate antidepressant use.

8.3.2 Policy implications

8.3.2.1 Policy makers

Depression management guidelines recommend SSRIs as first and second-line pharmacological treatment options for moderate to severe depression.[66, 67, 96, 181, 183] SSRIs account for up to 76% of antidepressant prescriptions across Europe, North America and Australasia,[3, 27, 31, 192, 201] and higher than standard SSRI doses are commonly being used to treat depression, Section 5.2.1.[17, 191, 201] The findings of the three interconnected studies have the potential to inform policy makers to develop better strategies, via guidelines, specialist groups (e.g. Royal Colleges of Psychiatry and General Practice), national indicators, formularies and general practice-based work, that focus efforts and resources to support the appropriate use of antidepressants.

The ceiling effect for efficacy may also be of interest to the FDA, EMA and MHRA to update drug licenses to better reflect current evidence for safety and efficacy, as they have previously done with citalopram and escitalopram and QTc prolongation.[198] This would then make it easier for policy makers to

update standard medical texts such as the British National Formulary and national and local guidelines, to highlight the differences in dose-response effects between different antidepressant drugs and drug classes. Similarly, the 8-12 week lag in treatment, may influence guideline developers to highlight early response rates as previously identified by others.[97, 98]

By 'doing the right thing', highlighting SSRI drug limitations and enabling proactive reviews, policy makers have the opportunity to potentially reduce overall antidepressant prescribing, or at least flatten the growth in prescribing. However, the application of the thesis findings can also be of use in informing service development and delivery, and working towards the strategic goals of Realising Realistic Medicine; to Achieving Excellence in Pharmaceutical Care; to the Scottish Practice Pharmacy and Prescribing Advisors Strategic Alignment; and the Royal Pharmaceutical Society's Mental Health Policy.[391-393]

8.3.2.2 Public concerns

A recent study involving patients with lived experience taking antidepressants identified a number of failure points in routine care. One was that 'drug treatment is continued despite drugs not helping and/or severe side effects'.[195] This links with the qualitative study's findings that there is often an 8-12 week lag in optimising antidepressant treatment at the start of treatment, a lack of proactive review with continued treatment, and the need to improve practice systems to better enable regular reviews when initiating and continuing treatment.

Patients are also concerned that antidepressants cause dependence and withdrawals, and that GPs are not suitably trained to support patients with managed withdrawal.[33, 195, 400, 401] While the studies in this thesis did not directly address this issue, the flat-dose response findings of the systematic review may help to inform practitioners of the need to limit their use of higher SSRI doses that may indirectly help to reduce the risk of withdrawal.[385]

8.3.3 Education implications

There are a number of implications for patients and healthcare professionals. For patients, in general, education is required about the pros and cons of antidepressant treatment; in particular: dose limitations and the need for regular review, time for effect, ADEs, duration of treatment, and the potential for withdrawal effects when stopping.[22, 195]

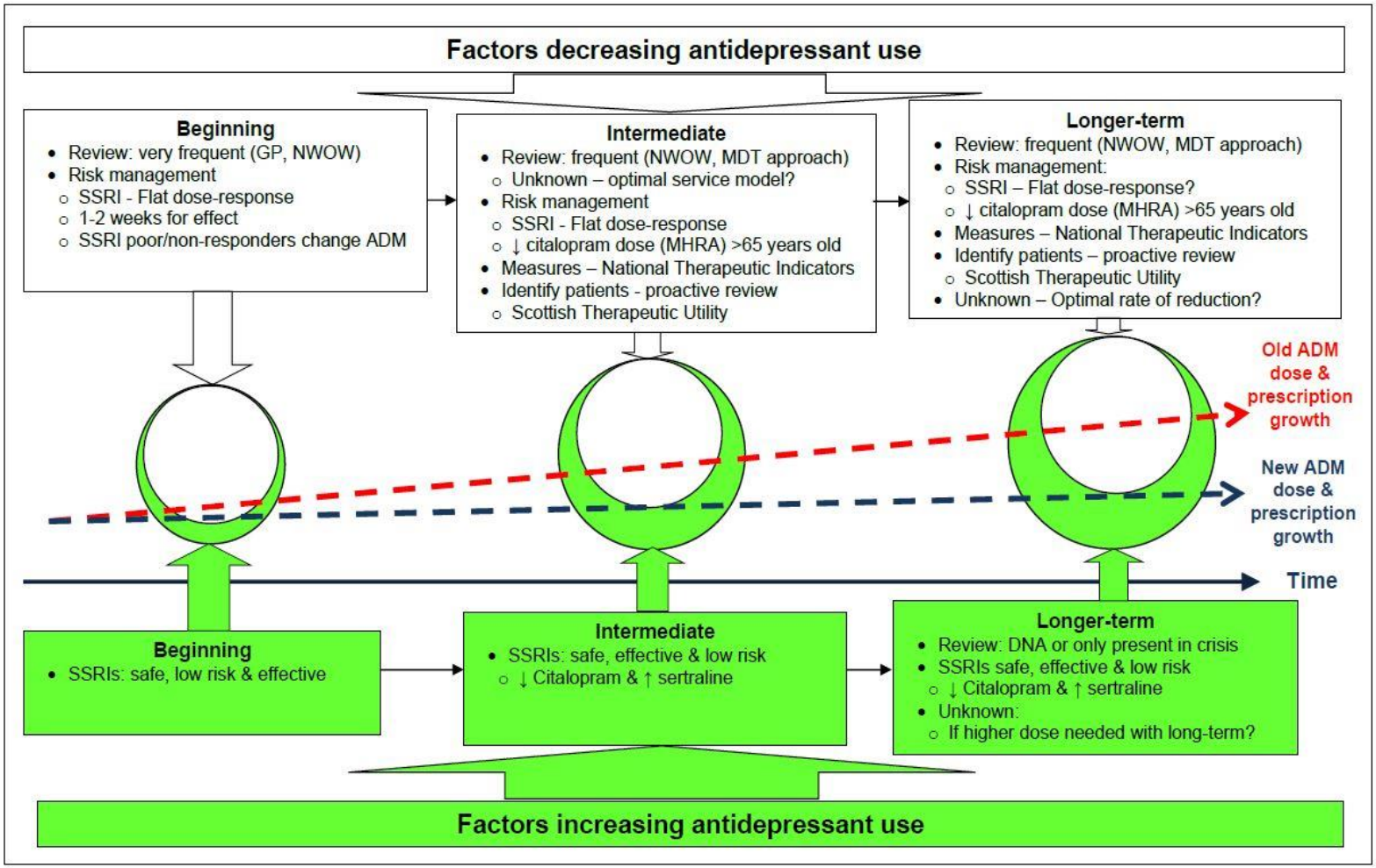
For healthcare professionals, it is more than educating GPs. There is a need to educate and update the broader healthcare team, as people with depression commonly have multimorbidity and are seen by numerous healthcare professionals during their depressive episode.[222] The number of non-medical prescribers e.g. nurses, pharmacists, physiotherapists, etc, is also growing, and these professionals routinely treat acute and long-term conditions as part of their clinical responsibilities. This often takes a 'silo' – single disease state – approach to optimising treatment and care,[402-404] and does not fit the vision of holistic care or Realising Realistic Medicine.[394] Therefore, there is a need to inform all healthcare professionals regarding the limitations and effects of SSRIs to better enable them to respond to patient's needs. This approach may also help to further develop new ways of working and the multidisciplinary team to better support and deliver patient care.[265]

Anecdotally I am also aware, from my teaching role, that the majority of undergraduate and postgraduate students are taught that SSRIs and other antidepressants require 6-8 weeks of treatment before exerting their effects, and that the dose should be pushed in poor/non-responders regardless of the drug class or dose. Therefore, there is a need to update educationalists and trainers regarding early antidepressant effects in the first 2 weeks of treatment, and dose limitations, as well as highlighting to students the need for regular proactive review to assess the need for ongoing antidepressant treatment.

Finally, implanting and embedding new knowledge into practice – knowledge translation, and knowledge-to-action – is challenging.[405] For example even though studies highlight that bendroflumethiazide had a flat dose-response curve and ceiling effect for blood pressure lowering effects in the late 1980s,[406] it took until the early 2000s for this to become routine practice. Therefore, while

the review of reviews and other recently published systematic reviews highlight the flat SSRI dose-response effects,[167, 312, 313, 345] it will take a number of years before we could hope that this would be routinely applied in clinical practice. Therefore theoretically, if this thesis' findings are applied to practice and policy, without significant changes in the practice populations or a new wonder drug coming to market, it may be possible to reduce overall antidepressant growth by focusing on SSRIs (Figure 21). Remember that SSRIs currently account for half of the antidepressant prescriptions, 67% of DDDs dispensed, and are prescribed to half of the people that receive antidepressants.[27] Therefore, I estimate that there is potential for a 20% in total antidepressant DDDs, (see Box 1, below) as the average SSRI doses for individual drugs in the regression analysis was up to 25% higher for <2 years use, and up to 42% higher for those prescribed the same SSRI for ≥2 years, when compared to previous cross-sectional studies.[17, 99, 235-237]

Figure 21. Applying thesis findings, and identifying a theoretical change in antidepressant prescribing growth



ADM: antidepressant. DNA: do not attend for review. esp. especially. MDT: multidisciplinary team. MHRA: Medicines and Healthcare products Regulatory Agency. NWOW: new ways of working. SSRI: selective serotonin re-uptake inhibitor. ↑ increase ↓ decrease ? unknown/unclear

Box 1 Derivation of estimated change in antidepressant prescribing by defined daily doses

Change in prescribing estimated by applying the following in sequence to antidepressant prescribing data for NHS Scotland 2019/20:[407]

	Prescriptions (million)	DDDs (million)
SSRIs	3.8	211.1
Other antidepressants	1.8	70.7
TCAs	1.8	32.3
MAOIs	0.0	0.3
Total	7.4	314.5

1. Proactive review of long-term SSRI and other antidepressant (mirtazapine, SNRIs etc) use.
   a. 48% of antidepressants are prescribed long-term (≥2 years) from UK literature.
   b. 9.5% reduction in prescribed doses (as DDDs) by reviewing long-termer use of SSRI excluding TCAs.[17]

	Point prevalence long-term (≥2 years)
Scottish Government 2022[408]	57%
Petty et al 2006[190]	55%
Moore et al 2009[5]	51%
Johnson et al 2012[17]	47%
Chapter 5	28%
Average	**48%**

2. Applying ceiling effects for depression to publicly available prescribing data
   a. 80% of antidepressants are prescribed for the treatment of depression/mixed anxiety depression, in UK studies.
   b. 48% of antidepressants are prescribed long-term use, ≥2 years.
   c. 52% short-term use, <2 years.
   d. 25% higher SSRI doses for short-term and 40% for long-term use (Section 5.6)

	Depression treatment prevalence for people receiving antidepressants
Johnson et al 2012[17]	87%
Sinclair et al 2014[199]	85%
Chapter 5	87%
Petty et al 2006[190]	61%
Average	**80%**

Box 1. Continued.

Part 1 – Estimated effect of proactively reviewing long-term (≥2 years) antidepressants

- 48% of people receive long-term antidepressants
  - Total SSRI DDDs = 221.1 mill.
    - 48% of 221.1 = 101.3 mill.
    - 9.5% of 101.3 = 9.6 million reduction in SSRI DDDs
  - Total other antidepressants DDDs = 70.7 mill.
    - 48% of 70,7 = 33.9 mill.
    - 9.5% of 33.9 = 3.2 million reduction in other antidepressant DDDs

Part 2 – Estimated effect of apply ceiling efficacy effects

- Total SSRI DDDs minus review effect = 221.1 – 9.6 = 211.5 mill
- If 80% of DDDs are prescribed to treat depression:
  - 80% of 211.5mill = 169.2 mill
  - Of the 169.2 million DDDs
    - 52% for short-term (<2 years): 52% of 169.2 mill = 88.0 mill
    - 25% reduction in short-term doses = 25% of 88.0 = 22.0 mill
    - 48% for long-term (≥2 years) use: 48% of 169.2 mill = 81.2 mill
    - 40% reduction in long-term doses: 40% of 81.2 mill = 32.5 mill

		Estimated reduction (DDD millions)
Proactive review of long-term use	SSRIs	9.6
	Other antidepressants	3.2
Apply SSRI dose ceiling effects to practice	Short-term use	22.0
	Long-term use	32.5
	Total	**67.3**

Estimated effect on total antidepressant DDD volumes.

- Total antidepressant DDDs 2019/20 Scotland = 314.5 million
- 67.3 million of 314.5 million = 21% of total DDDs.
- 21% estimated reduction in antidepressant DDD volumes.

DDDs: defined daily doses, SSRIs: selective serotonin re-uptake inhibitors, TCAs: Tricyclic antidepressants. Other antidepressants: mirtazapine, SNRIs, etc as defined in Section 3.1.
Note: Mixed depression and anxiety disorder is treated as depression see NICE guidelines.[67]

8.3.4 Future research

This thesis raises several potential opportunities for further exploration. The regression analysis highlighted the dose differences between short and long-term SSRI doses. This raises a range of complex questions: are patients receiving the most effective drug and dose, or are they spontaneously remitting;[369, 399, 409] do people truly develop a loss of antidepressant effect with longer treatment duration, or is it an acute on chronic episode that requires higher doses or not; does increasing or reducing doses provide non-specific non-pharmacological treatment effects;[409-411] and do neuroprogressive changes in depression affect drug response.[412] All of these issues warrant further investigation.

Identifying optimal methods for enabling regular proactive antidepressant reviews is a priority. This is important as long-term antidepressant prescribing is increasing.[5] Some of the growth may be inappropriate, due to a reduction in the frequency of antidepressant reviews with time,[199, 200] and the continued stigma and barriers associated with psychotropic medicines use.[7, 174, 178, 179, 413] However, it is important that study design, and intervention delivery should aim to normalise the medication review process: not inviting people for 'an antidepressant review', but focusing on reviewing medicines, particularly when most people being treated for depression are known to have greater multimorbidity and associated prescribing.[222] This may optimise engagement but also provide an opportunity for a complete medication or polypharmacy review that aligns itself with Realising Realistic Medicine, the GP contract in Scotland, and patients' needs.[394, 414]

Differences in drug and dose effects is another priority area to explore in relation to withdrawals, as highlighted in patient petitions to the UK parliaments and recommendations from Public Health England and the Scottish Government.[33, 195, 400, 401, 415] There is much debate and discussion regarding the true incidence and prevalence of withdrawals, which can vary by individual antidepressant (e.g. more commonly occurs with paroxetine and venlafaxine), duration of treatment, condition being treated and study design. Previous studies indicate that up to 12% of people receiving placebo and up to 32-86% of people receiving different antidepressants may be affected.[193, 194, 416]

However, some individual's may be more sensitive to withdrawals than others, and at present there is a gap in the literature regarding who will or will not experience withdrawal effects, therefore future large-scale studies should assess the incidence and prevalence of withdrawal effects and aim to identify factors associated with withdrawal in routine practice. It would also be useful to characterise patients that may be at higher risk of withdrawals by exploring patient-level variables that are associated with successful and problematic withdrawal e.g. drug, dose, indication, duration of treatment, etc, as well as prospectively assessing the long-term effects such as which patients restart treatment, and when for a new depressive episode.

Identifying optimal antidepressant discontinuation strategies is a potential area for further research as it is unclear what the most effective withdrawal interventions are. A recent systematic review however, demonstrated that the majority of published studies were small, delivered at specialist outpatient sites, involved psychological therapies, and did not enable general practices to better support their patients.[417] Furthermore, the optimum rate of dose reduction to prevent withdrawals is unknown, and while a range of options have been used and theorised as being effective,[387, 418] trialling and assessing different dose reduction schedules and methods is needed to better inform clinical practice.

The review of reviews found that increasing SSRI standard doses in the acute phase of treatment was not more efficacious. Therefore, longitudinal studies are needed to clarify if increasing SSRI doses in response to an acute depressive episode is effective for people that are already receiving long-term treatment with a SSRI. Longitudinal studies are also needed to assess the long-term effects of treatment beyond 2 years as evidence for such practice is lacking.[386] Such studies should also consider differentiating between drug and placebo effects, and spontaneous remission.[409]

Qualitative studies, on the other hand, should be conducted to provide insight to patient experiences: of medicines review strategies and methods; lived experience of antidepressant review and withdrawal; patient expectations regarding antidepressant doses and drug limitations; as well as being used to help contextualise findings from potential quantitative studies as outlined above.

Finally, economic evaluations should be incorporated into future studies. Due to limited health care resources, and the majority of patients having their antidepressant initiated and continued by their GP, proposed interventions need to be delivered within primary care. Therefore, new ways of working will need to be explored to help release GP capacity and utilise the wider general practice multidisciplinary team to deliver and embed effective interventions in routine practice.

Lastly, depression is a challenging condition that often has significant personal costs to individual's, their families and society. Globally, depression has been identified and consistently ranked as one of the leading causes of years lived with disability for more than a generation.[36-38] Therefore ensuring antidepressants are used effectively and efficiently, as part of a multifaceted approach to depression treatment and ongoing care, is more important than ever as the number of people receiving antidepressant prescriptions continues to grow. Some of this use will be appropriate, some will not. So future studies must work to find the right balance in prescribing and deprescribing that optimises patient care while minimising avoidable drug-related harms.

8.4 How the thesis findings are being used

The regression analysis and qualitative studies have been published in peer review journals, as well as being disseminated at national and international conferences, for more details and altmetrics see Appendix A4.

At a UK level the findings from the regression analysis and qualitative studies have been included as part of the Royal College of Psychiatry's position statement on antidepressants and depression.[419]

At a national-level in Scotland, thesis' findings have been shared with pharmacy colleagues as part of a number of continuing professional development webinars for depression via NHS Education Scotland. Some of the findings have been included as part of the Royal Pharmaceutical Society (Scotland) new mental health policy.[420] More widely however the findings are being used to help inform the development of the response to Public Health England's and

the Scottish Government's recommendations regarding 'dependence and withdrawal associated with some prescribed medicines', which included antidepressants.[33, 415] The Effective Prescribing and Therapeutics Branch of the Scottish Government is developing Quality Prescribing Advice for Antidepressants and National Therapeutic Indicators (NTIs).[421] The NTIs are designed to identify areas of prescribing improvement and benchmarking between health boards, HSCPs and practices. At a health board level the findings have been used to help inform the development of local NHSGGC clinical guidelines for depression treatment for adults in primary care.[379] These updated guidelines highlight SSRI ceiling effect for efficacy, response to antidepressants within 2 weeks, and 30mg daily of mirtazapine being a therapeutic dose.

At a general practice-level the NTIs are aligned with the Scottish Therapeutic Utility. The Scottish Therapeutic Utility tool enables healthcare professionals and general practice staff to interrogate their electronic prescribing systems in real time, at practice-level, using predetermined inbuilt searches such as NTIs.[422] In line with the thesis findings, and supporting literature as outlined in this thesis, the NTIs and the Scottish Therapeutic Utility will include measures and searches that identify people receiving: long-term antidepressants (same drug for ≥2 years); high dose SSRIs; low dose mirtazapine; and co-prescribing of antidepressants and B-Z treatment. It will be at the discretion of health boards, HSCPs and practices how they apply and implement work as it is now not possible to incentivise work via QOF targets or quality prescribing initiatives, in Scotland. It is however possible to encourage practices to look at these areas of prescribing with the support of the general practice pharmacy prescribing support teams, as part of the pharmacotherapy section of the new general practice contract in Scotland.[265, 414]

8.5 Conclusion

This series of three interconnected studies has focused on SSRI prescribing and use in general practice, and systematically reviewed the literature relating to SSRI dose-response effects in depression. The thesis has shown a mismatch between current practice, 'push the dose' prescribing, guidelines, and current evidence. It has demonstrated that standard SSRI doses provide optimal efficacy for depression treatment. It has identified delays in optimising pharmacological treatment, a lack of medication reviews, pressures and fears that maintain prescribing, and factors associated with the use of higher SSRI doses.

The published findings of this thesis have been used as part of local and national discussions on appropriate antidepressant use and SSRI dosing,[419, 420, 423] while the unpublished findings have been applied to local depression guidelines.[379] Yet, it is still to be seen what impact the systematic review of reviews may have on future discussions and clinical practice.

No matter what the effects of the thesis' published studies, and our gaps in knowledge, GPs strive 'to do the right thing' to help people. It is therefore important for me to continue to disseminate the findings of this thesis, to help to optimise patient care and reduce inappropriate antidepressant prescribing and avoidable drug-related harms.

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Appendices

Appendix 1 - Quantitative study: logistic regression analysis

A1.1 West of Scotland Ethics Service comments

In early 2012 I had a phone discussion with the NHSGGC Research and Development team regarding a secondary analysis of anonymised patient-level data from an audit of service review/evaluation.[245, 246] I was advised that full ethical approval was not required and to seek Caldicott Guardian approval and consent from each of the practices prior to inclusion. I obtained Caldicott Guardian consent from 11 of the 12 practices. I also discussed the study with the West of Scotland Research Ethics Service:

NHS
Greater Glasgow and Clyde

WoSRES
West of Scotland Research Ethics Service

Chris Johnson
Pharmacy & Prescribing Support Unit
Queens Park House
Langside Road
Glasgow
G42 9TT

West of Scotland Research Ethics Service
Ground Floor – The Tennent Institute
Western Infirmary
38 Church Street
Glasgow G11 6NT

Date	27th Nov 2014
Our Ref	WoS ASD 971
Direct line	0141 211 2126
Fax	0141 211 1847
E-mail	Judith.Godden@ggc.scot.nhs.uk

Dear Chris

Full title of project: **Patient Factors Associated with SSRI Dose for Depression Treatment in General Practice**

You have sought advice from the West of Scotland Research Ethics Service Office on the above project. This has been considered by the Scientific Officer and you are advised that based on the submitted documentation (email correspondence 7th & 14th Nov 2014) it does not need NHS ethical review under the terms of the Governance Arrangements for Research Ethics Committees (A Harmonised Edition). This advice is based on the following.

> The project is an audit using only data obtained as part of usual care but note the requirement for Caldicott Guardian approval to permit sharing or publication of anonymised data obtained from patient under the care of NHS Greater Glasgow and Clyde

Note that this advice is issued on behalf of the West of Scotland Research Ethics Service and does not constitute a favourable opinion from a REC. It is intended to satisfy journal editors and conference organisers and others who may require evidence of consideration of the need for ethical review prior to publication or presentation of your results.

However, if you, your sponsor/funder or any NHS organisation feels that the project should be managed as research and/or that ethical review by a NHS REC is essential, please write setting out your reasons and we will be pleased to consider further.

Where NHS organisations have clarified that a project is not to be managed as research, the Research Governance Framework states that it should not be presented as research within the NHS.

Kind regards

Dr Judith Godden, WoSRES Scientific Officer/Manager

A1.2 Practice information sheet

UNIVERSITY OF STIRLING

NHS Greater Glasgow and Clyde

Practice Information Sheet

Background and Purpose
Antidepressant prescribing continues to rise. Factors contributing to current growth are the increased use of long term antidepressants and the use of higher doses, without an increase in the incidence of depression. The purpose of this research is to use anonymous practice and practice patient data from the antidepressant HEAT target work, to identify factors associated with antidepressant prescribed daily doses.

This work will help to inform policy makers about the complexity of antidepressant use and management of common mental health problems, and may enable future mental health targets to be more appropriate. This is important as the majority of antidepressants are prescribed in primary care, with practices, Community Health Partnerships and Health Boards having their prescribing performance monitored.

Why has the practice been chosen?
Your practice participated and supported NHS Greater Glasgow and Clyde exploratory antidepressant work to understand current antidepressant prescribing and work towards appropriately addressing the antidepressant HEAT target. Anonymous patient level data was used during this work which we would like to use for further analysis.

What is involved in participating in this research study?
The anonymised practice data will be used to identify factors associated with individual prescribed antidepressant doses in a regression analysis. Data analysis will be supported by Nadine Dougall statistician at the CSO-funded Nursing, Midwifery and Allied Health Professions Research Unit, University of Stirling.

Confidentiality
All data used will be anonymised. No practice, practice staff or patients will be identified in any way in the final report. All computer files will be password protected. Practice consent forms will be stored in a locked cabinet. Data will be held for up to 5 years to allow for the long lag time between analysis and publication and will be destroyed at this time.

What will happen to the results of this research study?
The results of this study will be shared within the Health Board, Community Health Partnerships and non-NHSGGC prescribing support teams. A summary of the report will be sent to all participants and you can request a copy of the full report by contacting me. Results of this study will be submitted for publication in a relevant peer reviewed professional journal. At all times outputs will preserve patients' anonymity. Practice and CHCP data will be anonymously coded.

Contact information
If you wish further information regarding this research study, please email: c.johnson2@nhs.net or telephone on 07792537655.

A1.3 Practice consent

UNIVERSITY OF STIRLING

NHS Greater Glasgow and Clyde

Chris Johnson
Central Prescribing Team
Pharmacy & Prescribing Support Unit
Queens Park House, Victoria Infirmary
Langside Road,
Glasgow, G42 9TT

email: c.johnson2@nhs.net
Telephone: 07792537655

Dear

Date 2/5/12

Thank you for participating in the local antidepressant HEAT target work to better understand prescribing rates, which as you know continues to rise. Published studies identify that the increased use of SSRIs and more people being prescribed long-term antidepressants are contributing to growth, without a rise in the incidence of depression.

From our practice and CHCP work we have identified that antidepressants are being prescribed at larger doses than previously recorded: specifically SSRI doses being up to 30% higher than previous studies have shown. In order to further understand factors associated with the use of these higher doses, we would like your permission to use anonymised practice and patient data arising from the antidepressant HEAT target work.

In order to appropriately analyse this data we propose to work closely with Nadine Dougall, statistician and Lecturer at the CSO-funded NMAHP Research Unit, University of Stirling. We have enclosed a participant information leaflet for further information. If you wish to discuss further please contact me at c.johnson2@nhs.net or telephone 07792537655. Please complete and return this letter and retain a copy for your records.

We hope that this work can be used to further inform policy makers about the complexity of antidepressant use and management of common mental health problems, and may enable future mental health targets to be more appropriate.

Thank you for your help.

Chris Johnson
Antidepressant Pharmacist

The practice **agrees** to taking part in the above study. ☐

The practice **does not** agree to taking part in the above study ☐

GP (Print)_____ Signature_____ Date

GP (Print)* _____ Signature_____ Date

*May be appropriate for the practice manager to be the second signatory.

A1.4 STROBE checklist

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of cross-sectional studies

Section/Topic	Item	Recommendation	Reported in Section
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Chapter 5. title
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Not appropriate – Thesis abstract summarises 3 research studies. Limited word count does not allow.
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	1.1, 3.2, 3.3 & 5.1
Objectives	3	State specific objectives, including any prespecified hypotheses	1.1 & 5.1
Methods			
Study design	4	Present key elements of study design early in the paper	5., 5.2.2 & 5.2.4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5.2.2, 5.2.3 & A1.5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5.2.3
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5.2.4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5.2.3, 5.2.4
Bias	9	Describe any efforts to address potential sources of bias	5.2.3
Study size	10	Explain how the study size was arrived at	5.2.2
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5.2.4

Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5.2.4
		(*b*) Describe any methods used to examine subgroups and interactions	5.2.4
		(*c*) Explain how missing data were addressed	5.2.3
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	5.2.2 & 5.2.4
		(*e*) Describe any sensitivity analyses	5.2.4
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5.3.1
		(b) Give reasons for non-participation at each stage	5.3.1
		(c) Consider use of a flow diagram	5.3.1 & Figure 12
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	5.3.2 & Table 5
		(b) Indicate number of participants with missing data for each variable of interest	5.3.2
Outcome data	15*	Report numbers of outcome events or summary measures	Not appropriate
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	5.3.2
		(*b*) Report category boundaries when continuous variables were categorized	5.3.2
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not appropriate
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Not appropriate
Discussion			
Key results	18	Summarise key results with reference to study objectives	5.4
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	5.5

Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	5.4, 5.5, 5.6 & 8.1
Generalisability	21	Discuss the generalisability (external validity) of the study results	8.2
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Acknowledgements & 8.6

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies. **Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

A1.5 Read Codes and encounter extracts

Condition	Code	Clinical concept	Contract code†
Depression	E112.	Single major depressive episode	
	E113.	Recurrent major depressive episode	
	E118.	Seasonal affective disorder	
	E11y2	Atypical depressive disorder	
	E11z2	Masked depression	
	E135.	Agitated depression	
	E2003	Anxiety with depression	yes
	E291.	Prolonged depressive reaction	
	E2B..	Depressive disorder NEC	
	E2B1	Chronic depression	
	Eu204	[X]Post-schizophrenic depression	
	Eu32.	[X]Depressive episode	yes
	Eu33.	[X]Recurrent depressive disorder	yes
	Eu341	[X]Dysthymia	
	Eu412	[X]Mixed anxiety and depressive disorder	
	Encounters	depression, depressive, depre*	
Other co-morbidities			
Asthma	H33..	Asthma	
	H33zz	Asthma NOS	yes
	21262	Exclude if asthma resolved	
COPD	H3...	Chronic obstructive pulmonary disease	
	H3y..	Other specified chronic obstructive airways disease	
	H3z..	Chronic obstructive airways disease NOS	yes
	H31..	Chronic bronchitis	
	H32..	Emphysema	
	H36..	Mild chronic obstructive pulmonary disease	
	H37..	Moderate chronic obstructive pulmonary disease	
CVD	G3...	Ischaemic heart disease	
	G3z..	Ischaemic heart disease NOS	yes
	G30..	Acute myocardial infarction	
	G30z.	Acute myocardial infarction	yes
Stroke	G6...	Cerebrovascular disease	
	G64z.	Cerebral infarction NOS	yes
Hypertension	G2...	Hypertensive disease	yes
	G20..	Essential hypertension	
Diabetes	C10..	Diabetes mellitus	
	C10E.	Type 1 diabetes mellitus	yes
	C10F.	Type 2 diabetes mellitus	yes

Condition	Code	Clinical concept	Contract code†
Bipolar illness	E11..	Manic-depressive psychoses	
	Eu31.	[X]Bipolar affective disorder	yes
Schizophrenia	E10..	Schizophrenia	
	E10z.	Schizophrenia NOS	yes
	Encounters	Schizophren*	
OCD	E203.	Obsessive compulsive disorder	
	Encounters	Compul*	
Anxiety	E200.	Anxiety states	
	Eu431	[X]Post - traumatic stress disorder	
	E29y1	Post-traumatic stress disorder	
	E2001	Panic disorder	
	E2022	Panic disorder	
	E202.	Phobic states	
	Encounters	phob*	
Eating disorders	E271.	Anorexia nervosa	
	E2751	Bulimia nervosa	
Smoking	137R.	Current smoker	yes
	137S.	Ex-smoker	yes
	137L.	Current non-smoker	yes

†Defined by Scottish Clinical Information Management in Practice January 2009. http://www.scimp.scot.nhs.uk/better-information/clinical-coding/read-codingsummarising/

Appendix 2 – Qualitative

A2.1 Study invitation materials

A2.1.1 Cover letter

UNIVERSITY OF STIRLING

NHS Greater Glasgow and Clyde

NHS SCOTLAND

c/o Allan O'Neill
Central Prescribing Team
Pharmacy & Prescribing Support Unit
Queens Park House, Victoria Infirmary
Langside Road,
Glasgow, G42 9TT

email: c.johnson2@nhs.net
Fax: 0141 201 5217
Tel: 07792537655

Date 30/10/13

Dear Colleague,

Research Study: Exploration of factors influencing antidepressant prescribing and prescribed dose: a qualitative study.

This study will inform future development of NHSGGC antidepressant prescribing indicators and prescribing strategy supporting appropriate use of antidepressants, in line with the Scottish Governments request that all Scottish health boards continue to develop frameworks supporting appropriate antidepressant prescribing following the end of the antidepressant HEAT target in 2010.

The majority of antidepressants prescribed in Scotland are for the treatment of depression. NHSGGC HEAT target work identified that prescribers are prescribing larger antidepressant doses for depression with the majority of these medicines being selective serotonin re-uptake inhibitors (SSRIs) which are prescribed at up to 30% higher doses than previously reported. The use of higher SSRI doses for depression is not supported by current literature and is contributing to the increases in prescribing. Factors influencing the use of higher antidepressant doses are unknown. Quantitative methods are limited in providing clarity to this issue. The use of qualitative methods will enable a better subjective understanding of practitioners' rationales for prescribing larger doses of SSRIs and other antidepressants.

Yours sincerely

Chris Johnson
Antidepressant Specialist Pharmacist, NHSGGC

Study cover letter
Version 2
4th April 2013

A2.1.2 Partcipant information sheet

UNIVERSITY OF STIRLING

NHS Greater Glasgow and Clyde

NHS SCOTLAND

Participant Information Sheet

Exploring factors influencing antidepressant prescribing and prescribed dose: a qualitative study.

You are being invited to take part in a research study. Before you decide, it is important for you to understand why the research is being carried out and what it will involve. Please take a few minutes to read the following information carefully. If anything is not clear or you would like more information please contact Chris Johnson, Antidepressant Specialist Pharmacist, at c.johnson2@nhs.net or 07792537655.

Background and Purpose
Antidepressant prescribing continues to rise. Contributing factors are increased use of long-term antidepressants and the use of higher doses. For the treatment of depression current evidence supports the use of higher doses of some antidepressants but not selective serotonin re-uptake inhibitors (SSRIs). Many factors are known to influence prescribing behaviors and practice, although factors influencing antidepressant doses are unknown.

This work will help to inform policy makers about the complexity of antidepressant use and management of common mental health problems, and may enable future mental health targets to be more appropriate. This is important as the majority of antidepressants are prescribed in primary care, with practices, Community Health Partnerships and Health Boards having their prescribing performance monitored.

Why have I been chosen?
In order obtain a variety of opinions and views GPs practicing in a variety of practices: multiple and single handed practices, serving communities in areas of high, medium and low deprivation, and high, medium, low prescribing (identified from Prescribing Information System for Scotland (PRISMS)) are invited to participate. Your views will help our understanding of the practical issues of antidepressant use for depression management in primary care.

What is involved in participating in this research study?
This qualitative study involves participation in a short semi-structured one to one interview, within your practice at a time convenient to you. The interviews will be audio-taped. Names will not be used during the interview and all participants can be assured that at all times confidentiality will be observed. It is expected the interview will last no longer than 30 minutes and take place between May and August 2013. You will not be identified in the results of the research.

Confidentiality
All data collected will be anonymised. Neither you or your practice will be identified in any way in the final report. All computer files will be password protected. Consent forms and interview transcripts will be stored in a locked cabinet. Data will be held for up to 10 years in line with UK Research Council guidance.

What will happen to the results of this research study?
A summary of the report will be sent to all participants and you can request a copy of the full report by contacting me. The results of this study will be shared within the Health Board, Community Health Partnerships, NHSGGC prescribing support teams, NHS Scotland and at Mental Health Conferences where appropriate. Results will be submitted to the University of Stirling as part of my PhD requirements, and submitted for publication in a relevant peer reviewed professional journal. Published articles will be sent to participants. At all times participant and practice anonymity will be maintained.

Who has reviewed the study?
NHSGGC Pharmacy and Prescribing Support Unit, University of Stirling School of Nursing, Midwifery and Health Ethics Committee and University of Stirling Research and Development Unit have reviewed this study.

Who is organising and paying for the study?
NHSGGC is organising and supporting the study, and NHS Scotland is supporting the study with a small educational grant.

Contact information
If you wish further information regarding this research study, please email: c.johnson2@nhs.net or telephone on 07792537655. For general information please contact: *[Named administration support staff]* on 0141 5213.

Participant Information Sheet
Version 3
5th April 2013

A2.1.3 Invitation and expression of interest

UNIVERSITY OF STIRLING

c/o Allan O'Neill
Central Prescribing Team
Pharmacy & Prescribing Support Unit
Queens Park House, Victoria Infirmary
Langside Road,
Glasgow, G42 9TT

email: c.johnson2@nhs.net
Fax: 0141 201 5217
Tel: 07792537655

Dear Dr

Date

Invitation to Participate in Antidepressant Prescribing Research

We are seeking the views and experiences of general practitioners on the use and prescribing of antidepressants for depression. The research will provide a better understanding of local use and inform future NHSGGC's depression guidelines, prescribing policy and indicators. The research will also be used to support my PhD work with Professor Brian Williams director CSO-funded Nursing Midwifery and Allied Health Professional Research Unit, University of Stirling.

We are writing to ask if you would be willing to take part in this study. We are inviting GPs to participate from a variety of practices based on: 2011/12 antidepressant prescribing volumes, practice deprivation and size of practice. Participation will involve one short (approx. 30min) semi-structured interview within your practice during May to Aug 2013.

I have enclosed a participant information leaflet for further information about taking part in this study.

If you wish to take part in the study please complete the attached consent form and return by fax to the above number or email c.johnson2@nhs.net by *[date dependant on approval]* 2013.

Your decision to participate will not have any influence on your relationship with the NHSGGC Prescribing Team or University of Stirling. If you have any questions please do not hesitate to contact me.

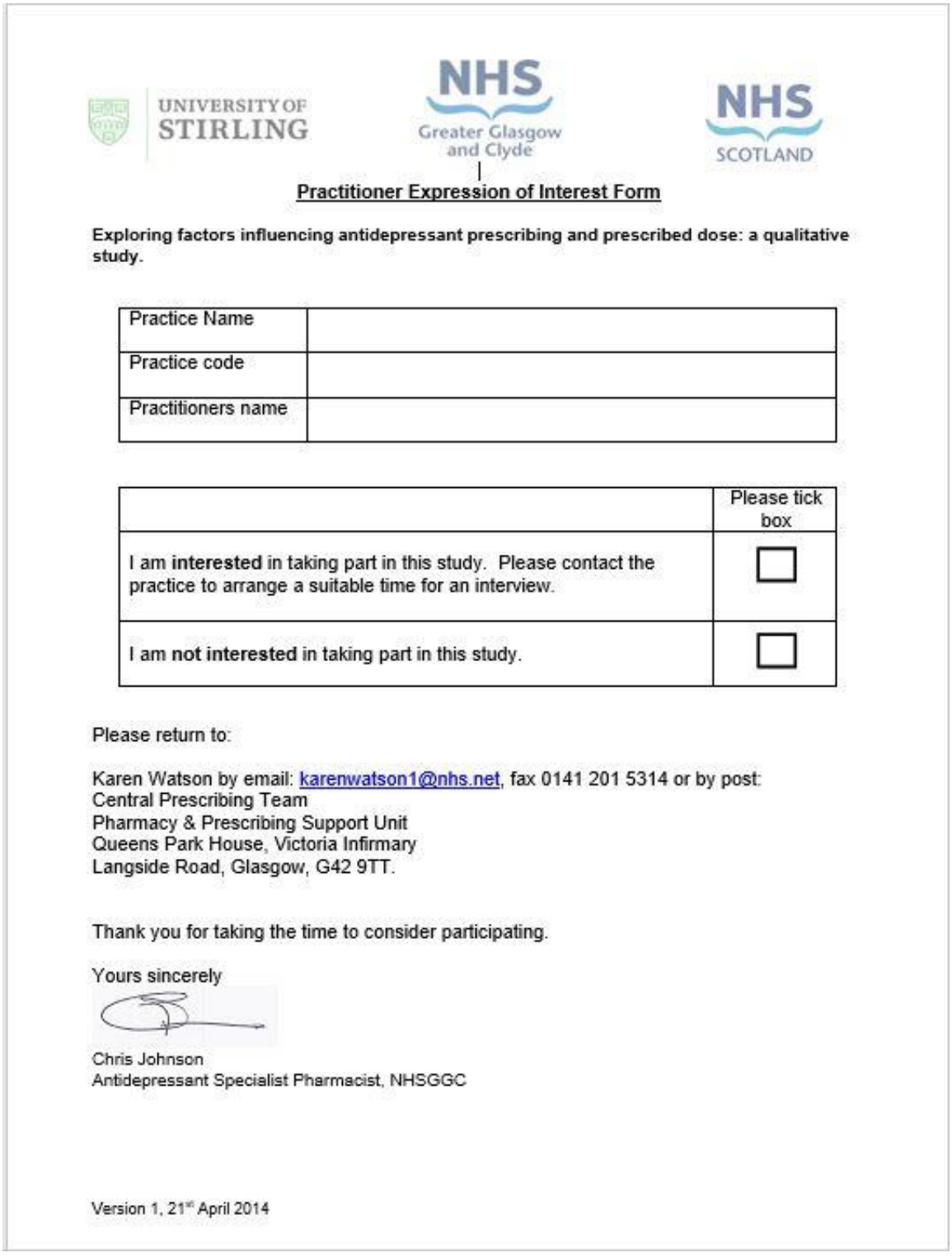
Thank you for taking the time to consider this request.

Yours faithfully

Chris Johnson
Antidepressant Specialist Pharmacist, NHSGGC

Participant Invitation letter
Version 2
4th April 2013

During the study period the key named administrative support changed, from Allen O'Neill to Karen Watson, requiring an update to be made to Opt-in form.



UNIVERSITY OF STIRLING

NHS Greater Glasgow and Clyde

NHS SCOTLAND

Practitioner Expression of Interest Form

Exploring factors influencing antidepressant prescribing and prescribed dose: a qualitative study.

Practice Name	
Practice code	
Practitioners name	

	Please tick box
I am **interested** in taking part in this study. Please contact the practice to arrange a suitable time for an interview.	☐
I am **not interested** in taking part in this study.	☐

Please return to:

Karen Watson by email: karenwatson1@nhs.net, fax 0141 201 5314 or by post:
Central Prescribing Team
Pharmacy & Prescribing Support Unit
Queens Park House, Victoria Infirmary
Langside Road, Glasgow, G42 9TT.

Thank you for taking the time to consider participating.

Yours sincerely

Chris Johnson
Antidepressant Specialist Pharmacist, NHSGGC

Version 1, 21st April 2014

UNIVERSITY OF STIRLING

NHS Greater Glasgow and Clyde

NHS SCOTLAND

Practitioner Expression of Interest Form

Exploring factors influencing antidepressant prescribing and prescribed dose: a qualitative study.

Practice Name	
Practice code	
Practitioners name	

	Please tick box
I am **interested** in taking part in this study. Please contact the practice to arrange a suitable time for an interview.	☐
I am **not interested** in taking part in this study.	☐

Please return to:

Allen O'Neill by email: allen.oneill@nhs.net , fax 0141 201 5214 or by post:
Central Prescribing Team
Pharmacy & Prescribing Support Unit
Queens Park House, Victoria Infirmary
Langside Road, Glasgow, G42 9TT.

Thank you for taking the time to consider participating.

Yours sincerely

Chris Johnson
Antidepressant Specialist Pharmacist, NHSGGC

Version 2, 23rd Nov 2015

A2.1.4 Consent form

Practitioner Consent Form

Exploring factors influencing antidepressant prescribing and prescribed dose: a qualitative study.

Practice code:
Practitioner code:

	Please tick box
1. I confirm I have read and understand the practitioner information sheet dated 31/12/12 (version 2) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily	☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time during the study period, without giving any reason, without my legal rights being affected.	☐
3. I understand that my participation in this study will be anonymous and data will be stored on password protected computers	☐
4. I understand that if some views are quoted in reports or published papers this will be done in a way that ensures that I cannot be identified.	☐
5. I understand that my views will be audio recorded for the purpose of the study and that any recordings will be destroyed at the end of the study. Anonymised transcripts will be kept for 10 years to ensure accurate reporting in any further publications	☐
6. I agree to take part in the above study	☐
7. I would like to receive summary results of the above study	☐

Name of Practitioner	Date	Signature
Name of researcher taking consent	Date	Signature

Consent Form
Version 2, 31st December 2012

A2.2 Interview schedules

Version 6 was submitted for School Research Ethics Committee approval and used to guide initial interviews. Version 14 evolved iteratively as the study progressed to capture new and emergent themes.

Interview Schedule

Exploration of factors influencing antidepressant prescribing and prescribed dose: a qualitative study

Research question: What influences prescribers' use of specific antidepressant and doses?

Interview questions:

1. Currently, what would you say are the most important factors influencing antidepressant prescribing and use for the treatment of depression in general practice?
2. How does your **experience** of general practice influence the use of antidepressants?
3. Do **service users** influence your antidepressant prescribing?
4. Does **psychiatry** influence your antidepressant prescribing? How?
5. How do you think your **training** affects your antidepressant prescribing?
6. Does the formulary influence your antidepressant prescribing? How?
7. Has the FDA/MHRA warnings influenced your citalopram/escitalopram prescribing?
8. Generally, what differences are there between antidepressants?
9. How long would you wait for an antidepressant effect when treating depression?
10. What are the therapeutic doses of SSRIs, TCAs, venlafaxine, and mirtazapine?
11. Are there any differences in dose response between SSRIs, TCAs, venlafaxine or mirtazapine for depression?
12. Do you initiate combination antidepressants?
13. When would you initiate combinations antidepressant?
14. Do you think co-prescribing of anxiolytics or hypnotics influences antidepressant response?
15. From our previous work we have found that people prescribed long-term (eg >2 years) antidepressant for depression are prescribed 20% larger doses. SSRIs made up 73% of all antidepressants. From your experience why do you think this may be?

Interview schedule
Version 6, 22/11/13

Interview Schedule

Exploration of factors influencing antidepressant prescribing and prescribed dose: a qualitative study

Research question: What influences prescribers' use of specific antidepressant and doses?

Age Gender How long since qualified? How long as a GP?
Psych rotation? Extra specialist psych training/experience Training practice?
Contract: GMS / 17C

Interview questions:

1. In general what factors are contributing to current antidepressant growth?
2. Factors influencing antidepressants use for depression in general practice?

Service users	Training	Experience	Guidelines
GP colleagues within	Out with your practice	Psychiatry/CMHTs	Talking therapies
Press/media	Prescribing Support		Industry/Pharma

3. **What are the challenges with diagnosing depression?**
4. **What are we trying to achieve with antidepressant use?**
5. **How do you qualify and quantify improvement?**
6. Do you think your prescribing is the same as your colleagues? Same, different, normal?
7. **Does gender influence prescribing? GP gender and/or patients?**
8. Policy effects: MHRA citalopram/escitalopram warning (alternatives?)

   Formulary Prescribing Indicators
9. Drug effects

Differences: SSRIs, TCAs SNRIs etc	Response
Time pressures and decision ↑/↓/cont	Therapeutic doses ?differences
Do you Rx combination ADMs	When?

10. **Guidelines: Able to access information for special groups: pregnant/breast feeding?**
11. How do you think co-prescribing of anxiolytics or hypnotics influences ADM response?
12. From our previous work we have found:
    a. **Practice patients** attended significantly affected the size of SSRI doses
    b. Same SSRI was prescribed for **≥2 years** the doses were significantly larger.
    c. Patients with **B&Zs** prescribed had significantly higher doses.
13. Did me being a PSP influence your answers?

Interview schedule, Version 14, 7/12/15

A2.3 Analysis

A2.3.1 Base Codes

Initial 'open coding' resulted in 241 codes, as outlined below. These were aggregated and assimilated as a single code where appropriate.

Base Code – 8th Oct 2014
Across society (strata)
ADM Appropriate - formulary choices
ADM appropriate - patient centred choices
ADM appropriate - preferred list
ADM avoid prescribing (conscious)
ADM avoids TCAs
ADM big dose - lack of response
ADM big dose - patient reluctance to reduce dose
ADM combinations – psych
ADM course – first episode 6 months
ADM differences
ADM differences - SEs
ADM differences - TCA difficult cases - good response
ADM dose limitations – based in evidence from trials
ADM effective
ADM efficacy - enabling
ADM follow up review – 4-8 weeks
ADM inappropriate – not the best treatment. Catch 22 – ADM or nothing
ADM Inappropriate prescribing – cost
ADM ineffective
ADM limitations
ADM prescribing - problematic
ADM push the dose with B-Zs - more chronicity/complex
ADM push dose - no
ADM push the dose – cognitive dissonance
ADM push the dose – time pressure, doing something
ADM push the dose – trying to do the right thing
ADM push the dose - unplanned intentional
ADM push the dose – various GPs
ADM push the doses - iller
ADM push the doses - off/stopped for break - less likely to stop when restarted
ADM push the doses - reluctance to stop
ADM response – 2 week window
ADM response – anxiety

ADM response – depression
ADM response – different drugs – unaware.
ADM response – patient factors – rule of thirds.
ADM Review
ADM switching guidance - used
ADMs dose and psychiatrists –
ADMs dose and psychiatrists – push the dose and it works?
Affluent - Resilience
Affluent expectations
Affluent expectations. I pay I get?
Affluent more capital (cultural/social)
alternative services - bereavement counselling, hospice, relationship, RAMH
Alternatives - online info
Alternatives - Signposting
Alternatives lacking
Amitrip for neuropathies
Anecdotes
Appropriate prescribing – assure
Appropriate prescribing – GP acknowledges limitations
Appropriate prescribing – non-formulary, non-preferred items (more cost effective)
Appropriate prescribing – not knee-jerk reaction
Appropriate prescribing – patient centred; match the drug to the patient.
Appropriate prescribing – cost
Avoid ADM - bereavement
Avoid ADM - social issue
Aware of standard dose
B-Z big doses - less like to get big ADM dose
B-Z dose sneaking up
B-Zs and ADM - bigger dose - people like tablets
B-Zs and ADM - effect unclear (better sleep, less anxious - positives)
B-Zs avoid prescribing
B-Zs for insomnia - 7 days
B-Zs started secondary care
barriers - catch 22 - GP unsure if referring to the correct place
Barriers - interpreters
Barriers to accessing alternatives
Benzo's and z-hypnotics causing depressive symptoms.- unsure
Bigger benefit – society
Bulge (Rx increase). Comment: where is the evidence – not from PRISMs or quantitative studies.
Carer - stressor

Challenged to think
Challenging patients'. Expectations, self-management, cultural capital
Clinical judgement - subjective
Cognitive dissonance - costs vs common sense
Colleagues opinion
Collectivism vs individualism
Combination ADMs - does not initiate
Come back and see me
Come back if needed – ADM f/u review
Complexity of diagnosis
Complex risk assessment
Confounders
Create space – like sick line
Crisis Team – CMHT
Culture - Asian patients less ADMs
Culture - B-Z use high - Roma
Culture - Big ADM doses Roma
Culture - Patient expectation - Roma - pill for every ill
Culture - Roma keen on psychotropics
Culture - Appropriate prescribing - difficult to assure - Roma pop.
Dep milder forms – community
Deprescribing GP reluctance to reduce dose
Deprescribing opportunity needed
Depression drivers
depression matrix (complex) - uncertainty about solutions
Depression resolving
Depression severity
Deprivation – lack of resilience
Deprived - Disenfranchised
Deprived – GP (expert) to solve prob.
Deprived areas more complex/difficult
Deprived no/minimal capital
Diagnosis - subjective assessment
Diagnostic complexity
Difficult consultation
Dissonance – SEs, who's telling the truth?
Dose increased with time –
Driver – certain (is sure)
Efficacy (real benefit)
Enabling

Engage with patient – non-judgemental
Evidence informed treatment
Expert patients - happier to increase dose
Fed up feeling down - ?not real depression
Stressors financial
Financial crisis
Follow up review – 2-4 weeks
GP awareness – good/bad prescribing
GP empathy
GP expert vs psychiatrist expert
GP knows own prescribing limitations
GP prescribing consensus
GP primed to think.
GP worries - more severe/lack of insight
Growing as a practitioner – finding way evidence, pragmatic, what worked in the past, patient centred
Guesstimate
Guidelines limitations
High deprivation – more compliant/accepting, go with GPs (experts) advice.
Holistic assessment
Hope
Iller but not too ill to be referred psych
Iller less expectation
Increasing Resilience
Industry - lack of influence now
Industry – prescriber primed
Influencer – guidance
Insight
Investigate – non-judgemental
Judging others – GP empathy
Lack of GP experience at the time
Lack of resilience
Lack of resilience (ran out)
limited alternatives (to ADMs)
Limited treatment options
Long consultations – time pressures – heart sink?
Low deprivation – challenge GPs advice confirmation of expectations
Low prescriber
Mature student – broadens perspective
MHRA - citalopram to sertraline
MHRA - QT prolongation

MHRA sertraline same to higher dose (2 DDDs)
MHRA switch - no difference in dose
Mirtazapine increases dose
Miss a trick - minor cues - non-English speakers
Miss a trick - nuances, subtleties - non-English speakers
Miss a trick (active listening, patient centred care, matching care to patient's needs)
More people struggling
More severe depression
Need for review – some stopped, some changed.
Non-ADM preference
Normalisation
Normalisation to realisation
Patient apathy
Patient expectation to get something
Patient helplessness - when present
Patient literacy an issue
Patients expectations for ADMs
Persistent symptoms – come back
Pilgrims - cultural challenges
Polypharm – slippery slope
Poor ADM response
Practice culture influencing doses used – and practice
Prescriber influences – colleagues
Prescriber influences – trainers
Prescribing behaviour change
Prescribing influences – GPs in a practice.
Prescribing targets - main rational cost saving
Prescribing tools – create time
Prescribing Tools – limited effectiveness (Scriptswitch)
Primary care depression different – 'not real depression' milder form.
Primary care expert - GP
Psych rotation – limitations
Psychiatry - disconnect (don't follow guidance)
Psychiatry - non-preferred list, non-formulary
Psychiatry - push ADM dose
Psychiatry - small influence on ADM prescribing
Push the dose - patients see as negative
Quick fix – not
Quick fix - panacea
Quick follow up – 2 days to 2 weeks

Rating scale - Underscoring
Rating scales - barrier to consultation
Rating scales - Training - rating scales not used - don't use
Rating scales – useful. Comment – throughout this interview sighs seem to acknowledge a 'forlorn hope' – no matter what you do... there will be limited or no success.
Rating scales useful
Recurrence of depression
Refer psychiatry – crisis
Refer to CMHT - more interested psychosis
Review - <7 days to 2-4weeks (severity influences)
Review Follow up - ADMs not on routine repeat
Review Follow up (ADM start) - 3-4 weeks
Revolving door CMHT then to PCMHT?
Seasonal variation – do not stop ADM.
Second line - mirtazapine
Seekers (patients engaging) expect more
Self – influencing perspective
Self-management
SEs profile influencing choice/actions
Severe dep
Sick line – create space
Sleep last symptoms to improve
Social capital
Social capital – aware of the bigger picture
social solutions
Stressors social
Society dealing with them (people with emotional distress). Big picture
Spontaneous remitters – no contact hard to quantify
SSRI Increases doses - more routine
SSRI up - 100mg
SSRI up - 40mg
SSRIs better tolerated - less SEs
Stressors - relapse
Subjective clinical assessment – patient centeredness.
Subjective complexity – diagnosis also Diagnostic confounder
Talking therapy
talking therapies - CBT
Talking therapies effective
Talking therapies have a role
TCA - push the dose

TCA SEs. – tolerance
Time pressures
Time to talk
Training – psych rotation inappropriate as dealing with different illness
Trial and error – evidence and anecdotal.
Venlafaxine increase doses
Watch and wait
Stressor Work

A2.3.2 Codes and nodes

Codes and nodes 30/3/16
1. ADM Growth factors
1. Rise in Depression - emotional distress
1a. Need for drugs - expectations
1. Patient expectations
2. Care expectations
3. GP expectations
4. Partnership
5. Disuading patients - drugs not appropriate
6. Affluence peoples- expectations
6a. Deprived peoples - expectations
Cultural differnences
Gender differences
2. Non-medical drivers
Debt - direct finacial issues
Finacial crisis
Political
Social
3. Alternatives - influences effects on Rx
1. More than antidepressants
2. Time to talk to patients
Alternatives available - yes
Alternatives not avaialble - lacking
4. Efficacy - driver
4. Safety - driver
5. Cost effective - driver
Pressure to prescribe
2. Treating mental health & non mental health problems
1. Alternatives
1. Watch & wait, sick line -Not ADM

2. Medical - PCMHTs
3. Non-medical - Counselling etc
3a. Self-management
4. Not refering onwards
5 Referring to CMHTs
2. Diagnosis - depression
1. Making time
2. Challenges - making the diagnosis
2a Severity of illness
2b. Patient centred
3. DSM-IV and other clasifications
4. Rating scales
5. Endogeous depression - real depression
6. Exogenous depression - drivers
Difference between groups under-over 70
Social history - GP insider knowledge
2a Medicalisation of society-normality
3. Quick fix
4. Responding to treatment
5. Guidelines - use
Deviation- guidance
Useful - enables
Useful to have
Useless - Barriers to practicel use
Suicide - self-harm
Training effects
3. ADM Prescribing
1. Preferred choice drugs
1a. Appropriateness
ADM - Reviewing

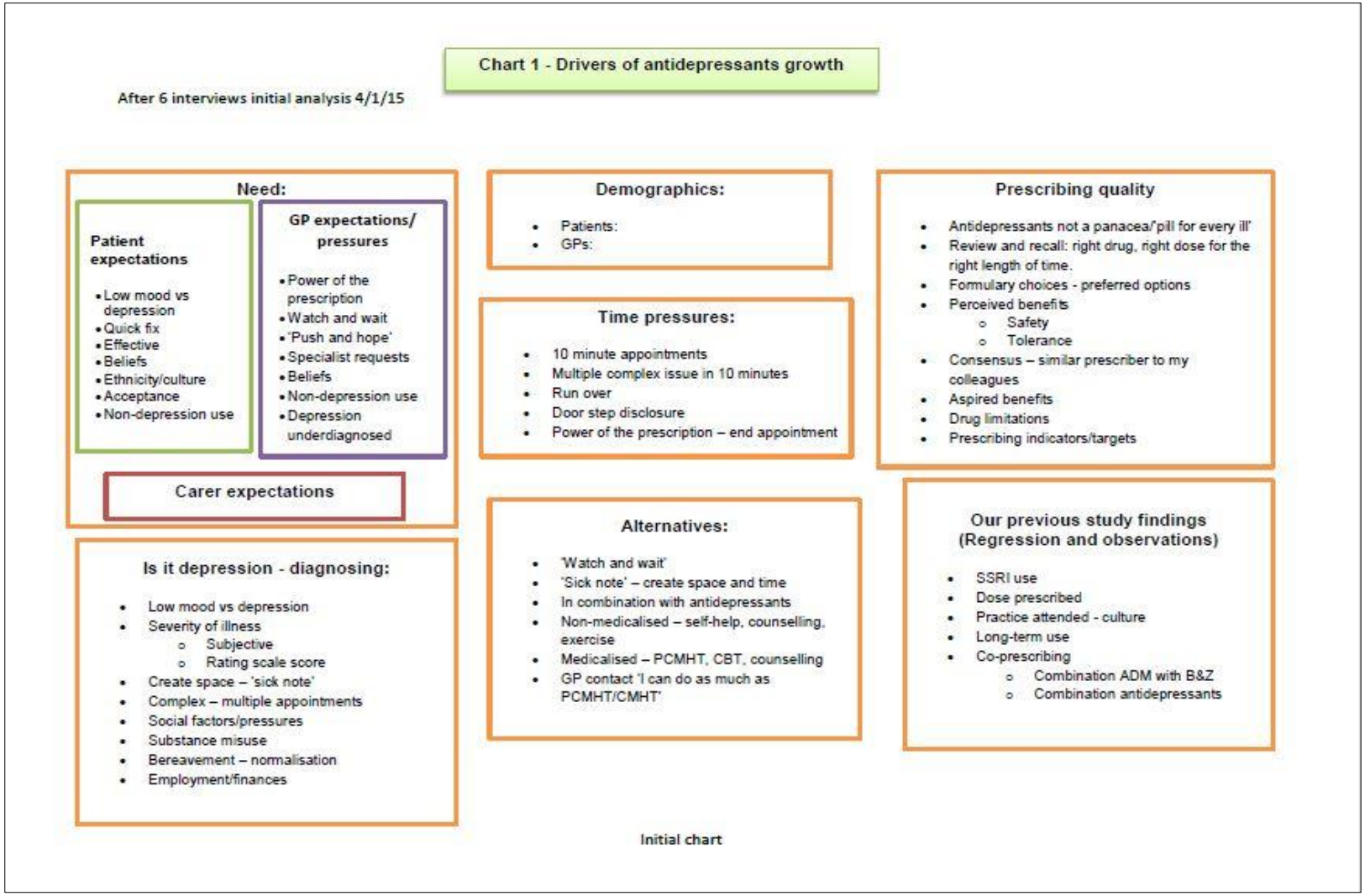
1b Inappropriate Rx
2. Choice of ADM - influencing GPs
1. Drug characteristics
2. Safety & SEs - ADM comparisons
3. Cost - infleunce
4, CMHTs and psychiatrists
5. Guidelines - influence
6. Media
7. Pharma
Private sector
3. Efficacy
1. Efficacy - effective
2. Efficacy - Not effective
3. Efficacy - placebo effect
4. Time to effect - 2-4 weeks
5. Time to effect - 4-8 weeks
6. Time to effect - 8 weeks plus
Drug limitations - not a panacea
4. Dose response effects
1. SSRI unaware - flat dose response
2. SSRI - aware flat dose response
3. Experience - observational
TCA dose response effect
5. Combination ADMs
5a Combo ADM and Benzo-type
6. Prescribe and hope
Standards
Formulary choice
Prescribing indicators
Scripswitch

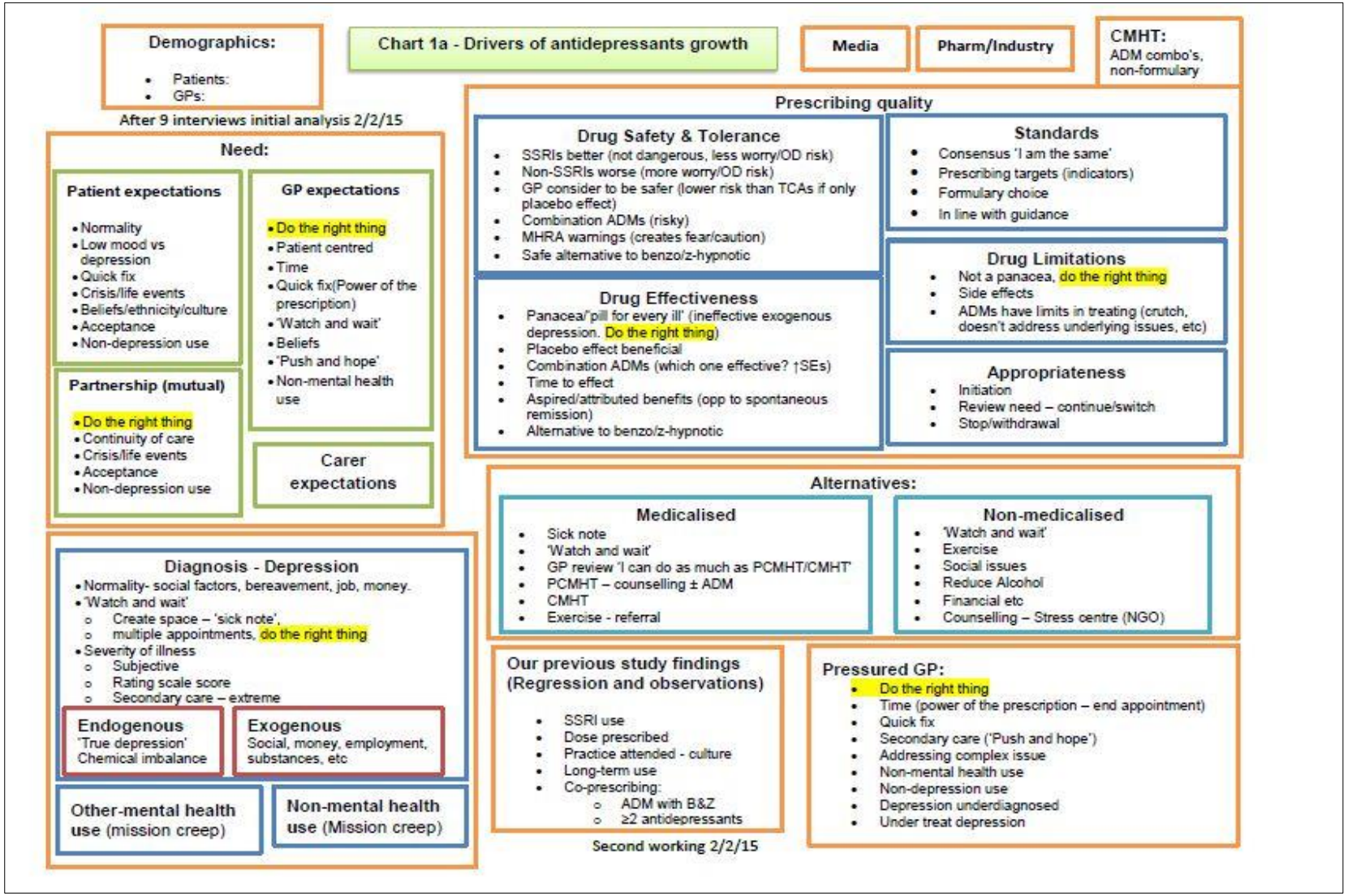
Standards - How do you compare to colleagues
4. ADM Non-depression use
Anxiety and other disorders
Non-mental health
4. MHRA citalopram warning & others
Efficacy - MHRA
1. Efficacy at lower dose - same
2. Efficacy at lower dose - worse
3. Efficacy at lower dose - lost therefore switch ADM
Fears associated with citalopram use
Patients response to MHRA warning
5. Previous studies
SSRI regression
1. Practice - bigger doses
2. Long-term use - bigger doses
3. Benzo - bigger doses
6. Other drugs
Benzos-type
Propranolol etc
Caution
Fear
GPs pressured tensions
The fit
1. Do the right thing
2. Do the wrong thing
3. Fits with
4. Poor fit
5. Best fit

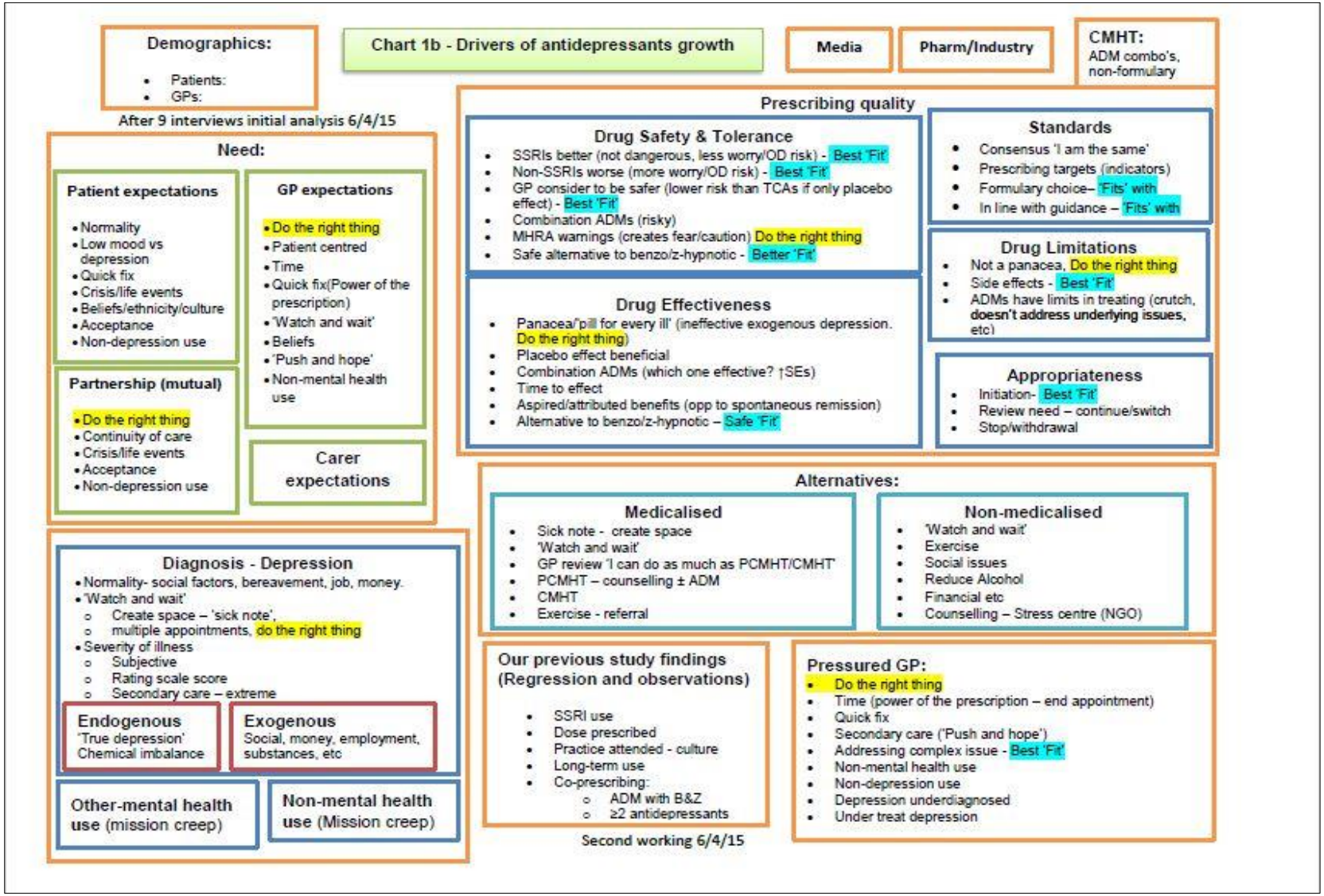
A2.3.3 Indexing

	A : 1 Drivers Antidepressant growth	B : 2. Diagnosis - challenges	C : 2.1 Dep endogenous - Real depression	D : 2.2 Depression exogenous	E : 2.3 Management and aims
1 : D1 ADM L-H = Low Age Group = >50 to ≤60 Gender = Male QOF = GMS	ADMs perceived to be effective, therefore increased demand/expectation (patients), more people struggling, lack of alternatives such as talking therapy. Patient culture expecting/receiving higher ADM doses (12)	Expectations e.g. post bereavement (6). **Cultural issues:** Language (non-English speakers) subtly of discussion lost through interpreter (10). **Referral to CMHTs:** hard to get people seen with depression (8). **Rating scales: N**ot keen, intrusive (54, 56)		Social events, bereavement, causing symptoms.	
17 : D2 ADM L-H = High Age Group = ≤40 Gender = Male QOF = GMS	**Drivers:** social issues, carer roles, help seeking behaviour (2). Unclear if more depression, or just mixed with more social problems (4) **Alts:** lack of alternatives (4). Don't meet patients' expectations: CBT etc (4). **Pts expect:** treatment (any treatment) that will work quickly (12) to get a Rx (14). **CMHT:** 3rd line agents, more unusual Rx, may affect overall figure but not GP's initial Rx (18). **TCAs:** small number receive these for depress (34)	**Drivers:** social issues, carer roles, help seeking behaviour (2). Unclear if more depression, or just mixed with more social problems (4). **Appear depressed:** CMHTs/CMHTs not helping this group (4) **Severity:** Iller patients lacking insight may need Rx but less willing to take, but milder may seek help and Rx (14),		**Drivers:** social issues, carer roles, help seeking behaviour (2). Unclear if more depression, or just mixed with more social problems (4). Unresolved social/abuse etc issues may mean people are on higher doses (86)	**Pts expect:** treatment (any treatment) that will work quickly (12) **Response:** sleep improves first (80)
2 : D3 ADM L-H = Low Age Group = >50 to ≤60 Gender = Male QOF = 17C	Social factors: problems with work, family and/or adjustment reactions - ***'have been medicalised'*** (2). Patient expectation of getting an Rx (4) Longer consultation times may reduce prescribing - ***Dr as the drug?*** - (36) [but why would it? If it is wrong to prescribe why prescribe]	Depression - usually mixed with anxiety (16) Does not rate rating scales (32). Feels uses more of a patient-centred approach (33,34) Making time to listen. Difficult with time pressures and QOF (40, 42)		ADMs as panacea for social issues (14) Lots of social factors make depression a challenging condition (18) ADM volumes higher due to multiple social factors (30)	
3 : D4 ADM L-H = Low Age Group = ≤40 Gender = Male QOF = GMS	Up: Financial crisis played a big part (2008). Due to debts: credit cards, mortgages, business (2) Amitriptyline - not used as an antidepressant (82)	Complex decision to make (4) Primary care depression (mild to moderate) different to secondary care (severe electroconvulsive therapy, etc.) CMHT patients (20) Judgement and the bigger picture. (4, 44) Cultural issues, 'cursed Scottish Male', scores low on rating scale but more depressed than they say. (4) Rating scales open up discussion, can be useful (4, 6, 8)		Lots of exogenous drivers: financial issues, lack of social networks and capital, employment issues. ***'The majority don't have true depression, but distressed state, they don't need Rx but society has not figured out a way to deal with them without giving them an ADM'*** (146)	

A2.3.4 Charting and mapping




Demographics:
Patients:
GPs:
After 9 interviews initial analysis 2/2/15
Chart 1a - Drivers of antidepressants growth
Media
Pharm/Industry
CMHT:
ADM combo's, non-formulary
Need:
Patient expectations
Normality
Low mood vs depression
Quick fix
Crisis/life events
Beliefs/ethnicity/culture
Acceptance
Non-depression use
GP expectations
Do the right thing
Patient centred
Time
Quick fix(Power of the prescription)
'Watch and wait'
Beliefs
'Push and hope'
Non-mental health use
Partnership (mutual)
Do the right thing
Continuity of care
Crisis/life events
Acceptance
Non-depression use
Carer expectations
Prescribing quality
Drug Safety & Tolerance
SSRIs better (not dangerous, less worry/OD risk)
Non-SSRIs worse (more worry/OD risk)
GP consider to be safer (lower risk than TCAs if only placebo effect)
Combination ADMs (risky)
MHRA warnings (creates fear/caution)
Safe alternative to benzo/z-hypnotic
Drug Effectiveness
Panacea/'pill for every ill' (ineffective exogenous depression. Do the right thing)
Placebo effect beneficial
Combination ADMs (which one effective? ↑SEs)
Time to effect
Aspired/attributed benefits (opp to spontaneous remission)
Alternative to benzo/z-hypnotic
Standards
Consensus 'I am the same'
Prescribing targets (indicators)
Formulary choice
In line with guidance
Drug Limitations
Not a panacea, do the right thing
Side effects
ADMs have limits in treating (crutch, doesn't address underlying issues, etc)
Appropriateness
Initiation
Review need – continue/switch
Stop/withdrawal
Alternatives:
Medicalised
Sick note
'Watch and wait'
GP review 'I can do as much as PCMHT/CMHT'
PCMHT – counselling ± ADM
CMHT
Exercise - referral
Non-medicalised
'Watch and wait'
Exercise
Social issues
Reduce Alcohol
Financial etc
Counselling – Stress centre (NGO)
Diagnosis - Depression
Normality- social factors, bereavement, job, money.
'Watch and wait'
Create space – 'sick note',
multiple appointments, do the right thing
Severity of illness
Subjective
Rating scale score
Secondary care – extreme
Endogenous
'True depression'
Chemical imbalance
Exogenous
Social, money, employment, substances, etc
Other-mental health use (mission creep)
Non-mental health use (Mission creep)
Our previous study findings (Regression and observations)
SSRI use
Dose prescribed
Practice attended - culture
Long-term use
Co-prescribing:
ADM with B&Z
≥2 antidepressants
Second working 2/2/15
Pressured GP:
Do the right thing
Time (power of the prescription – end appointment)
Quick fix
Secondary care ('Push and hope')
Addressing complex issue
Non-mental health use
Non-depression use
Depression underdiagnosed
Under treat depression


Demographics:
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GPs:
After 9 interviews initial analysis 6/4/15
Chart 1b - Drivers of antidepressants growth
Media
Pharm/Industry
CMHT:
ADM combo's, non-formulary
Need:
Patient expectations
Normality
Low mood vs depression
Quick fix
Crisis/life events
Beliefs/ethnicity/culture
Acceptance
Non-depression use
GP expectations
Do the right thing
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Partnership (mutual)
Do the right thing
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GP consider to be safer (lower risk than TCAs if only placebo effect) - Best 'Fit'
Combination ADMs (risky)
MHRA warnings (creates fear/caution) Do the right thing
Safe alternative to benzo/z-hypnotic - Better 'Fit'
Drug Effectiveness
Panacea/'pill for every ill' (ineffective exogenous depression. Do the right thing)
Placebo effect beneficial
Combination ADMs (which one effective? ↑SEs)
Time to effect
Aspired/attributed benefits (opp to spontaneous remission)
Alternative to benzo/z-hypnotic – Safe 'Fit'
Standards
Consensus 'I am the same'
Prescribing targets (indicators)
Formulary choice– 'Fits' with
In line with guidance – 'Fits' with
Drug Limitations
Not a panacea, Do the right thing
Side effects - Best 'Fit'
ADMs have limits in treating (crutch, doesn't address underlying issues, etc)
Appropriateness
Initiation- Best 'Fit'
Review need – continue/switch
Stop/withdrawal
Alternatives:
Medicalised
Sick note - create space
'Watch and wait'
GP review 'I can do as much as PCMHT/CMHT'
PCMHT – counselling ± ADM
CMHT
Exercise - referral
Non-medicalised
'Watch and wait'
Exercise
Social issues
Reduce Alcohol
Financial etc
Counselling – Stress centre (NGO)
Diagnosis - Depression
Normality- social factors, bereavement, job, money.
'Watch and wait'
Create space – 'sick note',
multiple appointments, do the right thing
Severity of illness
Subjective
Rating scale score
Secondary care – extreme
Endogenous
'True depression'
Chemical imbalance
Exogenous
Social, money, employment, substances, etc
Other-mental health use (mission creep)
Non-mental health use (Mission creep)
Our previous study findings (Regression and observations)
SSRI use
Dose prescribed
Practice attended - culture
Long-term use
Co-prescribing:
ADM with B&Z
≥2 antidepressants
Second working 6/4/15
Pressured GP:
Do the right thing
Time (power of the prescription – end appointment)
Quick fix
Secondary care ('Push and hope')
Addressing complex issue - Best 'Fit'
Non-mental health use
Non-depression use
Depression underdiagnosed
Under treat depression

Chart 2. MHRA – QT prolongation with citalopram/escitalopram

After 6 interviews 5/1/15

Patient:

- Severity of illness and previous history
- Past medical history
- Other medicines – interactions etc.
- Demographics – especially age

Demographics

- Patient
- GPs

Efficacy

- Reduced doses – maintain remission
- New vs old (higher) doses and control
- Switching to alternatives if poor control
- Patients continued on higher doses
- Severity of depression

Switching alternatives

- Reviewing patients
- Drugs now used in preference to citalopram
- Doses used for alternative SSRI/antidepressants
  - Standard vs higher
- Formulary - Preferred list
- Prescribing support influence

Chart 2a. MHRA – QT prolongation with citalopram/escitalopram

After 9 interviews, initial analysis 2/2/15

Safety

- Minimise risk – do the right thing
  - Perceive new danger
- Fear of missing drug risks (now prefers not to use citalopram) – do the right thing

Demographics

- Patient
- GPs

Efficacy

- New vs old (higher) doses and depression control
- New dose poor control: step back up or switching to alternatives
- Severity of depression
- Review need
- Local guideline awareness (dose limitations)

Pressured GP

- Do the right thing
- Patient centred

Patient:

- Severity of illness and previous history
- Past medical history
- Other medicines – interactions etc.
- Demographics – especially age

GP expectations

- Aspire to Do the right thing
- Patient centred

Switching alternatives

- Appropriateness - review patients
- Drugs now used in preference to citalopram (initiation)
- Doses used for alternative (initiation) SSRI/antidepressants
  - Standard vs higher
- Formulary - Preferred list
- Prescribing support influence

Increased awareness of dangers changes behaviours

Chart 2b. MHRA – QT prolongation with citalopram/escitalopram

After 9 interviews, initial analysis 6/4/15

Safety

- Minimise risk – do the right thing - Best 'fit'
  - Perceive new danger
- Fear of missing drug risks (now prefers not to use citalopram) – do the right thing

Demographics

- Patient
- GPs

Efficacy

- New vs old (higher) doses and depression control – Best 'fit'
- New dose poor control: step back up or switching to alternatives - Best 'fit'
- Severity of depression
- Review need
- Local guideline awareness (dose limitations)

Pressured GP

- Do the right thing
- Patient centred

Patient:

- Severity of illness and previous history - Best 'fit'
- Past medical history
- Other medicines – interactions etc.
- Demographics – especially age

GP expectations

- Aspire to Do the right thing
- Patient centred

Switching alternatives

- Appropriateness - review patients - Best 'fit'
- Drugs now used in preference to citalopram (initiation)
- Doses used for alternative (initiation) SSRI/antidepressants
  - Standard vs higher
- Formulary - Preferred list - Best 'fit'
- Prescribing support influence

Increased awareness of dangers changes behaviours

After 6 interviews 4/1/15

Chart 3. Prescribing guidance – local, NICE, SIGN etc

Patients:

- Collective vs Individual - ' individuals do not fit guidance'
- Expectation
- Willingness to engage
  - Alternatives
  - Self management
  - Pain of retelling story – counselling CBT
  - My doctor not a stranger
- Complex patients do not fit guidance
- Ethnicity/culture

GP:

- Patient not fitting standard
- Cognitive dissonance – evidence vs experience
- Drug limitations
- Psychiatryactions vs guidance
- Colleagues opinion
- Fatigue – with guidance plus other pressures

Antidepressants:

- First line treatment
- Dose response
- Psychiatrist unaware of drug limitations
- Time to affect

Alternatives

- Medicalised – access to alternatives
- Non-medicalised – access to alternatives
- PCMHT vs GP with established relationship
- CMHT for more severe illness – 'outwith ma ken'
- Revolving door/no mansland – CMHT to PCMHT to CMHT?
- Barriers

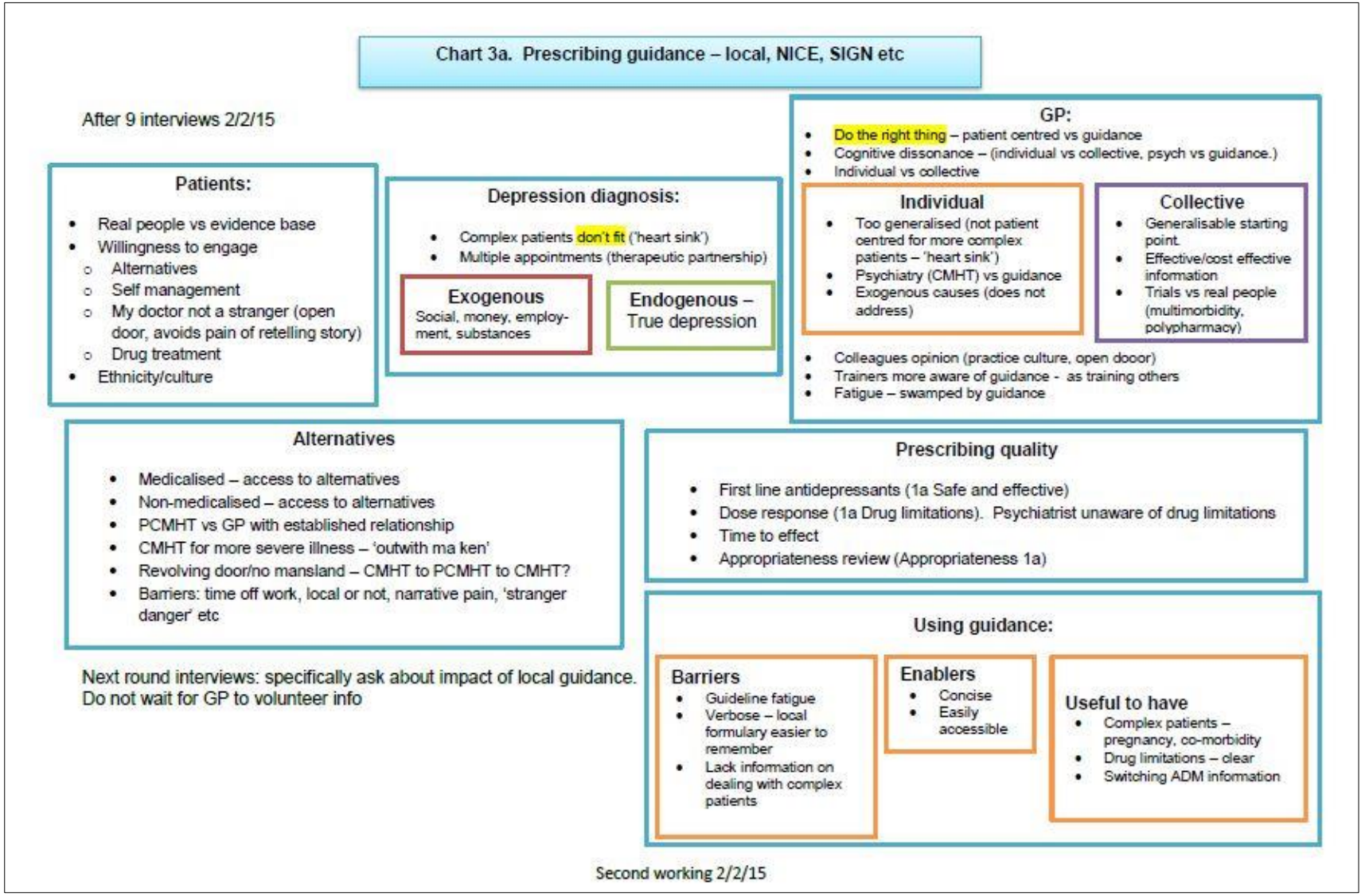


Chart 3a. Prescribing guidance – local, NICE, SIGN etc
After 9 interviews 2/2/15
Patients:
Real people vs evidence base
Willingness to engage
Alternatives
Self management
My doctor not a stranger (open door, avoids pain of retelling story)
Drug treatment
Ethnicity/culture
Depression diagnosis:
Complex patients don't fit ('heart sink')
Multiple appointments (therapeutic partnership)
Exogenous
Social, money, employ-ment, substances
Endogenous – True depression
GP:
Do the right thing – patient centred vs guidance
Cognitive dissonance – (individual vs collective, psych vs guidance.)
Individual vs collective
Individual
Too generalised (not patient centred for more complex patients – 'heart sink')
Psychiatry (CMHT) vs guidance
Exogenous causes (does not address)
Collective
Generalisable starting point
Effective/cost effective information
Trials vs real people (multimorbidity, polypharmacy)
Colleagues opinion (practice culture, open dooor)
Trainers more aware of guidance - as training others
Fatigue – swamped by guidance
Alternatives
Medicalised – access to alternatives
Non-medicalised – access to alternatives
PCMHT vs GP with established relationship
CMHT for more severe illness – 'outwith ma ken'
Revolving door/no mansland – CMHT to PCMHT to CMHT?
Barriers: time off work, local or not, narrative pain, 'stranger danger' etc
Prescribing quality
First line antidepressants (1a Safe and effective)
Dose response (1a Drug limitations). Psychiatrist unaware of drug limitations
Time to effect
Appropriateness review (Appropriateness 1a)
Next round interviews: specifically ask about impact of local guidance. Do not wait for GP to volunteer info
Using guidance:
Barriers
Guideline fatigue
Verbose – local formulary easier to remember
Lack information on dealing with complex patients
Enablers
Concise
Easily accessible
Useful to have
Complex patients – pregnancy, co-morbidity
Drug limitations – clear
Switching ADM information
Second working 2/2/15

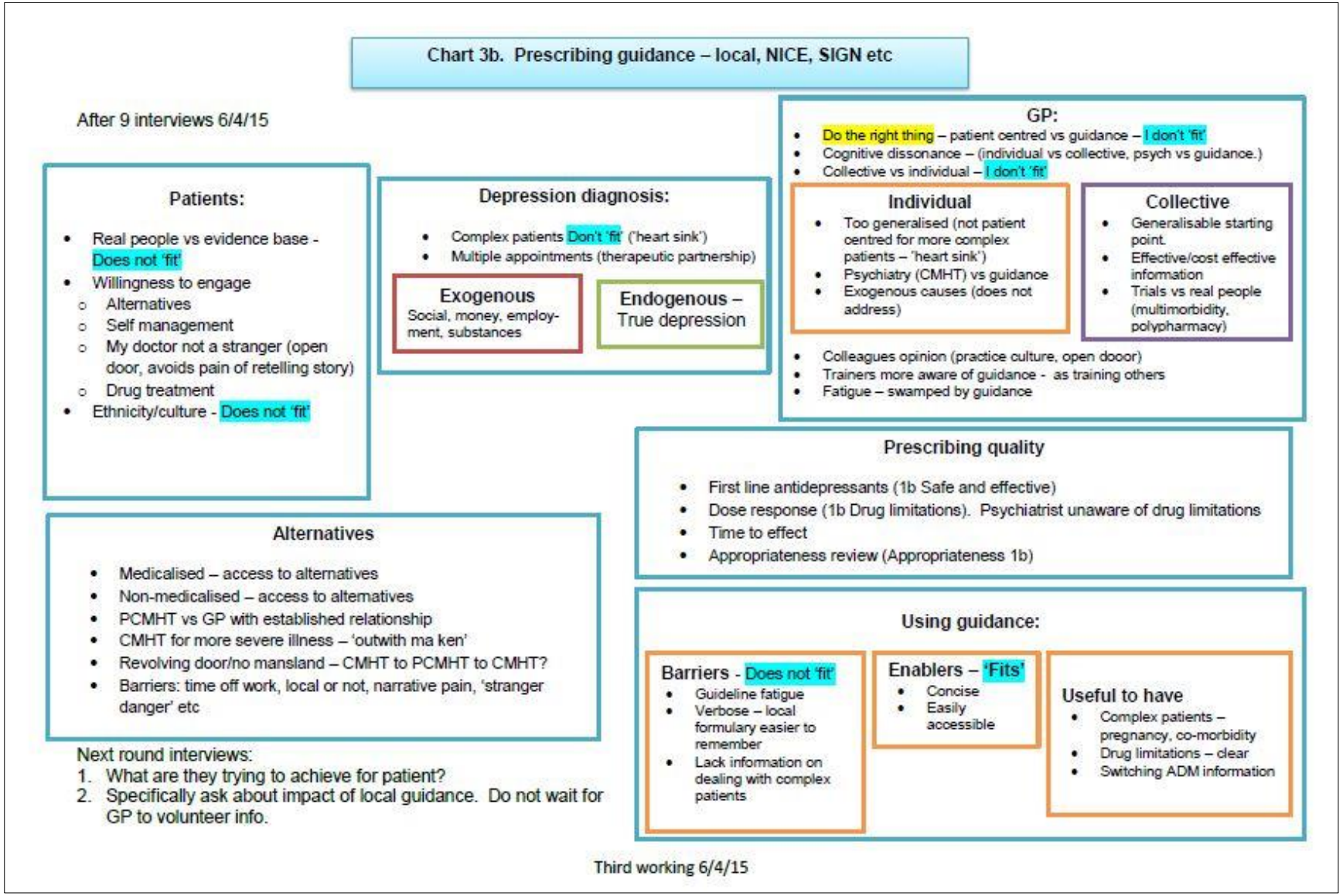


Chart 3b. Prescribing guidance – local, NICE, SIGN etc
After 9 interviews 6/4/15
Patients:
Real people vs evidence base - Does not 'fit'
Willingness to engage
Alternatives
Self management
My doctor not a stranger (open door, avoids pain of retelling story)
Drug treatment
Ethnicity/culture - Does not 'fit'
Depression diagnosis:
Complex patients Don't 'fit' ('heart sink')
Multiple appointments (therapeutic partnership)
Exogenous
Social, money, employ-ment, substances
Endogenous – True depression
GP:
Do the right thing – patient centred vs guidance – I don't 'fit'
Cognitive dissonance – (individual vs collective, psych vs guidance.)
Collective vs individual – I don't 'fit'
Individual
Too generalised (not patient centred for more complex patients – 'heart sink')
Psychiatry (CMHT) vs guidance
Exogenous causes (does not address)
Collective
Generalisable starting point
Effective/cost effective information
Trials vs real people (multimorbidity, polypharmacy)
Colleagues opinion (practice culture, open dooor)
Trainers more aware of guidance - as training others
Fatigue – swamped by guidance
Prescribing quality
First line antidepressants (1b Safe and effective)
Dose response (1b Drug limitations). Psychiatrist unaware of drug limitations
Time to effect
Appropriateness review (Appropriateness 1b)
Alternatives
Medicalised – access to alternatives
Non-medicalised – access to alternatives
PCMHT vs GP with established relationship
CMHT for more severe illness – 'outwith ma ken'
Revolving door/no mansland – CMHT to PCMHT to CMHT?
Barriers: time off work, local or not, narrative pain, 'stranger danger' etc
Using guidance:
Barriers - Does not 'fit'
Guideline fatigue
Verbose – local formulary easier to remember
Lack information on dealing with complex patients
Enablers – 'Fits'
Concise
Easily accessible
Useful to have
Complex patients – pregnancy, co-morbidity
Drug limitations – clear
Switching ADM information
Next round interviews:
1. What are they trying to achieve for patient?
2. Specifically ask about impact of local guidance. Do not wait for GP to volunteer info.
Third working 6/4/15

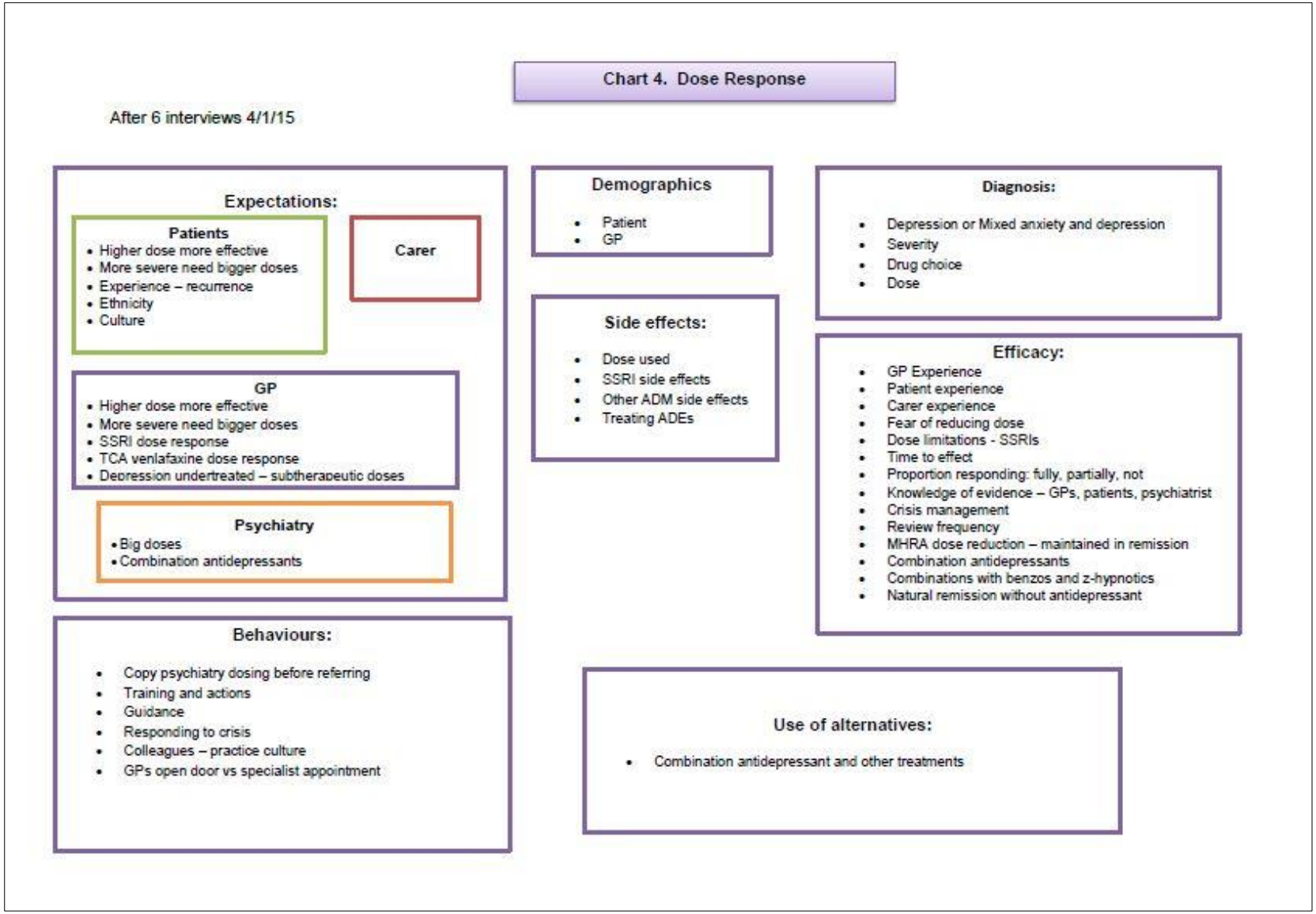


Chart 4. Dose Response
After 6 interviews 4/1/15
Expectations:
Patients
Higher dose more effective
More severe need bigger doses
Experience – recurrence
Ethnicity
Culture
Carer
GP
Higher dose more effective
More severe need bigger doses
SSRI dose response
TCA venlafaxine dose response
Depression undertreated – subtherapeutic doses
Psychiatry
Big doses
Combination antidepressants
Demographics
Patient
GP
Side effects:
Dose used
SSRI side effects
Other ADM side effects
Treating ADEs
Diagnosis:
Depression or Mixed anxiety and depression
Severity
Drug choice
Dose
Efficacy:
GP Experience
Patient experience
Carer experience
Fear of reducing dose
Dose limitations - SSRIs
Time to effect
Proportion responding: fully, partially, not
Knowledge of evidence – GPs, patients, psychiatrist
Crisis management
Review frequency
MHRA dose reduction – maintained in remission
Combination antidepressants
Combinations with benzos and z-hypnotics
Natural remission without antidepressant
Behaviours:
Copy psychiatry dosing before referring
Training and actions
Guidance
Responding to crisis
Colleagues – practice culture
GPs open door vs specialist appointment
Use of alternatives:
Combination antidepressant and other treatments

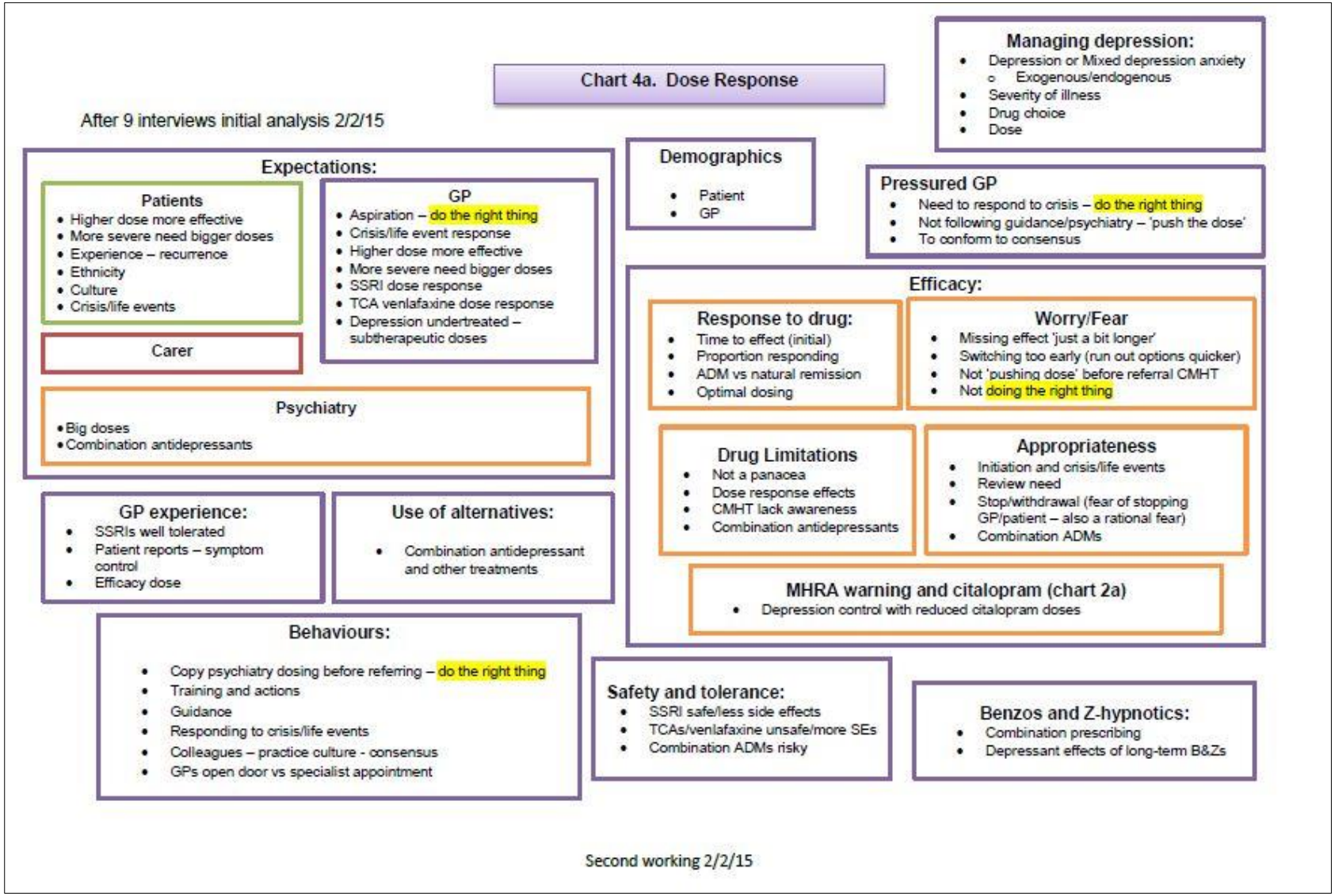


Chart 4a. Dose Response
After 9 interviews initial analysis 2/2/15
Managing depression:
Depression or Mixed depression anxiety
Exogenous/endogenous
Severity of illness
Drug choice
Dose
Demographics
Patient
GP
Pressured GP
Need to respond to crisis – do the right thing
Not following guidance/psychiatry – 'push the dose'
To conform to consensus
Expectations:
Patients
Higher dose more effective
More severe need bigger doses
Experience – recurrence
Ethnicity
Culture
Crisis/life events
GP
Aspiration – do the right thing
Crisis/life event response
Higher dose more effective
More severe need bigger doses
SSRI dose response
TCA venlafaxine dose response
Depression undertreated – subtherapeutic doses
Carer
Psychiatry
Big doses
Combination antidepressants
Efficacy:
Response to drug:
Time to effect (initial)
Proportion responding
ADM vs natural remission
Optimal dosing
Worry/Fear
Missing effect 'just a bit longer'
Switching too early (run out options quicker)
Not 'pushing dose' before referral CMHT
Not doing the right thing
Drug Limitations
Not a panacea
Dose response effects
CMHT lack awareness
Combination antidepressants
Appropriateness
Initiation and crisis/life events
Review need
Stop/withdrawal (fear of stopping GP/patient – also a rational fear)
Combination ADMs
MHRA warning and citalopram (chart 2a)
Depression control with reduced citalopram doses
GP experience:
SSRIs well tolerated
Patient reports – symptom control
Efficacy dose
Use of alternatives:
Combination antidepressant and other treatments
Behaviours:
Copy psychiatry dosing before referring – do the right thing
Training and actions
Guidance
Responding to crisis/life events
Colleagues – practice culture - consensus
GPs open door vs specialist appointment
Safety and tolerance:
SSRI safe/less side effects
TCAs/venlafaxine unsafe/more SEs
Combination ADMs risky
Benzos and Z-hypnotics:
Combination prescribing
Depressant effects of long-term B&Zs
Second working 2/2/15

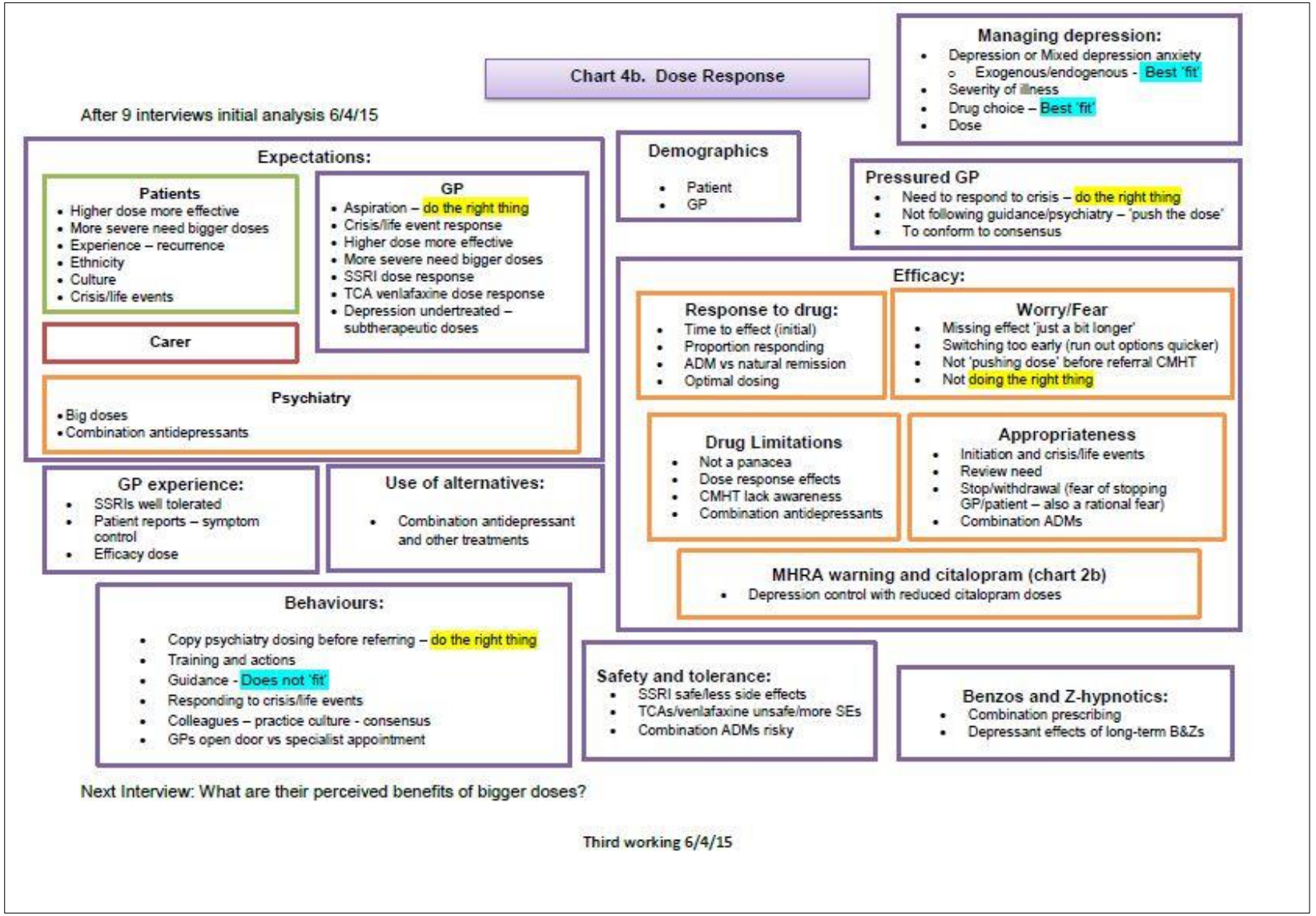


Chart 4b. Dose Response
After 9 interviews initial analysis 6/4/15
Managing depression:
Depression or Mixed depression anxiety
Exogenous/endogenous - Best 'fit'
Severity of illness
Drug choice – Best 'fit'
Dose
Expectations:
Patients
Higher dose more effective
More severe need bigger doses
Experience – recurrence
Ethnicity
Culture
Crisis/life events
GP
Aspiration – do the right thing
Crisis/life event response
Higher dose more effective
More severe need bigger doses
SSRI dose response
TCA venlafaxine dose response
Depression undertreated – subtherapeutic doses
Carer
Psychiatry
Big doses
Combination antidepressants
Demographics
Patient
GP
Pressured GP
Need to respond to crisis – do the right thing
Not following guidance/psychiatry – 'push the dose'
To conform to consensus
Efficacy:
Response to drug:
Time to effect (initial)
Proportion responding
ADM vs natural remission
Optimal dosing
Worry/Fear
Missing effect 'just a bit longer'
Switching too early (run out options quicker)
Not 'pushing dose' before referral CMHT
Not doing the right thing
Drug Limitations
Not a panacea
Dose response effects
CMHT lack awareness
Combination antidepressants
Appropriateness
Initiation and crisis/life events
Review need
Stop/withdrawal (fear of stopping GP/patient – also a rational fear)
Combination ADMs
MHRA warning and citalopram (chart 2b)
Depression control with reduced citalopram doses
GP experience:
SSRIs well tolerated
Patient reports – symptom control
Efficacy dose
Use of alternatives:
Combination antidepressant and other treatments
Behaviours:
Copy psychiatry dosing before referring – do the right thing
Training and actions
Guidance - Does not 'fit'
Responding to crisis/life events
Colleagues – practice culture - consensus
GPs open door vs specialist appointment
Safety and tolerance:
SSRI safe/less side effects
TCAs/venlafaxine unsafe/more SEs
Combination ADMs risky
Benzos and Z-hypnotics:
Combination prescribing
Depressant effects of long-term B&Zs
Next Interview: What are their perceived benefits of bigger doses?
Third working 6/4/15

After 6 interviews 5/1/15

Chart 5. Previous findings – regression and review of long-term ADMs

Size of dose

- Patient expectation
- Patient's culture/ethnicity
- GP expectation
- Psychiatry influence (CMHT)
- Knowledge gap – dose response curves
- Panacea – 'push in hope'
- Crisis management – 'push the dose'
- Severity of illness

Demographics

- Patients
- GPs

Same SSRI for ≥2 years bigger

- Crisis management 'push in hope'
- 'Step up effect' – increased during crisis no trial reducing and stopping
- Review frequency
- Patient expectations
- Severity of illness
- Chronicity of illness
- CMHT influence

Benzos and z-hypnotics

- Drug seeking behaviours
- Negative effects on depression
- Negative effects on antidepressant response
- Severity of illness
- CMHT influence

Practice variations

- Culture
- Colleagues
- Service users
- CMHT influence

Chart 5a. Previous findings – regression and review of long-term ADMs

After analysis of 9 interviews 2/2/15

Size of dose

- Patient expectation
- Patient's culture/ethnicity
- GP expectation
- Psychiatry influence (CMHT)
- Knowledge gap – dose response curves
- Panacea – 'push in hope'
- Crisis management – 'push the dose'
- Severity of illness

Demographics

- Patients
- GPs

Same SSRI for ≥2 years bigger

- Crisis management, 'push in hope' 'Step effect;' with multiple crisis/life events
- Review appropriateness – do the right thing
- Patient expectations
- Severity of illness
- Chronicity of illness
- CMHT influence
- Fear/worry – stepping down, withdrawal

Benzos and z-hypnotics

- Drug seeking behaviours
- Negative effects on depression
- Negative effects on antidepressant response
- Severity of illness
- CMHT influence

Practice variations

- Culture – targets acheived
- Colleagues - consensus
- Service users
- CMHT influence

Chart 5b. Previous findings – regression and review of long-term ADMs

After analysis of 9 interviews 6/4/15

Size of dose

- Patient expectation
- Patient's culture/ethnicity
- GP expectation
- Psychiatry influence (CMHT)
- Knowledge gap – dose response curves – Poor 'fit'
- Panacea – 'push in hope'
- Crisis management – 'push the dose'
- Severity of illness

Demographics

- Patients
- GPs

Same SSRI for ≥2 years bigger

- Crisis management, 'push in hope' 'Step effect;' with multiple crisis/life events
- Review appropriateness – do the right thing
- Patient expectations
- Severity of illness
- Chronicity of illness
- CMHT influence
- Fear/worry – stepping down, withdrawal

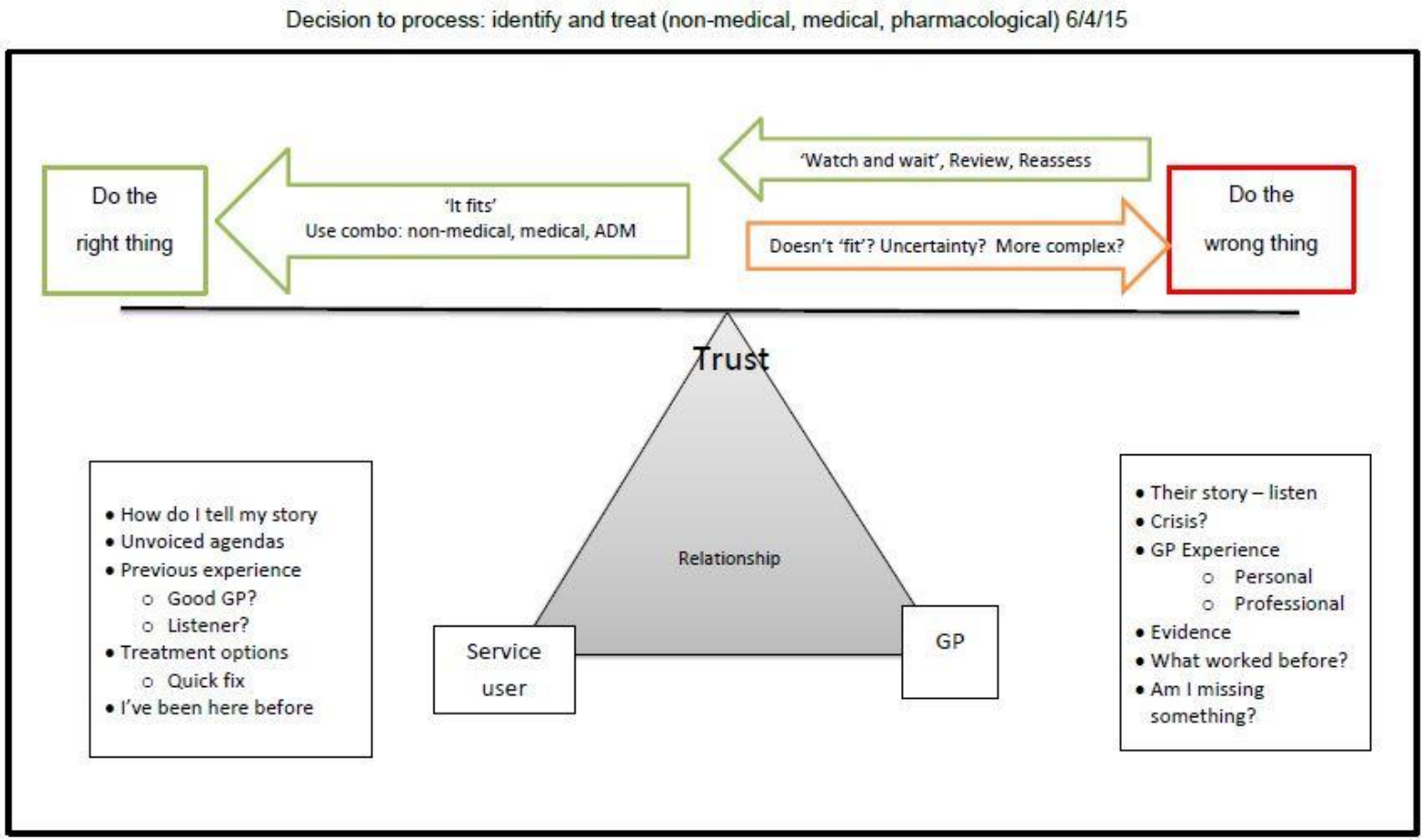
Benzos and z-hypnotics

- Drug seeking behaviours
- Negative effects on depression - Bad 'fit'
- Negative effects on antidepressant response- Bad 'fit'
- Severity of illness
- CMHT influence
- Avoid – do the right thing – best 'fit'

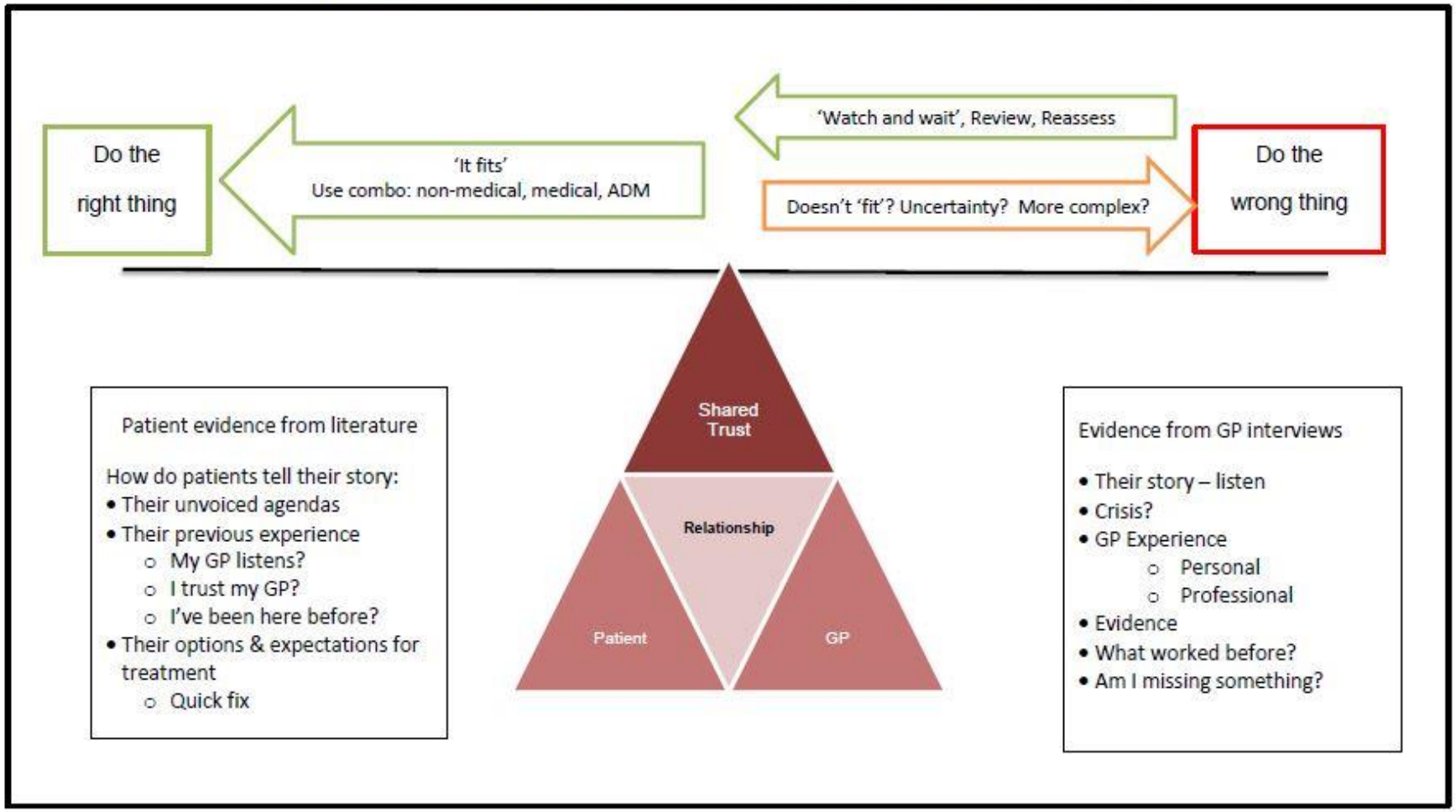
Practice variations

- Culture – targets achieved
- Colleagues - consensus
- Service users
- CMHT influence

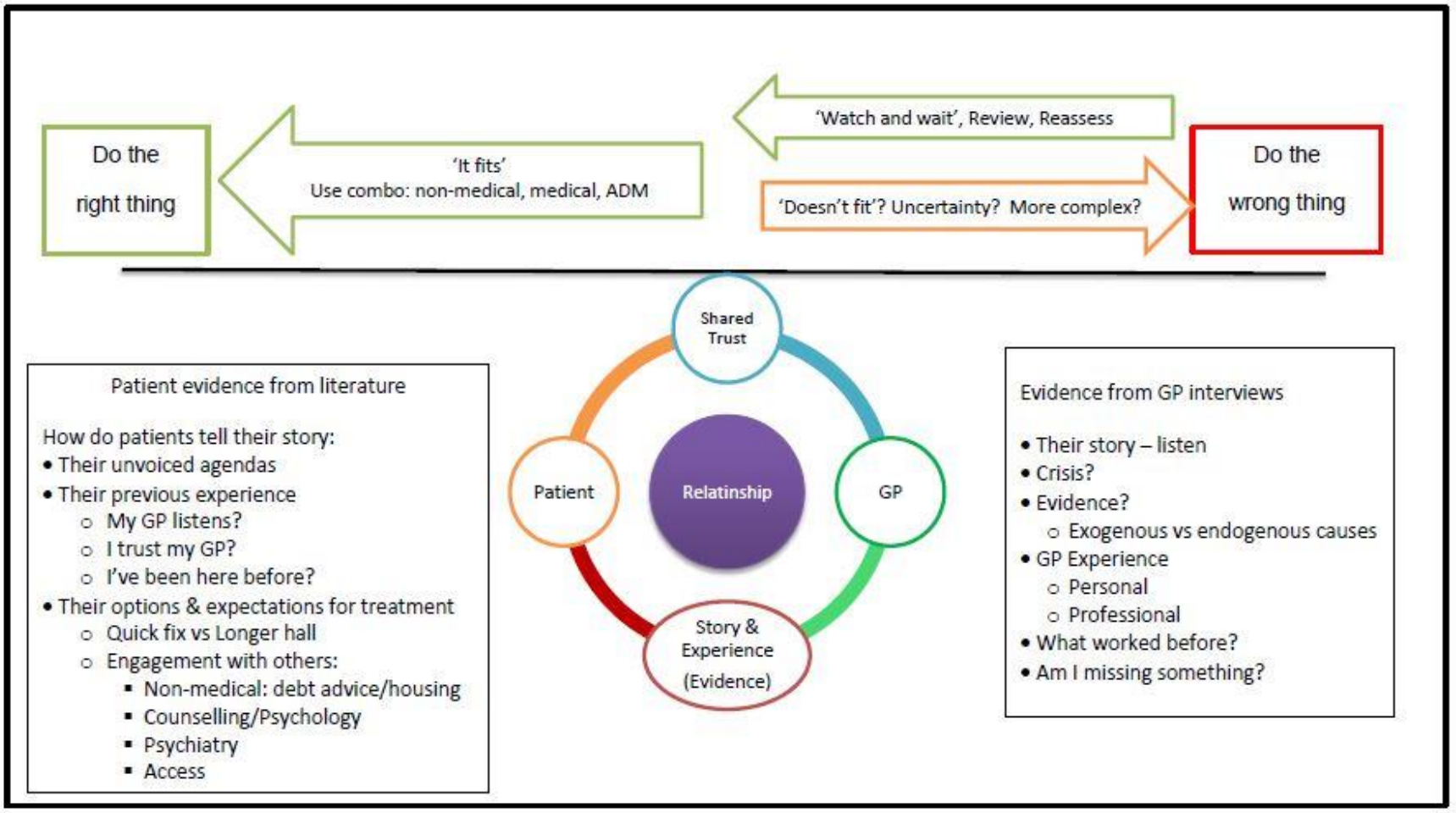
A2.3.5 Modelling – Balancing treatment and decision to prescribe



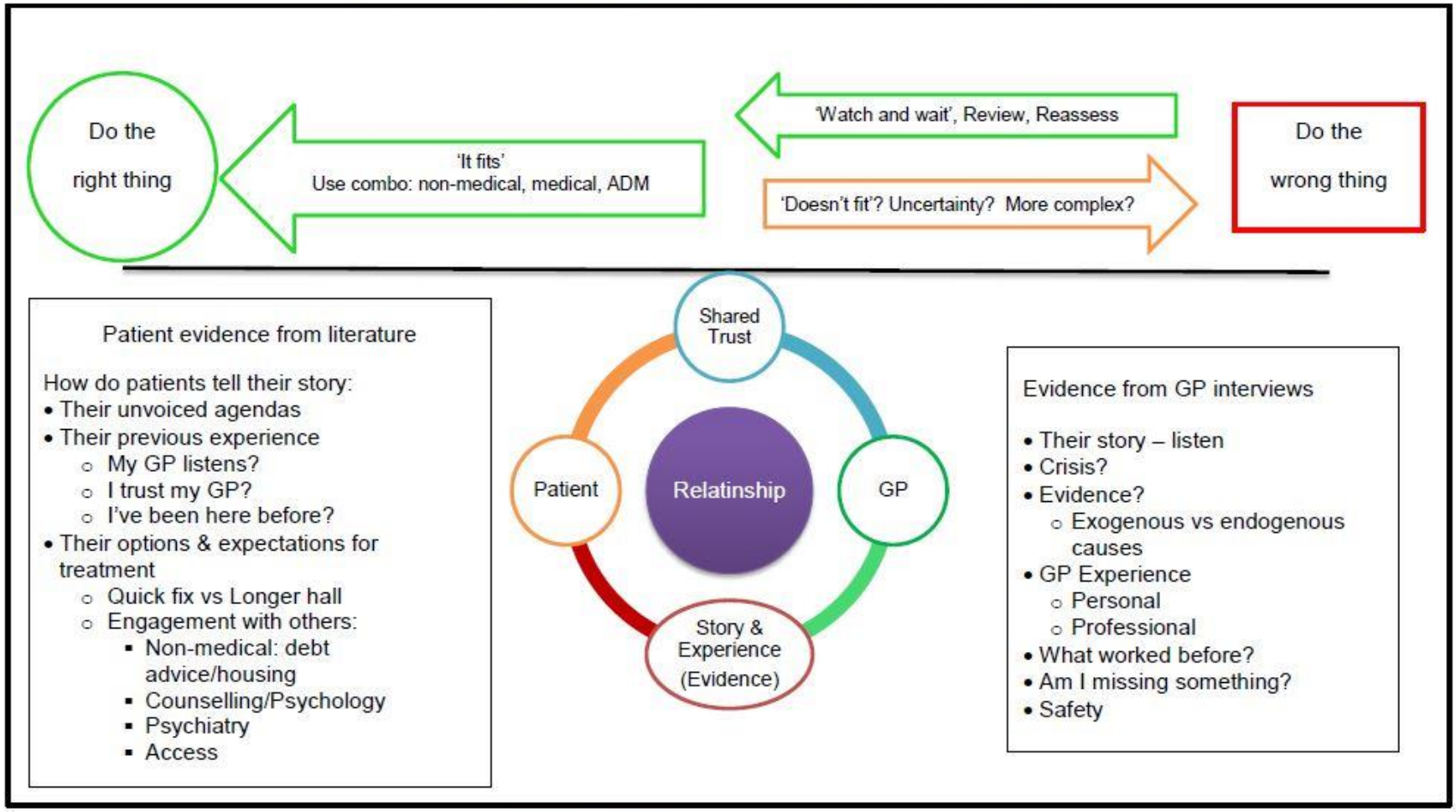
Decision to process: identify and treat (non-medical, medical, pharmacological) 4/5/15 Draft 2



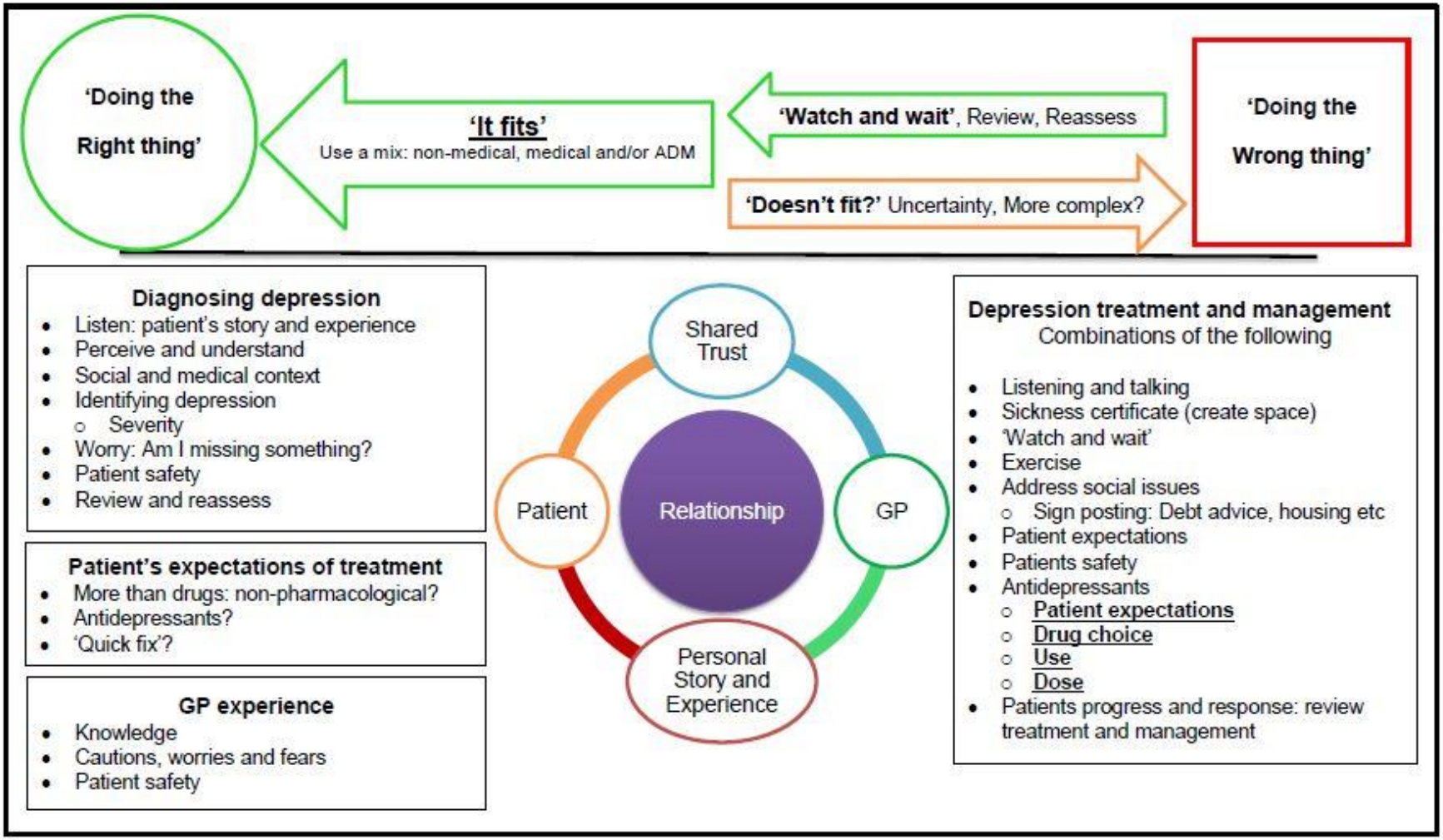
Decision to process: identify and treat (non-medical, medical, pharmacological) 28/8/15 – Draft 3



Decision to process: identify and treat (non-medical, medical, pharmacological) 27/9/16 – Draft 4

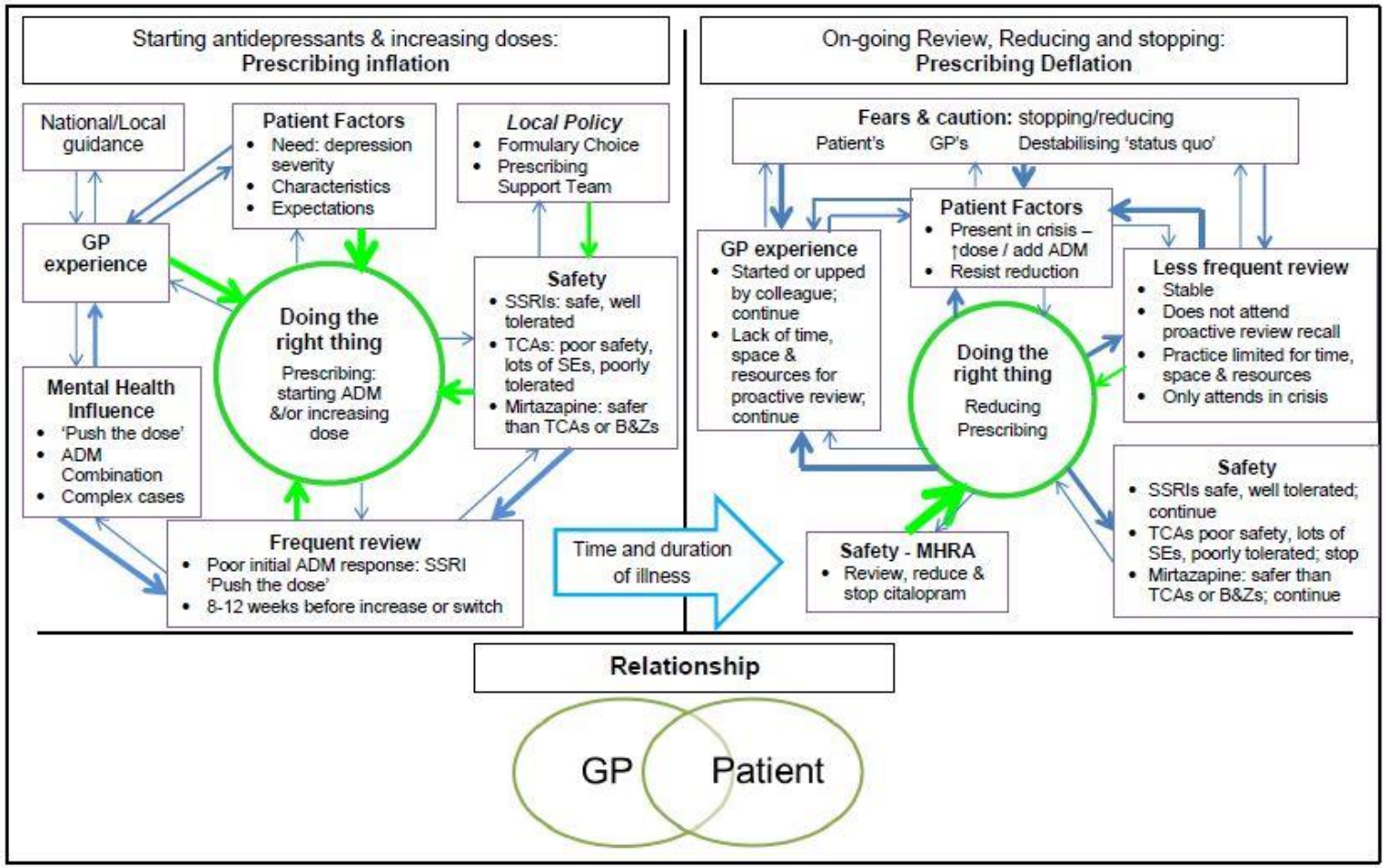


Balancing treatment options: non-medicalised, medicalised and/or pharmacological Draft 5 280916

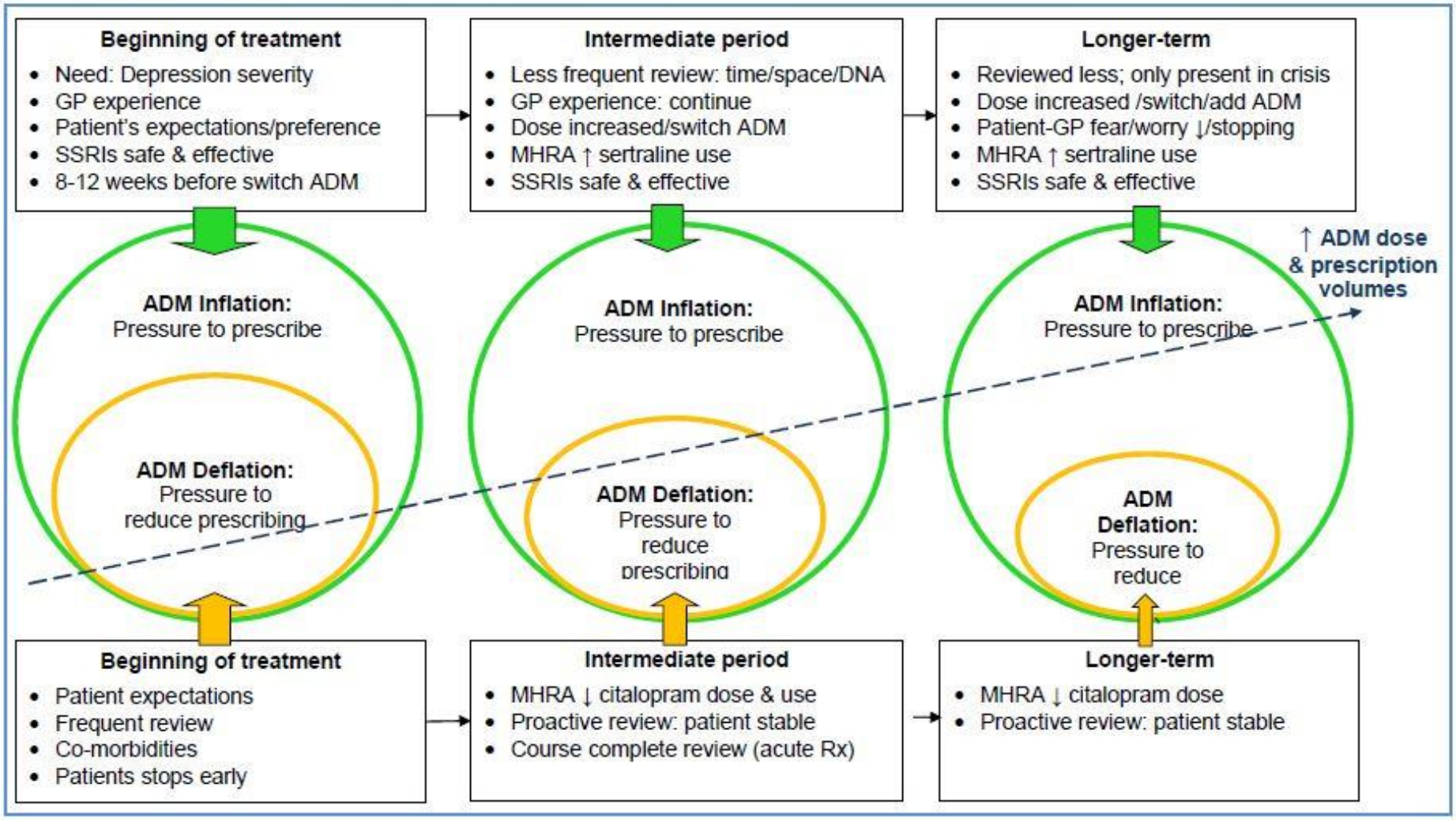


A2.3.6 Modelling – Factors influencing antidepressant growth

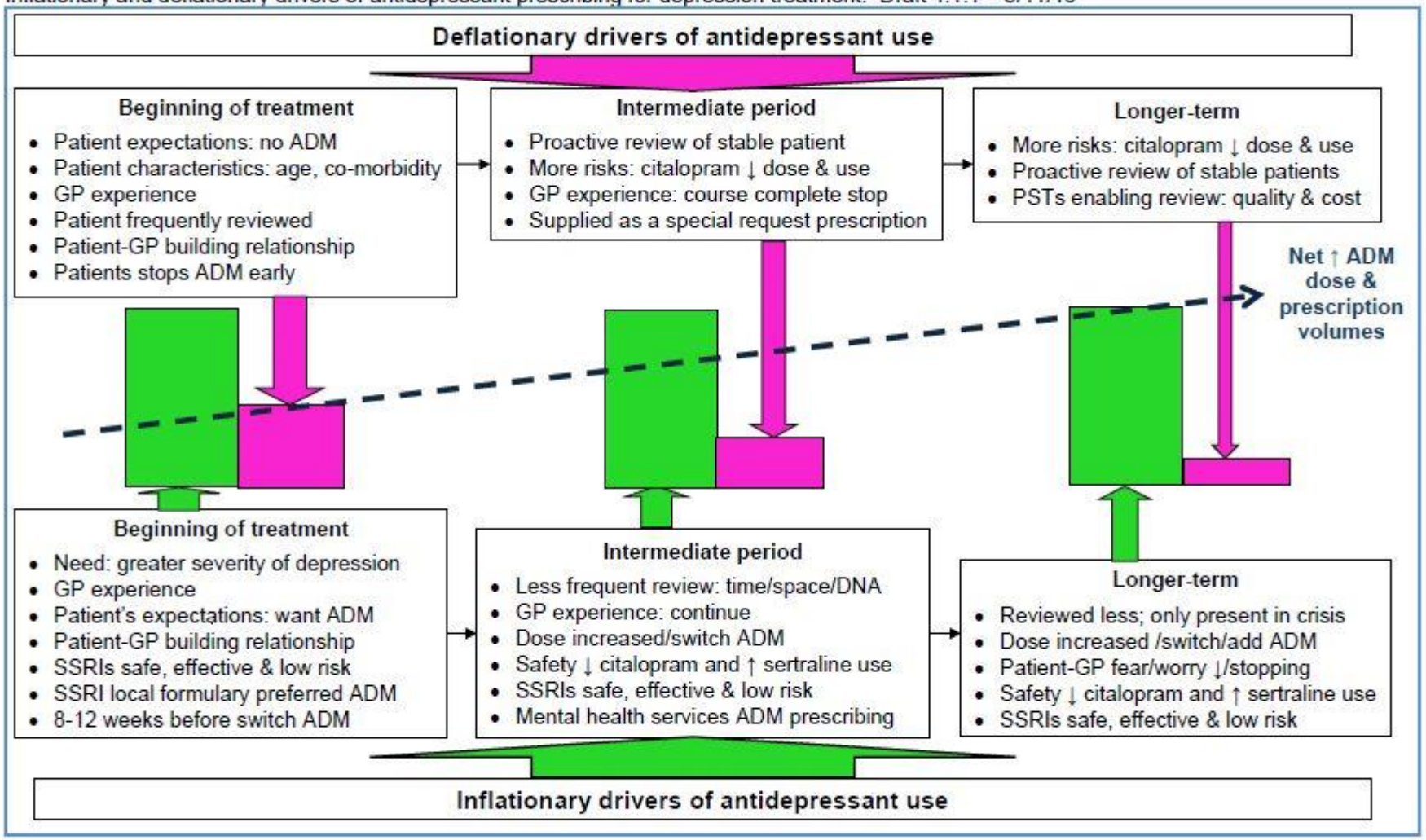
Antidepressant inflation Draft 1 – 27/9/15



Drivers of antidepressant growth – Draft 3 – 11/10/16

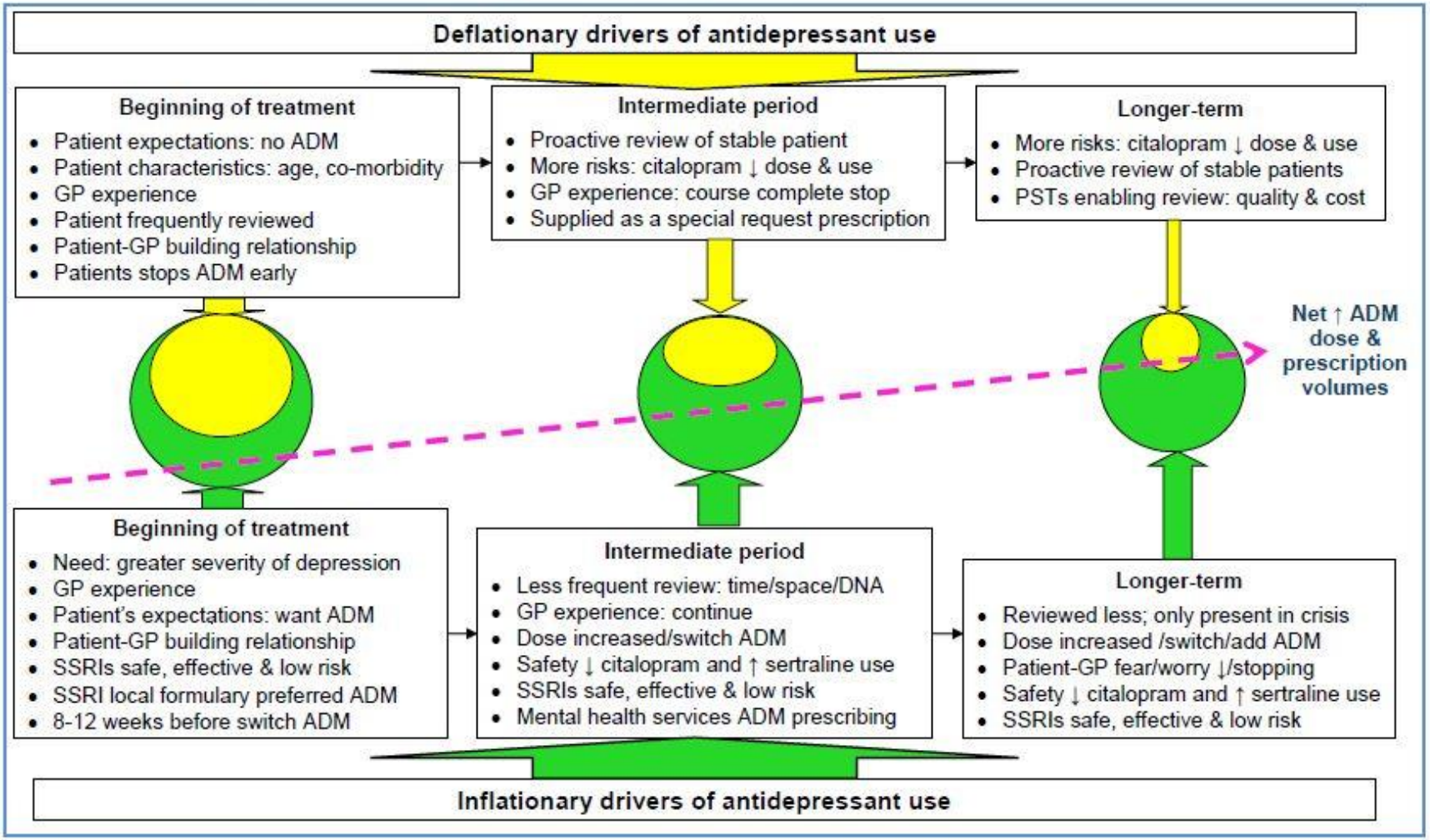


Inflationary and deflationary drivers of antidepressant prescribing for depression treatment. Draft 4.1.1 – 3/11/16



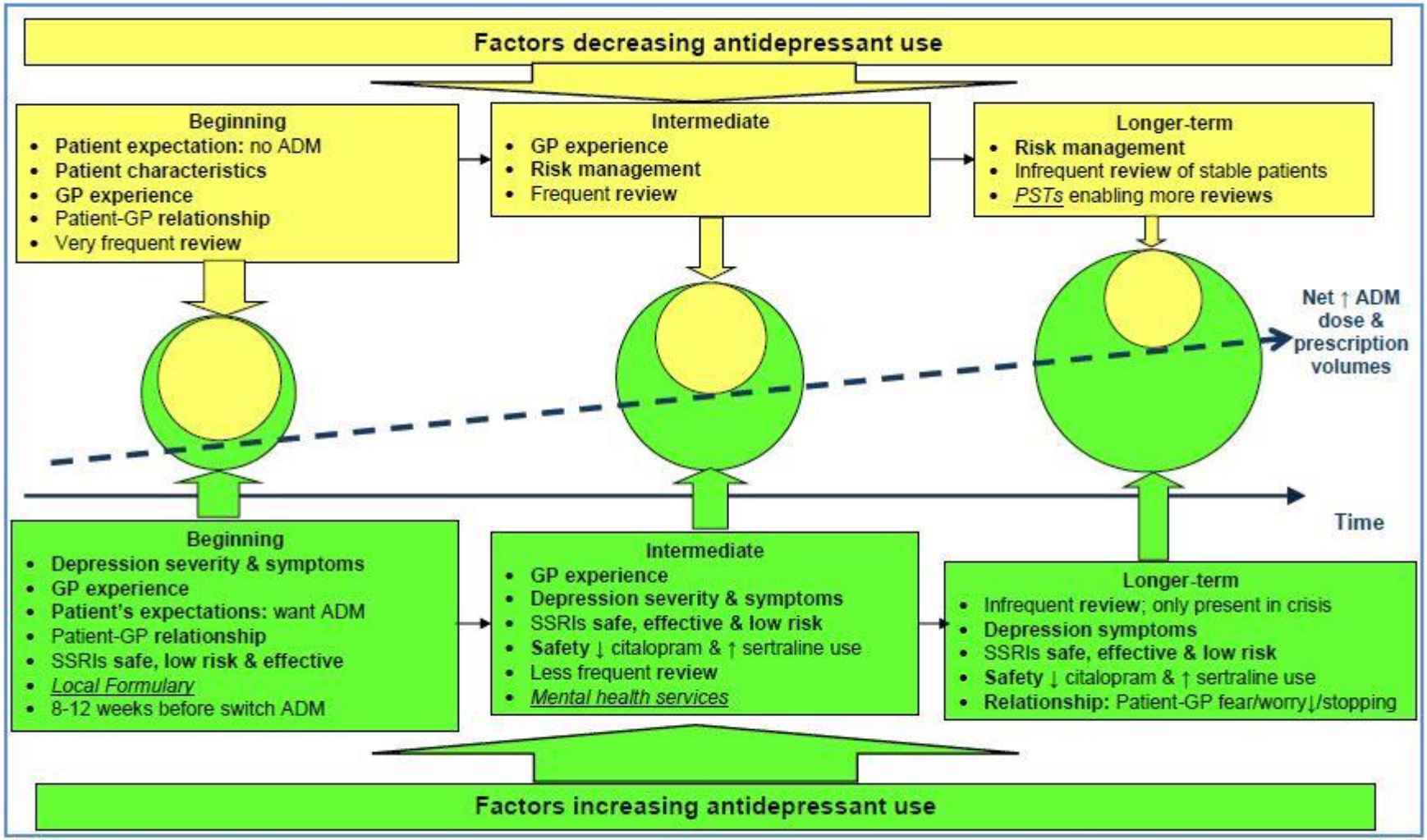
ADM: antidepressant DNA: do not attend SSRI: selective serotonin re-uptake inhibitor

Inflationary and deflationary drivers of antidepressant prescribing for depression treatment. Draft 4.2.1 – 3/11/16



ADM: antidepressant. DNA: do not attend. SSRI: selective serotonin re-uptake inhibitor

Factors increasing and decreasing antidepressant prescribing for depression treatment. Draft 4.2.5 – 30/1/17



Note: Factors strongly influencing antidepressant prescribing bold and moderately influential factors in italics and underlined.
ADM: antidepressant. DNA: do not attend. SSRI: selective serotonin re-uptake inhibitor

A2.4 Ethics approval, process and supporting study documentation

SMcC/SG

22 May 2014

UNIVERSITY OF STIRLING

SCHOOL OF NURSING, MIDWIFERY AND HEALTH

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Dear Chris

Exploration of factors influencing antidepressant prescribing and prescribed dose

Thank you for your SREC application, which was considered at the meeting on 09 January 2014 and responding to queries and clarifications.

I can now confirm the study has now been approved

May I take this opportunity to remind you that a site-file of *all* documents related to the research should be maintained throughout the life of the project, and kept up to date at all times. The site file template can be found on the SREC page of the School's website. Please bear in mind that your study could be audited for adherence to research governance and research ethics protocols.

Yours sincerely

Sandy McComish
(Deputy Chair)
School of Nursing, Midwifery and Health Research Ethics Committee

Highland Campus:
Centre for Health Science
Old Perth Road
Inverness IV2 3JH

Tel: +44 (0) 1463 255555
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MacAulay Road
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A2.4.1 Research ethics application form

School Research Ethics Committee

UNIVERSITY OF STIRLING

SCHOOL OF NURSING, MIDWIFERY AND HEALTH

Application Form for projects NOT requiring NHS approval

This form must be submitted as part of your application.

NAME	Chris Johnson
DESIGNATION	Specialist Antidepressant Pharmacist
INSTITUTION	NHS Greater Glasgow and Clyde
ADDRESS	Pharmacy & Prescribing Support Unit Queens Park House Langside Road, Glasgow, G42 9TT
EMAIL ADDRESS	c.johnson2@nhs.net
TELEPHONE NUMBER	07792537655
STUDENT NO. *(where relevant)*	1929079
SUPERVISOR	Prof Brian Williams
FUNDING BODY *(where relevant)*	NHS Greater Glasgow and Clyde, as part of Chris Johnson routine general practice work and PhD by publication.
PROJECT TITLE	Exploration of factors influencing antidepressant prescribing and prescribed dose
PROJECT PROPOSED START DATE	3/2/14
PROJECT PROPOSED COMPLETION DATE	3/2/15
APPLICANT'S SIGNATURE	
SUPERVISOR'S SIGNATURE (where relevant)	
ADDITIONAL COMMENTS FROM SUPERVISOR INCLUDED	☐
DATE	*18/12/13*

UNIVERSITY OF STIRLING

SCHOOL OF NURSING, MIDWIFERY AND HEALTH

School Research Ethics Committee

Application Checklist Form

This form must be submitted as part of your application.

1 copy of the SREC application form and an electronic version with all supporting documentation are required.

Applications will only be processed on receipt of the appropriate documents.

Please mark	
√	This form: The completed SREC application form
√	Participant information sheet v3
√	Written consent forms v2
√	Interview schedules v6
√	Research tracking form
√	Others (please specify) • Pdf of IRAS proposal • Cover letter v2 • Proposal v5 • Participant study invitation letter v2 • University of Stirling sponsorship letter • Flow chart study outline v3

Please also ensure that patient information sheets, letters and other documents are on headed paper and have version numbers and version dates recorded on them.

Please return this checklist together with your application form to the address below:

John Paley
c/o Sarahjane Gilvear
R.G Bonnott Building
School of Nursing, Midwifery & Health
University of Stirling
STIRLING FK9 4LA

Telephone: 01786 466404
Email: nm.research@stir.ac.uk

A2.4.2 Proposal for qualitative study

UNIVERSITY OF STIRLING

NHS Greater Glasgow and Clyde

NHS SCOTLAND

Proposal for Antidepressant Study

Title: Exploration of factors influencing antidepressant prescribing and prescribed dose: a qualitative study

Background: Antidepressant prescribing continues to rise. Contributing factors are use of higher doses, increased use of long-term antidepressants and the use of selective serotonin reuptake inhibitors (SSRIs).[1-3] Current evidence does not support the use of higher SSRI doses for the treatment of depression.[4,5] Many factors are known to influence prescribing behaviors and practice,[6-9] although factors influencing antidepressant doses are unknown.

NHSGGC committed to supporting appropriate use of antidepressants in response to the Scottish Governments Health improvement, Efficiency, Governance, Access to services and Treatment (HEAT) targets to reduce prescribing and put in place the required support framework to achieve a 10% reduction in future years. This study supports NHSGGC commitment, and further develops an understanding of prescribing informing the further development of the boards' framework to supporting appropriate antidepressant use.

Research question: What influences prescribers' use of specific antidepressant and doses?

Secondary questions:
What is the influence of prescribing indicators on prescribing behaviour?
What effect has the FDA and MHRA warnings about citalopram and escitalopram safety altered prescribing practice?
Has the new local NHSGGC depression guideline influenced prescribing behaviour?

Aim: To identify prescriber orientated issues which influence antidepressant choice and prescribed dose

Design: Qualitative interview study.

Method: 15-30minute one to one semi-structured interviews with prescribers. A framework approach will guide analysis.

Sample: Purposive sample of GPs including high, medium, low prescribers, multiple and single handed practitioners, serving communities in areas of high, medium and low deprivation. Sample size approximately 30.

Risks, burdens and benefits: The main risk identified is that the interview process may identify poor or substandard practice, although it is expected that this risk is low. Where poor or substandard practice is identified information will be provided to update practice in line with current guidelines (NICE, SIGN, BAP and NHSGGC).

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NHS Greater Glasgow and Clyde

NHS SCOTLAND

Estimated time to complete over a 12 month period:

Activity	Time (days)	Total time (hours)
Study preparation: proposal, IRAS, paper work	10	75
Invite to participate and follow up	2	15
Interviews	2	15
Transcript review and analysis	10	75
Summarize and report	3	22.5
Article for publication, review and amendments	5	37.5
Contingency for delays – cancelled interviews etc	2	15
Total time	**34**	**255**

Aim fully complete by October 2014. Time commitment 0.2 FTE for 4 months, with 0.4 FTE for 2 months.

Funding

This study will be undertaken as part of Chris Johnson, Antidepressant Specialist Pharmacist, work plan and is therefore funded as part of NHSGGC service delivery and development. Part of Chris Johnsons' continuing professional development: PhD by publication, with the Nursing Midwifery and Allied Health Professional Research Unit, University of Stirling, enables the support of experienced qualitative researchers which is funded by educational bursary prize money, from Chris Johnson presenting at the NHS Scotland Event June 2012.

Who will be involved

Chris Johnson Antidepressant Specialist Pharmacist NHSGGC
Prof Brian Williams, Director, Nursing, Midwifery and Allied Health Professionals Research Unit, University of Stirling
Nadine Dougall, Lecturer, Nursing, Midwifery and Allied Health Professionals Research Unit, University of Stirling
Dr Stephen MacGillivary, Senior Lecturer, Social Dimensions of Health Institute, University of Dundee.
Supported by prescribing support teams where appropriate: administrative support as independent point of reference.

What the results will be used for

To inform future development of NHSGGC antidepressant prescribing indicators and prescribing strategy supporting appropriate use of antidepressants.
Results will be disseminated within NHSGGC (specifically Prescribing Management Group – Primary Care and Mental Health, Mental Health Interface Group, and Mental Health Area Drug and Therapeutics Committee), out with NHSGGC at National NHS conferences and Mental Health Conferences where appropriate.
Results will be published in an appropriate peer review journal.
Submitted as part of PhD by publication for Chris Johnson at University of Stirling

References
1. Johnson CF, Macdonald HJ, Atkinson P, et al. Reviewing long-term antidepressants can reduce drug burden: a prospective observational cohort study. Br J Gen Pract 2012; DOI: 10.3399/bjgp12X658304
2. Middleton N, Gunnell D, Whitley E, et al. Secular trends in antidepressant prescribing in the UK, 1975–1998. J Public Health Med 2001; 23(4): 262–267.
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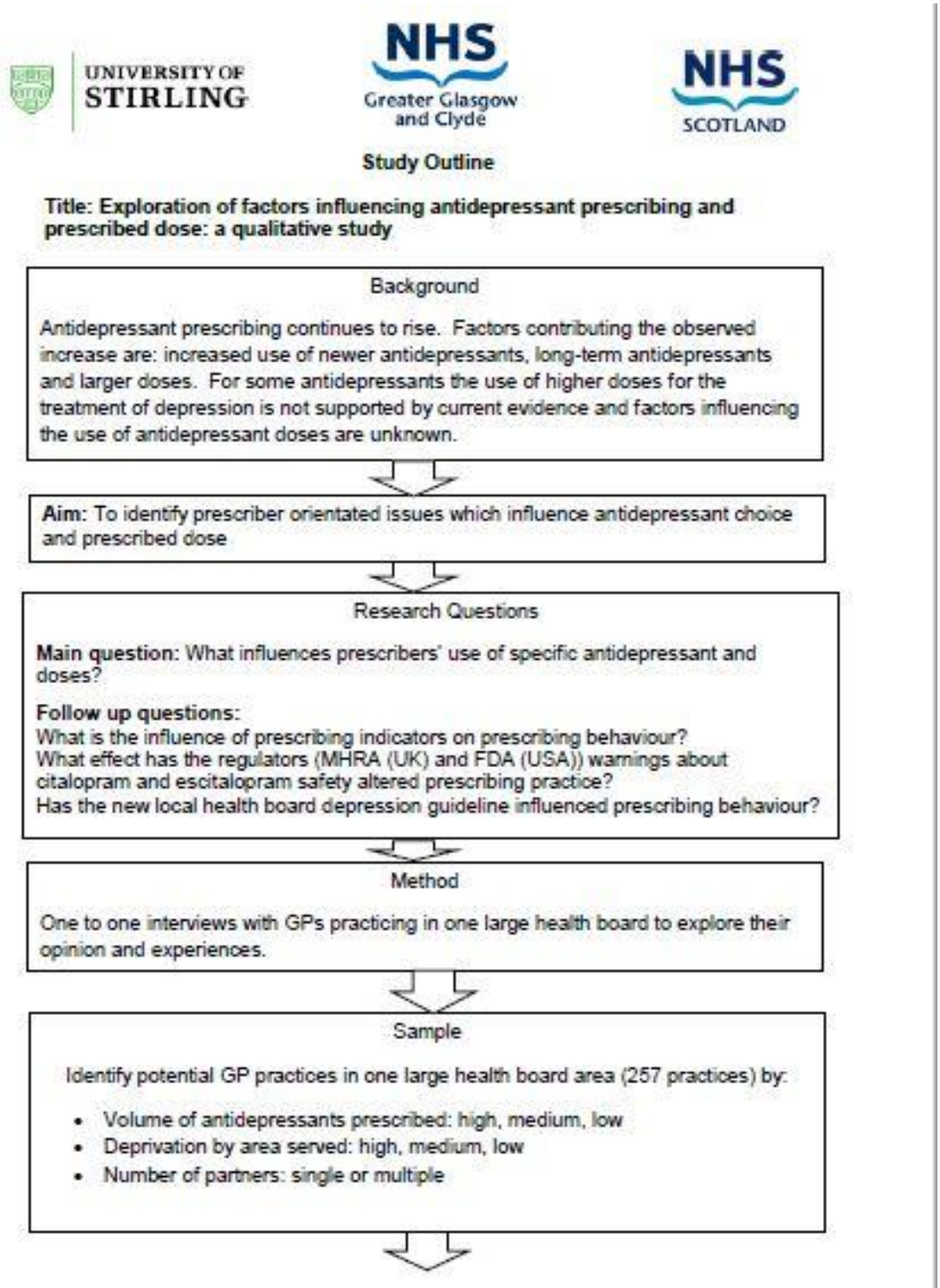
4. Adli M, Baethge C, Heinz A, et al. Is dose escalation of antidepressants a rational strategy after a medium-dose treatment has failed? A systematic review. Eur Arch Psychiatry Clin Neurosci 2005; 255(6): 387–400.
5. Corruble E, Guelfi JD. Does increasing dose improve efficacy in patients with poor antidepressant response: a review. Acta Psychiatr Scand 2000; 101(5): 343–348.
6. Aronson JK, Henderson G, Webb DJ, et al. A prescription for better prescribing. BMJ 2006;333:459–460.
7. Busfield J. 'A pill for every ill': Explaining the expansion in medicine use. Social Science & Medicine 2010; 70: 934–941.
8. Little P, Dorward M, Warner K, et al. Importance of patient pressure and perceived pressure and perceived medical need for investigations, referral, and prescribing in primary care: nested observational study. BMJ 2004; 328: 444-447.
9. Parker M. False dichotomies: EBM, clinical freedom, and the art of medicine. Med Humanities 2005; 31: 23-30.
10. The Scottish Government. Depression Workstream Overview. http://www.scotland.gov.uk/Publications/2010/01/18120533/3 (accessed 31 Dec 2012).

Proposal
Version 5
25th Oct 2013

A2.4.3 Study outline flow chart



Consent:
Contact practitioners in practices with desired characteristics as above:

- Contact 60 practices, of 257 board practices, initially by invitation letter containing: introductory letter, participant information sheet and consent form.
- Follow up invite letter with phone call if no response

Where appropriate agree time for interview and consent:

- At mutually agreed time within GPs practice
- Seek written consent.
- Audio recording of interview
- Researcher notes: record key issues/reflection on interview

Start analysis:

- Audio recording to transcript.
- Review transcript for accuracy.
- Analyse transcript (Framework analysis supported by computer programme NVivo)
- On-going until 30 GP interviews analysed

Sharing of results:

- Written report to participants
- Written report to health board prescribing teams and NHS Scotland Health Care Improvement Scotland
- Present at NHS and non-NHS mental health conferences where appropriate
- Submit for publication to suitable peer review journal
- Submit as part of PhD by publication degree

Study outline
Version 3
2nd January 2013

A2.4.4 School Research Ethics Committee tracking form

Tracking Projects

UNIVERSITY OF STIRLING

SCHOOL OF NURSING, MIDWIFERY AND HEALTH

Project Title	Exploration of factors influencing antidepressant prescribing and prescribed dose
Project Number/Cost Centre	
Project Description	Qualitative study
Principal Investigator	Chris Johnson
Principal's Department and University	NMAHP University of Stirling

Will Ethical Review be Sought?	Yes √	No ☐
Reasons if No		
Authorised by		

All Staff Employed in Project					
Other Investigators (University of Stirling)		Prof Brian Williams, NMAHP Research Unit. Nadine Dougall, NMAHP Research Unit.			
Other Investigators (External)		Dr Stephen McGillvary, Social Dimensions of Health Institute, University of Dundee.			
Financial Year Funds Awarded		**Start Date**	3/2/14	**End Date**	3/2/15

Funding Body (In Full)	NHS Greater Glasgow and Clyde, as part of Chris Johnson routine general practice work and PhD by publication.		
Total Amount Requested	£ None	**Total Amount Awarded**	£ None
Eligible for inclusion in RAE?			

Extension Date		**Additional Funds**	£

Programme	PhD by publication
Links to Other Programmes	
Research Group or Centre (if applicable)	

Contact Person (Research Assistant)	Chris Johnson. c.johnson2@nhs.net
Key Words	

	submitted	accepted	unacceptable	Date
Interim Report	❑	❑	❑	
Final Report	❑			

A2.4.5 Conditions for study approval addressed

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NHS Greater Glasgow and Clyde

NHS SCOTLAND

To:
John Paley,

Research Ethics Committee
School of Nursing Midwifery and Health
University of Stirling,
Stirling, FK 9 4LA

From:
Chris Johnson
Antidepressant Specialist Pharmacist
NHS Greater Glasgow and Clyde

Central Prescribing Team
Pharmacy & Prescribing Support Unit
Queens Park House, Victoria Infirmary
Langside Road,
Glasgow, G42 9TT

email: c.johnson2@nhs.net
Fax: 0141 201 5217
Tel: 07792537655

Date 31/3/14

Dear John,

Exploration of factors influencing antidepressant prescribing and prescribed dose

Thank you for your response to our SREC application, 9/1/14. Regarding the two conditions subject to approval:

- University regulations not permitting PhD students to supervise, therefore references to Nadine Dougall will be changed to Steve McGillivary PhD, (Senior Lecturer - Evidence Synthesis, Social Dimensions of Health Institute, University of Dundee) who is current one of my other supervisors.
- Potential conflict of interest: Where substandard practice is identified this will be brought to the attention of the Clinical Director of the CHCP that the practice and practitioner is based in. The CHCP Clinical Directors are autonomous practitioners (usually GPs) with governance responsibilities independent of NHSGGC Central Prescribing Team.

Advisory amendments will made as advised.

Dr Ashley Shepherd was advised as an independent person for participants/prospective participants to refer to if needed. I would be happy to have a University representative as a reference source. What do I need to do for Dr Shepherd to provide independent support for this study?

Thank you for your advice and help.

You sincerely

Chris Johnson
Antidepressant Specialist Pharmacist

A2.4.6 Amendment to study paperwork

I considered that study cover letter version 2 may influence participants due to the following sentence, which was removed in version 3:

'The use of higher SSRI doses for the depression is not supported by current literature and is contributing to the increase in prescribing.'

UNIVERSITY OF STIRLING

NHS Greater Glasgow and Clyde

NHS SCOTLAND

c/o Allen O'Neill
Central Prescribing Team
Pharmacy & Prescribing Support Unit
Queens Park House, Victoria Infirmary
Langside Road,
Glasgow, G42 9TT

email: c.johnson2@nhs.net
Fax: 0141 201 5217
Tel: 07792537655

Date *[insert date]*

Dear Colleague,

Research Study: Exploration of factors influencing antidepressant prescribing and prescribed dose: a qualitative study.

This study will inform future development of NHSGGC antidepressant prescribing indicators and prescribing strategy supporting appropriate use of antidepressants, in line with the Scottish Governments request that all Scottish health boards continue to develop frameworks supporting appropriate antidepressant prescribing following the end of the antidepressant HEAT target in 2010.

The majority of antidepressants prescribed in Scotland are for the treatment of depression. NHSGGC HEAT target work identified that prescribers are prescribing larger antidepressant doses for depression with the majority of these medicines being selective serotonin re-uptake inhibitors (SSRIs) which are prescribed at up to 30% higher doses than previously reported. Factors influencing the use of higher antidepressant doses are unknown. Quantitative methods are limited in providing clarity to this issue. The use of qualitative methods will enable a better subjective understanding of practitioners' rationales for prescribing larger doses of SSRIs and other antidepressants.

Yours sincerely

Chris Johnson
Antidepressant Specialist Pharmacist, NHSGGC

Study cover letter
Version 3
19th Sept 2014

PH/SG

UNIVERSITY of STIRLING

24 September 2014

Web: http://www.stir.ac.uk/nmhealth/research/ethics/

Professor Pat Hoddinott
Chair
School Research Ethics Committee

School of Health Sciences
University of Stirling
Stirling FK9 4LA

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Email: shs.ethics@stir.ac.uk

Chris Johnson
Specialist Antidepressant Pharmacist
Pharmacy & Prescribing Support Unit
Queen Park House
Langside Road
Glasgow
G42 9TT

Dear Chris

Exploration of factors influencing antidepressant prescribing and prescribed dose

SREC 14/15 – Paper No 1 – Version 1

I am pleased to inform you that I have approved by Chair's Action the amendment to the participant information sheet and cover letter.

May I remind you of the need to inform SREC prior to making any amendments to this protocol, of any changes to the duration of the project and provide notification of study completion. A site-file of *all* documents related to the research should be maintained throughout the life of the project, and kept up to date at all times. The site file template can be found on the SREC page of the School's website. Please bear in mind that your study could be audited for adherence to research governance and research ethics.

Ref: SREC 14/15 – Paper No 1 – Version 2
Please quote this number on all correspondence

Yours sincerely

PROF. PAT HODDINOTT
(Chair)
School of Health Sciences Research Ethics Committee

A2.5 Sponsorship and indemnity

UNIVERSITY OF STIRLING

STIRLING FK9 4LA SCOTLAND

Carol Johnstone
Research Development Manager
RESEARCH & ENTERPRISE OFFICE
Tel: (01786) 466690
Fax: (01786) 466688
E-mail: carol.johnstone@stir.ac.uk

14 August 2014

To Whom It May Concern:

Research Study: Exploring factors influencing antidepressant prescribing and prescribed dose: a qualitative study

This study is included in the following cover put in place by Aon Ltd. These policies are renewed annually and the current period of insurance is 1 August 2014 – 31 July 2015.

I confirm that the following cover is in place:

Professional Indemnity policy provides indemnity for legal liability to third parties arising from breach of professional duty, neglect, error or omission in the course of the business of the University of Stirling. The limit of the Professional Indemnity cover is £5,000,000 for any one event/aggregate any one period of insurance.

Combined Liability Insurance: Employers Liability cover is provided for legal liability to employers for death, injury, illness and disease arising out of the business of the University of Stirling. Public/Products Liability is provided for legal liability for accidental loss of or damage to Third Party property or for death, injury, illness or disease arising out of the business of The University of Stirling including liability arising from goods sold or supplied. Indemnity Limit for each is £10,000,000.

Combined Excess Liability Insurance: Employers Liability & Public/Products Liability cover limit is £10,000,000 in excess of £10,000,000 with a total limit of indemnity in respect of Employers Liability and Public Liability of £20,000,000.

I trust that this is sufficient for your requirements. Please do not hesitate to get in touch with me should you have any further queries.

Yours sincerely

Carol Johnstone
Research Development Manager

A2.6 Standards for Reporting Qualitative Research

Standards for Reporting Qualitative Research (SRQR)[a]

No.	Topic	Item	Reported in section
	Title and abstract		
S1	Title	Concise description of the nature and topic of the study Identifying the study as qualitative or indicating the approach (e.g., ethnography, grounded theory) or data collection methods (e.g., interview, focus group) is recommended.	Chapter 6. title
S2	Abstract	Summary of key elements of the study using the abstract format of the intended publication; typically includes background, purpose, methods, results, and conclusions.	Not appropriate – Thesis abstract summarises 3 research studies. Limited word count does not allow.
	Introduction		
S3	Problem formulation	Description and significance of the problem/phenomenon studied; review of relevant theory and empirical work; problem statement.	1.1, 2.6, 2.7, 3.2, 3.3, 5.4 & 6.1
S4	Purpose or research question	Purpose of the study and specific objectives or questions.	6.1, 6.2
	Methods		
S5	Qualitative approach and research paradigm	Qualitative approach (e.g., ethnography, grounded theory, case study, phenomenology, narrative research) and guiding theory if appropriate; identifying the research paradigm (e.g., postpositivist, constructivist/interpretivist) is also recommended; rationale[b].	4.1, 6.3
S6	Researcher characteristics and reflexivity	Researchers' characteristics that may influence the research, including personal attributes, qualifications/experience, relationship with participants, assumptions, and/or presuppositions; potential or actual interaction between researchers' characteristics and the research questions, approach, methods, results, and/or transferability.	6.3.4 paragraph 1 to 4

S7	Context	Setting/site and salient contextual factors; rationale[b].	4.2, 6.2
S8	Sampling strategy	How and why research participants, documents, or events were selected; criteria for deciding when no further sampling was necessary (e.g., sampling saturation); rationale[b].	6.3.2
S9	Ethical issues pertaining to human subjects	Documentation of approval by an appropriate ethics review board and participant consent, or explanation for lack thereof; other confidentiality and data security issues.	6.3.6, A2.4
S10	Data collection methods	Types of data collected; details of data collection procedures including (as appropriate) start and stop dates of data collection and analysis, iterative process, triangulation of sources/methods, and modification of procedures in response to evolving study findings; rationale[b].	6.3.4
S11	Data collection instruments and technologies	Description of instruments (e.g., interview guides, questionnaires) and devices (e.g., audio recorders) used for data collection; if/how the instrument(s) changed over the course of the study.	6.3.4, 6.3.5 & A2.2
S12	Units of study	Number and relevant characteristics of participants, documents, or events included in the study; level of participation (could be reported in results).	6.3.3, Table 7 & Table 8
S13	Data processing	Methods for processing data prior to and during analysis, including transcription, data entry, data management and security, verification of data integrity, data coding, and anonymization/deidentification of excerpts.	6.3.4, 6.3.5 & A2.3
S14	Data analysis	Process by which inferences, themes, etc., were identified and developed, including the researchers involved in data analysis; usually references a specific paradigm or approach; rationale[b].	6.3.5 & A2.3
S15	Techniques to enhance trustworthiness	Techniques to enhance trustworthiness and credibility of data analysis (e.g., member checking, audit trail, triangulation); rationale[b].	6.3.5

	Results/findings		
S16	Synthesis and interpretation	Main findings (e.g., interpretations, inferences, and themes); might include development of a theory or model, or integration with prior research or theory.	6.4.1, Figure 14 & Figure 15
S17	Links to empirical data	Evidence (e.g., quotes, field notes, text excerpts, photographs) to substantiate analytic findings.	6.4
	Discussion		
S18	Integration with prior work, implications, transferability, and contribution(s) to the field	Short summary of main findings; explanation of how findings and conclusions connect to, support, elaborate on, or challenge conclusions of earlier scholarship; discussion of scope of application/generalizability; identification of unique contribution(s) to scholarship in a discipline or field.	6.5, 6.7, 8.2 & 8.3
S19	Limitations	Trustworthiness and limitations of findings.	6.6
	Other		
S20	Conflicts of interest	Potential sources of influence or perceived influence on study conduct and conclusions; how these were managed.	4.3.1, 6.3.4
S21	Funding	Sources of funding and other support; role of funders in data collection, interpretation, and reporting.	Acknowledgements & 8.6

a. The authors created the SRQR by searching the literature to identify guidelines, reporting standards, and critical appraisal criteria for qualitative research; reviewing the reference lists of retrieved sources; and contacting experts to gain feedback. The SRQR aims to improve the transparency of all aspects of qualitative research by providing clear standards for reporting qualitative research.

b. The rationale should briefly discuss the justification for choosing that theory, approach, method, or technique rather than other options available, the assumptions and limitations implicit in those choices, and how those choices influence study conclusions and transferability. As appropriate, the rationale for several items might be discussed together.

Appendix 3 - Systematic review and narrative synthesis

A3.1 Protocol: Systematic review of reviews

Background

Antidepressant prescribing continues to grow (1,2). In part this is due to the use and availability of SSRIs (3), increased long-term prescribing (4), and the use of higher doses (5-7). In Scotland, SSRI accounted for 51% of antidepressant prescriptions and 66% of defined daily doses dispensed in 2014/15 (2). There is ambiguity in guidelines regarding SSRI dose related efficacy (8,9)

Review question

Is there a dose-response relationship for SSRI in the treatment of depression?

Aim

To review previous published reviews to assess and clarify the relationship between SSRI dose efficacy, acceptability (early treatment discontinuation – drop outs) and tolerability (reported ADEs), and critically evaluate the methods previously used to examine SSRI dose-response effects for the treatment of depression in adults.

Method

Search strategy, and criteria of eligibility and inclusion

Recommendations from the Cochrane Handbook for Systematic Reviews of Interventions informed the design of this systematic review (10). The predefined inclusion criteria for this systematic review and synthesis are presented according to PICOS (Population, Intervention, Comparator, Outcomes, Study design) criteria, Table 1.

Article titles and abstracts will be screened for inclusion. Subsequently, potentially relevant full-text articles from the literature search will then be screened for inclusion, using a structured process and standard terms supporting inclusion and exclusion. Studies that do not meet the criteria outlined above were excluded.

Reviews were excluded that involved children and adolescents aged <18 years with depression, as this cohort demonstrate variable antidepressant response rates possibly due to differences in neural development (11), and are not routinely treated in primary care by general practitioners. Reviews including older people with dementia were excluded as antidepressants are known to be of questionable benefit for depressive symptoms in this cohort (12). Additional exclusions included: depression during pregnancy, perinatal or postnatal; bipolar; concomitant psychiatric disorders, people who use drugs, concomitant opioid replacement therapy and/or co-morbidity.

Table 1 PICOS inclusion criteria	
Population	• Adult human ≥18 years old • Major depressive disorder
Intervention	• Monotherapy • Selective serotonin re-uptake inhibitors (SSRI): escitalopram, citalopram, fluoxetine, fluvoxamine, paroxetine and sertraline
Comparison	• Placebo • SSRI
Outcome	• Antidepressant response • Efficacy: reduction in depression signs and symptoms • Acceptability: early treatment discontinuation • Tolerability: any reported adverse drug effects
Study design	• Dose-response • Review • Narrative review • Systematic review • Meta-analysis • Meta-regression • Network meta-analysis

Reviews assessing SSRI monotherapy for the treatment of depression for all licensed SSRIs were included: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline. The SSRI zimelidine was not included as it has been withdrawn from the market as Guillain-Barré syndrome was associated with its use (13). Antidepressants outwith the SSRI class with novel serotonin or mixed receptor effects were excluded: vortioxetine a direct modulator of serotonergic receptor activity and inhibitor serotonin re-uptake; vilazodone with mixed SSRI and buspirone-like activity; the SNRIs venlafaxine and duloxetine; and clomipramine a TCA (14-16).

Reviews examining concomitant combination treatments: using two or more antidepressants; psychotropic and non-psychotropic medicine augmentation strategies; antidepressant with psychotherapies; and switching antidepressant studies were excluded as these strategies can be more effective than monotherapy and may be reserved for treatment resistant depression (8, 17). As the majority of national guidelines (8, 9) and drug licenses recommend standard starting doses (14) which are routinely prescribed in practice (6, 18-

21) and represent standardised DDD as defined by the WHO (22). It was considered appropriate to assess baseline standardised comparator doses to assess effects against placebo and higher SSRI doses

Data sources
The following electronic databases will be searched: Embase, Medline, PsycINFO, Scopus and Cochrane Collaboration library. We will search for reviews by scrutinising and hand-searching reference lists of national and international depression treatment guidelines, and study reference lists.

As fluoxetine studies were first published in the mid 1970's and it is the SSRI that has been available on the market for the longest period (23); 1975 was used as the start date until the end of December 2020. Reviews were limited to English language

Data extraction
The following data will be extracted for each review article using a structured standardised data collection form specifically designed for this systematic review (Appendix 1). Review characteristics (e.g. lead author; type of review; protocol driven review; patient-level data or not; type of depression being treated; review setting primary or secondary care, etc.), antidepressant and comparator information (e.g. SSRI used; fixed or flexible dose study; placebo controlled; dose standardisation technique; treatment duration; etc.), and dose-response effects (e.g. efficacy, dropouts and ADEs).

Risk of bias assessment
Each review article was assessed according to the Risk of Bias in Systematic Reviews (ROBIS) tool (24), in line with Cochrane recommendations (10). Reviews were assessed using ROBIS by myself and checked by one of my supervisors. The ROBIS tool has been specifically developed and designed to assess reviews within health care settings: interventions, diagnosis, prognosis and etiology. The tools are completed in three phases: 1) assessment of relevance, 2) identify concerns with the review process and 3) judge risk of bias. Phase 2 covers four domains: study eligibility criteria; identification and selection of studies; data collection and study appraisal; and synthesis of findings. Phase 3 assesses overall risk of bias (low, high, unclear) from interpretation of review findings, and considers limitations identified in any of the phase 2 domains (24).

Data analysis, synthesis, and ethics
As different rating scales are used in primary studies (25) and a range of review techniques and meta-analytical approaches may have been used in reviews, the synthesis may require meta-synthesis rather than a meta-analysis (26, 27).

References

1. Chen Y, Kelton CML, Jing Y, et al. Utilization, price, and spending trends for antidepressants in the US Medicaid program. Research Soc Admin Pharm. 2008;4(3):244-57.
2. ISD Scotland. Medicines used in Mental Health, Years 2004/05 - 2014/15.
3. Middleton N, Gunnell D, Whitley E, et al. Secular trends in antidepressant prescribing in the UK, 1975-1998. J Public Health Med 2001;23(4):262-7.
4. Moore M, Yuen H, Dunn N, et al. Explaining the rise in antidepressant prescribing: A descriptive study using the general practice research database. BMJ. 2009;339(7727):956.
5. Johnson CF, Dougall NJ, Williams B, et al. Patient factors associated with SSRI dose for depression treatment in general practice: a primary care cross sectional study. BMC Family Practice. 2014;15:210.
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A3.2 Database search strategies

A3.2.1 Embase 1975 to Dec 2021

	Searches	Results
1	systematic review$.mp. or exp "systematic review"/	422957
2	meta analysis/	233016
3	dose-response.mp. or exp dose response/	459419
4	1 or 2 or 3	965431
5	antidepressants$.mp. or exp antidepressant agent/	522746
6	ssri.mp. or exp serotonin uptake inhibitor/	291876
7	exp serotonin uptake inhibitor/ or selective serotonin inhibitor$.mp.	291324
8	citalopram.mp. or exp citalopram/	24483
9	escitalopram.mp. or exp escitalopram/	13786
10	fluoxetine.mp. or exp fluoxetine/	50458
11	fluxetine.mp.	33
12	fluvoxamine.mp. or exp fluvoxamine maleate/ or exp fluvoxamine/	14665
13	paroxetine.mp. or exp paroxetine/	29256
14	sertraline.mp. or exp sertraline/	28225
15	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14	524221
16	4 and 15	41674
17	depression.mp. or exp depression/ or exp major depression/	789628
18	major depressive disorder.mp. or exp major depression/	79382
19	unipolar depression.mp.	4133
20	17 or 18 or 19	790950
21	16 and 20	12630
22	limit 21 to human	10975
23	limit 22 to english language	10408
24	limit 23 to yr="1975 - 2021"	10375

A3.2.2 Ovid Medline (R) All 1975 to 2021

	Searches	Results
1	systematic review$.mp.	257991
2	meta-analysis.mp. or exp Meta-Analysis/	232434
3	exp Dose-Response Relationship, Drug/ or dose response.mp.	527175
4	1 or 2 or 3	893529
5	Antidepressant$.mp. or exp Antidepressive Agents/	181670
6	exp Serotonin Uptake Inhibitors/ or ssri.mp.	46233
7	selective serotonin inhibitor$.mp.	31
8	citalopram.mp. or exp Citalopram/	7401
9	escitalopram.mp.	2836
10	fluoxetine.mp. or exp Fluoxetine/	14859
11	fluxetine.mp.	7
12	fluvoxamine.mp. or exp Fluvoxamine/	3104
13	paroxetine.mp. or exp Paroxetine/	6572
14	sertraline.mp. or exp Sertraline/	5592
15	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14	197756
16	4 and 15	18050
17	depression.mp. or exp Depression/	445870
18	exp Depressive Disorder/ or exp Depressive Disorder, Major/ or mdd.mp.	120528
19	unipolar depression.mp.	2915
20	17 or 18 or 19	479550
21	16 and 20	6916
22	limit 21 to humans	5337
23	limit 22 to english language	4997
24	limit 23 to yr="1975 - 2021"	4973

A3.2.3 Embase, Ovid Medline (R) All, and PsychInfo 1975 to Dec 2021

	Searches	Results
1	Systematic review.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, nm, ox, px, rx, ui, sy, tc, id, tm]	688896
2	meta-analysis.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, nm, ox, px, rx, ui, sy, tc, id, tm]	611577
3	dose-response.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, nm, ox, px, rx, ui, sy, tc, id, tm]	977707
4	1 or 2 or 3	1951504
5	citalopram.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, nm, ox, px, rx, ui, sy, tc, id, tm]	35516
6	escitalopram.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, nm, ox, px, rx, ui, sy, tc, id, tm]	18398
7	fluxetine.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, nm, ox, px, rx, ui, sy, tc, id, tm]	45
8	fluoxetine.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, nm, ox, px, rx, ui, sy, tc, id, tm]	72941
9	fluvoxamine.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, nm, ox, px, rx, ui, sy, tc, id, tm]	19567
10	paroxetine.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, nm, ox, px, rx, ui, sy, tc, id, tm]	39506
11	sertraline.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, nm, ox, px, rx, ui, sy, tc, id, tm]	37117
12	ssri.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, nm, ox, px, rx, ui, sy, tc, id, tm]	23575
13	serotonin uptake inhibitor$.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, nm, ox, px, rx, ui, sy, tc, id, tm]	78664
14	selective serotonin re-uptake inhibitor$.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, nm, ox, px, rx, ui, sy, tc, id, tm]	2129
15	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14	185018
16	depression.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, nm, ox, px, rx, ui, sy, tc, id, tm]	1549267
17	major depressive disorder.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, nm, ox, px, rx, ui, sy, tc, id, tm]	88507
18	major depression.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, nm, ox, px, rx, ui, sy, tc, id, tm]	252537
19	unipolar depression.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, nm, ox, px, rx, ui, sy, tc, id, tm]	10391
20	16 or 17 or 18 or 19	1561530
21	4 and 15 and 20	10272
22	limit 21 to humans	9167
23	limit 22 to english language	8732
24	limit 23 to yr="1975 - 2021"	8728

A3.3 Data collection form

Article (Reference)	
Indication	
Antidepressants	
Efficacy & Dose	
ADEs (Dropouts)	
Review type (Syst, M-A, etc.)	
Protocol	
Placebo included	
Patient-level	
Flexible dose	
Dose standardisation	
Study duration	
Primary/secondary care	
Comment	

A3.4 PRISMA 2020 Check list

The thesis abstract summarises three research studies and the overall thesis findings. Word count was limited therefore PRISMA abstract check list was considered inappropriate.

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Chapter 7 title
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Not appropriate – Thesis abstract summarises 3 research studies. Limited word count does not allow
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	2.7, 3.3, 6.5, 6.7 & 7.1
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	7.1
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	7.2.2 & Table 9. PICOS
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	7.2.2.5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	A3.2
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	7.2.3
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	7.2.3, A3.1 & A3.3

Section and Topic	Item #	Checklist item	Location where item is reported
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	7.2.1 & 7.2.5
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	7.2.3
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	7.2.4
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Not appropriate, narrative synthesis
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	7.2.5
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Not appropriate, narrative synthesis
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	7.2.5
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	7.2.5
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Not appropriate, narrative synthesis
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	7.2.4
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	7.2.4
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	7.2.4
RESULTS			

Section and Topic	Item #	Checklist item	Location where item is reported
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	7.3.1 and PRISMA flowchart Figure 18
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	7.3.1 and PRISMA flowchart Figure 18
Study characteristics	17	Cite each included study and present its characteristics.	7.3.1, Table 11 & A3.7
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	7.3.4, Figure_19 & A3.6
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	7.3.1, Table 11, 7.3.2 &Table 12
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	7.3.4, Table 11, A3.6 & A3.8
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Not appropriate, narrative synthesis
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	7.3.1 & Table 11
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	7.3.4 & 7.3.5
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	7.3.4
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	7.3.5
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	7.4 & 7.6
	23b	Discuss any limitations of the evidence included in the review.	7.5 & 8.2
	23c	Discuss any limitations of the review processes used.	7.5 & 8.2
	23d	Discuss implications of the results for practice, policy, and future research.	8.3

Section and Topic	Item #	Checklist item	Location where item is reported
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	7.2.2
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	http://hdl.handle.net/1893/33209
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	7.2.4
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Acknowledgements & 8.6
Competing interests	26	Declare any competing interests of review authors.	4.3.1
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	All data are contained with in Chapter 7 & Appendix 3.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

A3.5 RAMESES meta-narrative review reporting guideline

RAMESES publication standards: meta-narrative review guideline.[337]

RAMESES: List of items to be included when reporting a meta-narrative review		
	Title	**Action/comment**
1.	In the title, identify the document as a meta-narrative review or synthesis	Title of Chapter 7
	Abstract	
2.	While acknowledging publication requirements and house style, abstracts should ideally contain brief details of: the study's background, review question or objectives; search; strategy; methods of selection, appraisal, analysis and synthesis of sources; main results; and implications for practice.	Not appropriate – Thesis abstract summarises 3 research studies. Limited word count does not allow
	Introduction	
3.	Rationale for review Explain why the review is needed and what it is likely to contribute to existing understanding of the topic area.	1.1, 3.3, 6.4.6, 6.7, & 7.1
4.	Objectives and focus of review State the objective(s) of the review and/or the review question(s). Define and provide a rationale for the focus of the review.	3.3, 6.4.6 & 7.1
	Methods	
5.	Changes in the review process Any changes made to the review process that was initially planned should be briefly described and justified.	7.2.1, 7.2.4, & 7.2.5
6.	Rationale for using meta-narrative review Explain why meta-narrative review was considered the most appropriate method to use.	7.2.1 & 7.2.5
7.	Evidence of adherence to guiding principles of meta-narrative review Where appropriate show how each of the six guiding principles have been followed:	
	Pragmatism	7.2.2 & Table 9 PICO
	Pluralism	7.2.2.4 Range of review methodologies included
	Historicity	2.7 & Chapter 2
	Contestation	7.2.2.4
	Reflexivity	From self and thesis supervisory team.
	Peer review	Informally findings have been shared with GPs and psychiatrists as part of the NHSGGC depression guideline review 2020.

RAMESES: List of items to be included when reporting a meta-narrative review		
	Methods (continued)	
8.	Scoping the literature Describe and justify the initial process of exploratory scoping of literature.	2.7, 5.3, 5.4, 6.4.5, 6.4.6, 6.5, 7.1 & 7.2.2.5
9.	Searching processes While considering specific requirements of the journal or other publication outlet, state and provide a rationale for how the iterative searching was done. Provide details on all the sources accessed for information in the review. Where searching in electronic databases has taken place, the details should include (for example) name of database, search terms, dates of coverage and date last searched. If individuals familiar with the relevant literature and/or topic area were contacted, indicate how they were identified and selected.	7.2.2.5, A3.2.1, A3.2.2 & A3.2.3,
10.	Selection and appraisal of documents Explain how judgements were made about including and excluding data from documents, and justify these.	7.2.3
11.	Data extraction Describe and explain which data or information were extracted from the included documents and justify this selection.	7.2.3
12.	Analysis and synthesis processes Describe the analysis and synthesis processes in detail. This section should include information on the constructs analysed and describe the analytic process.	7.2.5
	Results	
13.	Document flow diagram Provide details on the number of documents assessed for eligibility and included in the review with reasons for exclusion at each stage as well as an indication of their source of origin (for example, from searching databases, reference lists and so on). You may consider using the example templates (which are likely to need modification to suit the data) that are provided.	7.3.1 & Figure 18 PRISMA flowchart
14.	Document characteristics Provide information on the characteristics of the documents included in the review.	7.3.1, Table 11 & A3.7
15.	Main findings Present the key findings with a specific focus on theory building and testing.	Table_11 & Table_12 Theory building not appropriate in this review.
	Discussion	
16.	Summary of findings: Summarise the main findings, taking into account the review's objective(s), research question(s), focus and intended audience(s).	7.4

RAMESES: List of items to be included when reporting a meta-narrative review		
	Discussion (continued)	
17.	Strengths, limitations and future research: Discuss both the strengths of the review and its limitations. These should include (but need not be restricted to) (a) consideration of all the steps in the review process and (b) comment on the overall strength of evidence supporting the explanatory insights which emerged. The limitations identified may point to areas where further work is needed.	7.5 & 8.2
18.	Comparison with existing literature: Where applicable, compare and contrast the review's findings with the existing literature (for example, other reviews) on the same topic.	7.6
19.	Conclusion and Recommendations: List the main implications of the findings and place these in the context of other relevant literature. If appropriate, offer recommendations for policy and practice.	8.3
20.	Funding: Provide details of funding source (if any) for the review, the role played by the funder (if any) and any conflicts of interests of the reviewers.	Acknowledgements & 8.6

A3.6 Risk of bias table of included reviews

Review			Phase 2				Phase 3
	Author	Year	1. Study eligibility criteria	2. Identification and selection of studies	3. Data collection and study appraisal	4. Synthesis and findings	RISK OF BIAS IN THE REVIEW
1	Adli	2005	Low	High	High	Low	High
2	Altamura	1988	High	High	High	High	High
3	Baker	2003	Low	High	High	High	High
4	Barburi	2002	Low	Low	High	Unclear	High
5	Beasley	1990	Low	High	High	Low	High
6	Beasley	1993	Unclear	High	High	High	High
7	Benkert	1996	Unclear	Unclear	High	Unclear	Unclear
8	Berney	2005	Unclear	High	High	Low	High
9	Bollini	1999	Low	Low	Unclear	High	High
10	Braun	2020	Low	Low	Low	Low	Low
11	Cheng	2020	Low	Unclear	Low	Low	Low
12	Caley	2002	Unclear	Unclear	High	Unclear	High
13	Corruble	2000	Low	Unclear	Unclear	Unclear	High
14	Dold	2017	Low	Low	Low	Low	Low
15	Dunner	1992	Unclear	Unclear	High	Low	Unclear
16	Furukawa	2019	Unclear	Low	Low	Low	Low
17	Furukawa	2020	Low	Low	Low	Low	Low
18	Gutsmiedl	2020	Low	Unclear	Low	Unclear	Unclear
19	Hamza	2021	Low	Unclear	Unclear	Low	Unclear
20	Hansen	2009	Low	Unclear	High	High	High
21	Hieronymus	2016	Low	High	Unclear	High	High
22	Holper	2019	Low	Low	Low	High	High
23	Jakubovski	2016	High	High	High	High	High
24	Jenner	1992	Unclear	High	High	Low	High
25	Khan	2003	Low	Unclear	High	Low	Unclear
26	Klemp	2011	Low	Low	Unclear	Unclear	Unclear
27	Lam	2006	Low	High	High	High	High
28	Lane	1995	Unclear	Unclear	High	High	High
29	Montgomery	1995	High	High	High	High	High
30	Montgomery	1995	Unclear	Unclear	Unclear	Low	Unclear
31	Montgomery	1994	Unclear	Unclear	High	High	High
32	Murdoch	2005	Low	Unclear	Unclear	Unclear	Unclear
33	Oliva	2021	Low	Low	High	High	High
34	Papakostas	2010	Low	High	High	Unclear	High
35	Parker	2000	Low	High	Unclear	Low	High
36	Preskorn	1995	Unclear	Unclear	Unclear	Low	Unclear
37	Purgato	2015	Unclear	Low	Unclear	Low	Unclear
38	Rifkin	1997	Unclear	Unclear	Unclear	Unclear	High
39	Ruhe	2006	Unclear	High	Low	Low	High
40	Safer	2016	Unclear	Unclear	Unclear	Unclear	Unclear
41	Tan	1999	Unclear	Unclear	Unclear	Low	Unclear
42	Vaswani	2003	Unclear	Unclear	Unclear	Unclear	Unclear

A3 .7 Characteristics of reviews meeting inclusion criteria

Study	Indication	Number of primary studies included	Review design	Efficacy & Dose	ADEs & dropouts	Protocol	Placebo included	Patient -level	Flexible dose studies included	Dose Standardisation	Study duration	Primary or secondary care
Adli 2005 [1]	Major depression	12	Syst. Narr.	↑ fluv. ↔ cit, fluox, par, sert	↑	Unclear	Yes	No	Reported separately	Study doses used	4-8 wks	Unclear
Altamura 1988 [2]	Depression	2	Narr.	↔ fluox	↑	No	Yes	No	No	Fluox dose	6 wks	Outpatients
Baker 2003 [3]	Major depression	4	Syst. M-A.	? fluox, par, sert	↑	No	No	No	Reported separately	Yes: Low, Medium, High. No clear definition	≤8 wks	Unclear
Barbui 2002 [4]	Depression	103	Syst. M-A.	↑ fluox	↑	No	No	No	Yes	Yes: 20-30mg/d, >30mg/d. Dose range 20-40mg/d & >40mg/d	≤9 wks	Both
Beasley 1990 [5]	MDD	Pooled (n=669)	Pooled. Not Syst.	↔ fluox	↑	No	Yes	No	Yes	Fluox dose	≤8 wks	Outpatients
Beasley 1993 [6]	MDD	3	Narr.	n-a	fluox: ↑ anxiety, agitation, insomnia., drowsiness, asthenia.	No	Yes	Yes	Yes	None	6 wks	Primary care
Benkert 1996 [7]	MDD	7 (+7 Rev)	Narr.	↔ cit, fluox, fluv, par, sert	n-a	No	Yes	No	Yes	Actual doses from other reviews	Not defined	Not defined
Berney 2005 [8]	Depression	14 (+4 Revs)	Narr.	↔ cit, escit, fluox, par, sert. ? fluv	↑ fluox, dropout[a]	No	Yes	No	No	Study doses used	6-8 wks	Both
Bollini 1999 [9]	Depression	33	Syst. M-A.	∩ curvy linear SSRI & non-SSRI grouped	↑	Unclear	Yes	No	Yes	Imip Equiv	6 wks (4-24 wks)	Unclear
Braun 2020 [10]	Depressive disorder	33	Syst. M-A. Net-M-A	↔ SSRI grouped ↔ cit, escit, fluox, fluvox par, sert	↑ SSRI grouped	Yes	Yes	No	Yes	Low, Med, High.	6 wks (2-12 wks)	Unclear
Caley 2002 [11]	Depression	5 (+7 Revs)	Narr.	↑ cit, ∩ fluv, ↔ fluox, sert, ?par	↑	No	Yes	No	Yes	Study doses used	4-6 wks	Both
Cheng [12]	Major depression	115	Model-Bases M-A	↔ cit, escit, fluox, fluvox par, sert	n-a	No	Yes	No	No	Fluox Equiv	4-12wks	Both
Corruble 2000 [13]	Depression	10 (+6 Revs)	Syst. Narr.	SSRI grouped	n-a	No	No	No	No	SSRI study doses used	4-8 wks	Unclear
Dold 2017 [14]	Unipolar depression	5	Syst. M-A. M-R	↔ fluox, par, sert	↑fluox,	No	No	No	Rand. fixed v increased dose	Standard dose: fluox, par 20mg/d, sert 50mg/d, versus higher doses	5 wks (3-8 wks)	Unclear
Dunner 1992 [15]	Depression	Pooled (n=460)	Pooled SKB data only	↔ Par	n-a	No	Yes	Yes	Yes	Par. dose	Acute ≤6 wks Long-term 52 wks	Unclear
Furukawa 2019 [16]	Major depression	66	Syst. M-A	↑ SSRI grouped (to 40mg/d) ↑ cit (to 30mg/d), ↔ escit, fluox, par, ∩ sert.	↑	Yes	Yes	No	No	Fluox Equiv	8 wks (4-12wks)	Both
Furukawa 2020 [17]	Major depression	108	Syst. M-A	↔ SSRI grouped ↔ cit, escit, fluox, par, sert	↑ flexible dose	Yes	Yes	No	Fixed v flex dosing	Fluox Equiv	7 wks (4-12 wks)	Both
Gutsmiedl 2020 [18]	MDD	44	Syst. M-A. M-R	↔ SSRIs & non-SSRI grouped	n-a	Yes	Yes	Yes	Yes	Fluox Equiv	9 wks (4-26 wks)	Both
Hansen 2009 [19]	Depression	74	Syst. M-A. M-R	↑ SSRIs & non-SSRI grouped	n-a	No	Yes	No	Yes	Yes: licensed dose range e.g. fluox <45mg/d low >45mg/d high	7 wks (6-24 wks)	Outpatients

Review characteristics – continued

Study	Indication	Number of primary studies included	Review design	Efficacy & Dose	ADEs & dropouts	Protocol	Placebo included	Patient-level	Flexible dose studies included	Dose Standardisation	Study duration (range)	Primary or secondary care
Hamza 2021 [20]	MDD	60	M-A	SSRI grouped (↑ to 40mg/d) ↑ cit (to 30mg/d), par, sert (to 75mg/d), ↔ escit, fluox,,	n-a	No	Yes	No	No	Fluox Equiv. Individual drug effects as fluox equiv not actual drug dose.	8 wks (4-12wks)	Both
Hieronymus 2016 [21]	Depression	11	M-A. Ind. Data.	↑ cit, par, sert	n-a	Yes	Yes	Yes	Yes	Patient-level doses	≤6 wks	Unclear
Holper 2020 [22]	MDD	153	Net-M-A	↑ escital, fluox, ↔ cit, par	↑ (≤70y) ↑↑ (>70y)	Yes	Yes	No	Yes	Fluox Equiv	4-12 wks	Both
Jakubovski 2016 [23]	MDD	40	Syst. M-A.	↑ SSRIs grouped	↑	Unclear	Yes	No	Yes	Imip Equiv	6 wks (4-24 wks)	Unclear
Jenner 1992 [24]	Depression	Pooled (n=4668)	Pooled. SKB data only	↔ par	↑	No	Yes	Yes	Reported separately	Par. dose	Mostly 6 wks (≤2 yr)	Both
Khan 2003 [25]	MDD	36	FDA submissions M-A	↔ SSRIs & non-SSRI grouped	↑	No	Yes	No	Reported separately	SSRI study doses used	6-8wks	Unclear
Klemp 2011 [26]	Depression	26	Syst. M-R.	↔ par	n-a	No	Yes	No	Yes	Par dose	8 wks (6-56 wks)	Outpatients
Lam 2006 [27]	MDD	3	M-A. Lundbeck data only	↔ escital	n-a	No	Yes	No	Yes	Escit dose	8 wks	Both
Lane 1995 [28]	Depression	5 (+2 Revs)	Narr.	↔ cit, fluox, par, sert	↑	No	Yes	Not defined	Yes	Not defined	Not defined	Not defined
Montgomery 1994 [29]	Depression	9	M-A. Not Syst.	↔ cit	n-a	No	Yes	No	Yes	Cit dose	4-6 wks	Unclear
Montgomery 1995 [30]	Depression	1	Narr.	↔ sert	↑	No	Yes	No	No	Sert dose	Acute 6-8 wks Long-term 44 wks	Not defined
Montgomery 1995 [31]	Depression	2 (+2 Revs)	Narr.	↔ cit	n-a	No	Yes	No	Yes	Cit dose	≤24 wks	Both
Murdoch 2005 [32]	MDD	Pooled (n=1307)	Pooled Lundbeck Forrest	n-a	↑ escital	No	Yes	No	Yes	Escit dose	Not defined	Not defined
Oliva 2021 [33]	MDD	Not defined	Syst. M-A.	n-a	↑ N&V cit, escital	Yes	Yes	No	Unclear	Low v high dose	6-12 wks	Not defined
Papakostas 2010 [34]	MDD	9	Syst. M-A.	↑ SSRIs grouped	↑	No	Yes	No	Yes	Usual dose (10mg/d escit, 20mg/d cit, fluox, par, 50mg/d sert, fluv), intermediate, double (double usual) & higher.	6 wks	Not defined
Parker 2000 [35]	Depression	1 (+1 Rev)	Narr.	↑ cit	↑	No	Yes	No	Yes	Cit dose	4-6 wks	Not defined
Purgato 2015 [36]	Unipolar major depression	173	Syst. M-R.	↔ fluox	n-a	No	Yes	No	Yes	Yes: Mean doses poorly reported: min and max doses to DDDs then PDD/DDD. Grouped: ≤20mg/d or 20-80mg/d	Majority ≤6 wks	Both

Review characteristics – continued

Study	Indication	Number of primary studies included	Review design	Efficacy & Dose	ADEs & dropouts	Protocol	Placebo included	Patient-level	Flexible dose studies included	Dose Standardisation	Study duration (range)	Primary or secondary care
Preskorn 1995 [37]	Depression	3	Narr.	↔ sert	↑	No	Yes	No	No	Sert dose	≤8 wks	Outpatients
Rifkin 1997 [38]	Depression	4	Narr.	↔ fluox, par, sert	n-a	No	Yes	No	No	SSRI study doses used	Not defined	Not defined
Ruhe 2006 [39]	Depression	8	Syst. Narr.	↔ cit, fluox, par, sert ∩ fluv,	n-a	Unclear	No	No	Yes	SSRI study doses used	8 wks (3-12 wks)	Unclear
Safer 2016 [40]	MDD & other MH conditions	33	Narr.	↔ SSRI & non-SSRI grouped ↔ cit, escit, fluox, fluv, par, sert	↑	No	Yes	No	No	SSRI study doses used	8-28 wks	Not defined
Tan 1999 [41]	MDD & other MH conditions	2 (+1 Rev)	Narr.	?cit	↑	No	Yes	No	Yes	Cit dose	6 wks (3-24 wks)	Not defined
Vaswani 2003 [42]	MDD & other MH conditions	3 (+5 Revs)	Narr.	↑ cit (to 40mg/d), ↔ fluox, fluv, par, sert	↑	No	Yes	Not defined	Yes	Not defined	Not defined	Not defined

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A3.8 Primary studies quality rating for low risk of bias reviews

160 primary studies included in the reviews (N=5) assessed as being at low risk of bias. Of the 160 primary studies overall risk of bias was rated as low 34 (21%), moderate 120 (75%) and high 6 (4%).

Study ID	Dep. severity	Braun 2020	Cheng 2020	Dold 2017	Furukawa 2019	Furukawa 2020	Overall risk of bias
1. Alexopoulos 2004 (Poster SCT-MD-27)		n/a	Mod.	n/a	n/a	Mod.	Mod.
2. Amin 1984		n/a	Mod.	n/a	n/a	n/a	Mod.
3. Barber 2011		n/a	n/a	n/a	n/a	Mod.	Mod.
4. Benkert 1997		n/a	n/a	Mod.	n/a	n/a	Mod.
5. Binnemann2008 (NCT00143091)		n/a	Mod.	n/a	Mod.	n/a	Mod.
6. Bjerkenstedt 1985		Mod.	n/a	n/a	n/a	n/a	Mod.
7. Bjerkenstedt2005		n/a	Low	n/a	Low	Low	Low
8. Bosc 1997a (Study 014 - Andreoli2002)		n/a	Mod.	n/a	n/a	Mod.	Mod.
9. Bose 2008 (SCT-MD-13)		n/a	n/a	n/a	n/a	Mod.	Mod.
10. Brunoni 2012		n/a	Low	n/a	Low	Low	Low
11. Buchsbaum 1997		n/a	Mod.	n/a	n/a	n/a	Mod.
12. Burke2002 (SCT-MD-01)		Mod.	Mod.	n/a	Mod.	Mod.	Mod.
13. Byerley1988		n/a	Low	n/a	n/a	n/a	Low
14. CAGO178A2303 (NCT00463242)		n/a	Mod.	n/a	n/a	Mod.	Mod.
15. Cassano 2002 (29060/421)		n/a	Mod.	n/a	n/a	n/a	Mod.
16. CL3-20098-022		n/a	n/a	n/a	Mod.	Mod.	Mod.
17. CL3-20098-023		n/a	n/a	n/a	Low	Low	Low
18. CL3-20098-024		n/a	n/a	n/a	Low	Low	Low
19. Claghorn 1996		n/a	Mod.	n/a	n/a	n/a	Mod.
20. Clayton 2003 (Study 050)		n/a	Mod.	n/a	n/a	Mod.	Mod.
21. Clayton 2006a (WELL AK130926)		n/a	n/a	n/a	n/a	Mod.	Mod.
22. Clayton 2006b (WELL AK130927)		n/a	Mod.	n/a	n/a	Mod.	Mod.
23. CN104-054 (FDA)		n/a	n/a	n/a	Mod.	Mod.	Mod.
24. Cohn 1985a		n/a	Mod.	n/a	n/a	Mod.	Mod.
25. Coleman 1999 (AK1A4002)		n/a	Mod.	n/a	n/a	Mod.	Mod.
26. Coleman 2001 (AK1A4007)		n/a	Mod.	n/a	n/a	Mod.	Mod.
27. Corrigan 2000		n/a	Mod.	n/a	Mod.	Mod.	Mod.
28. Croft 1999 (AK1A4001)		n/a	Low	n/a	n/a	Mod.	Mod.
29. Davidson 2002 (HDTSG) (NCT00005013)		n/a	Low	n/a	n/a	Low	Low
30. Detke 2004 (HMAY Study Group A)	Mild	n/a	Low	n/a	Low	Low	Low
31. Doogan 1994		n/a	Low	n/a	n/a	Low	Low
32. Dornseif 1998		n/a	n/a	High	n/a	n/a	High
33. Dube 2010 (NCT00420004)		n/a	n/a	n/a	n/a	Mod.	Mod.

34. Dunbar 1993a (Claghorn1992, Rickels1989, Rickels1992, PAR 02-001 - FDA)		n/a	Mod.	n/a	n/a	Mod.	Mod.
35. Dunbar 1993b (Claghorn1992, PAR 02-002 - FDA)		n/a	Mod.	n/a	n/a	Mod.	Mod.
36. Dunbar 1993c (Smith1992, PAR 02-003 - FDA)		n/a	Mod.	n/a	n/a	Mod.	Mod.
37. Dunbar 1993d (Kiev1992, PAR 02-004 - FDA)		n/a	Mod.	n/a	n/a	Mod.	Mod.
38. Dunner 1992 (PAR 29060.09)		Mod.	Mod.	n/a	Mod.	Mod.	Mod.
39. Edwards1989 (MD/PAR/009 PAR-276)		n/a	Mod.	n/a	Mod.	n/a	Mod.
40. Fabre 1987	Mild	High	n/a	n/a	n/a	n/a	High
41. Fabre 1995 (SER 103 FDA)		Low	Mod.	n/a	Mod.	Mod.	Mod.
42. Fabre 1996		n/a	Low	n/a	n/a	n/a	Low
43. Fava 1998		n/a	Mod.	n/a	n/a	n/a	Mod.
44. Fava 2005	Mild	n/a	Mod.	n/a	Mod.	Mod.	Mod.
45. Feighner 1989a		n/a	Mod.	n/a	n/a	n/a	Mod.
46. Feighner 1989b		n/a	Low	n/a	n/a	n/a	Low
47. Feighner 1993a (Feighner 1989c PAR 03 001 - FDA)		n/a	Mod.	n/a	n/a	n/a	Mod.
48. Feighner 1993b (Cohn1990 Cohn1992 PAR 03 002 - FDA)		n/a	Mod.	n/a	n/a	n/a	Mod.
49. Feighner 1993c (PAR 03 003 - FDA)		n/a	Mod.	n/a	n/a	n/a	Mod.
50. Feighner 1993d (Shrivastava1992 PAR 03 004 - FDA)		n/a	Mod.	n/a	n/a	n/a	Mod.
51. Feighner 1993e (Peselow1989 PAR 03 005 - FDA)		n/a	Mod.	n/a	n/a	n/a	Mod.
52. Feighner 1993f (Fabre1992 PAR 03 006 - FDA)		n/a	Mod.	n/a	n/a	n/a	Mod.
53. Feighner 1999 (Study 91206 FDA)		Low	Mod.	n/a	Mod.	Mod.	Mod.
54. Fieve 1986		High	n/a	n/a	n/a	n/a	High
55. Frank 2004		n/a	n/a	n/a	Mod.	Mod.	Mod.
56. Gastpar 2006		n/a	Low	n/a	Low	Low	Low
57. Ghose 1997		Low	n/a	n/a	n/a	n/a	Low
58. Golden 2002a (29060/448)		n/a	Mod.	n/a	n/a	Mod.	Mod.
59. Golden 2002b (29060/449)		n/a	Mod.	n/a	n/a	Mod.	Mod.
60. Goldstein 2002 (HMAQ - Study Group A)	Mild	n/a	Mod.	n/a	n/a	Mod.	Mod.

61. Goldstein 2004a (HMAT - Study Group A, ID#4091)	Mild	n/a	Mod.	n/a	Mod.	Mod.	Mod.
62. Goldstein 2004b (HMAT - Study Group B, ID#4091)	Mild	n/a	Mod.	n/a	Mod.	Mod.	Mod.
63. Gorman 2002 (SCT-MD-02)		n/a	Mod.	n/a	n/a	Mod.	Mod.
64. Griebel 2012 (Study DF15878) (NCT00358631)		n/a	Mod.	n/a	Mod.	Mod.	Mod.
65. Griebel 2012b (Study DF15879) (NCT00361491)		n/a	Mod.	n/a	Mod.	Mod.	Mod.
66. Guy (1986)[27]		Mod.	n/a	n/a	n/a	n/a	Mod.
67. Hebenstreit 1989		Mod.	n/a	n/a	n/a	n/a	Mod.
68. Heiligenstein 1994	Mild	n/a	Low	n/a	Low	Low	Low
69. Higuchi 2009		n/a	Low	n/a	n/a	Low	Low
70. Higuchi 2011 (PCR112810, NCT00866294)		n/a	Low	n/a	n/a	Low	Low
71. Hirayasu 2011a		Low	Low	n/a	Low	Low	Low
72. Hirayasu 2011b		Low	Low	n/a	Low	Low	Low
73. Hunter 2010 (Study 1)		n/a	n/a	n/a	Mod.	Mod.	Mod.
74. Jefferson 2000 (29060/785)		Mod.	Mod.	n/a	Mod.	Mod.	Mod.
75. Kasper 2005a (Study 99024)		n/a	n/a	n/a	Mod.	Mod.	Mod.
76. Kasper2012 (NCT00807248)		n/a	Mod.	n/a	Mod.	n/a	Mod.
77. Kato 2018		Mod.	n/a	n/a	n/a	n/a	Mod.
78. Katz 2004		n/a	n/a	n/a	n/a	Low	Low
79. Keller 2006a (Study059) (NCT00035009)		n/a	n/a	n/a	Mod.	Mod.	Mod.
80. Keller 2006b (Study061) (NCT00035295)		n/a	n/a	n/a	Mod.	Mod.	Mod.
81. Keller 2006c (Study062) (NCT00048607)		n/a	Mod.	n/a	Mod.	Mod.	Mod.
82. Kramer 1998		n/a	n/a	n/a	Mod.	Mod.	Mod.
83. Lam 1995		n/a	Mod.	n/a	Mod.	Mod.	Mod.
84. Learned 2012 (NCT00420641)		n/a	Mod.	n/a	Mod.	n/a	Mod.
85. Lepola 2003 (ESC 99003)		n/a	Low	n/a	n/a	Low	Low
86. Loo 2002 (CL2-014)		n/a	Low	n/a	Mod.	Mod.	Mod.
87. Lopez Rodriguez 2004		n/a	Mod.	n/a	Mod.	Mod.	Mod.
88. Lydiard 1997		n/a	Mod.	n/a	n/a	Mod.	Mod.
89. M/2020/0046 (Study 046)		n/a	Mod.	n/a	n/a	Mod.	Mod.
90. M/2020/0047 (Study 047)		n/a	Mod.	n/a	n/a	Mod.	Mod.
91. Mao 2015 (NCT01098318)	Mild	n/a	Mod.	n/a	n/a	Mod.	Mod.
92. Mathews 2015 (NCT01473381)		Low	Low	n/a	Low	n/a	Low
93. McGrath 2000		n/a	n/a	n/a	n/a	Mod.	Mod.
94. Mendels 1999 (Study 85A - FDA)		n/a	Mod.	n/a	n/a	Mod.	Mod.

95. Miller 1989 (MDUK/29060/III/82/006 (PAR-274) PAR UK 06 - FDA)		n/a	Mod.	n/a	Mod.	n/a	Mod.
96. Mischoulon 2014 (NCT00101452)		n/a	Mod.	n/a	n/a	Mod.	Mod.
97. Montgomery 1992 (Study 89303 FDA)		Mod.	Mod.	n/a	Mod.	Mod.	Mod.
98. Moreno 2005		n/a	Mod.	n/a	Mod.	Mod.	Mod.
99. Moscovitch 2004		n/a	Low	n/a	n/a	Low	Low
100. Mundt 2012 (NCT00406952)		n/a	Mod.	n/a	n/a	Mod.	Mod.
101. MY-1008/BRL-029060/2/CPMS-076		n/a	n/a	n/a	Mod.	n/a	Mod.
102. MY-1042/BRL-029060/CPMS-251		n/a	Mod.	n/a	n/a	Mod.	Mod.
103. MY-1043/BRL-029060/115		n/a	n/a	n/a	n/a	Mod.	Mod.
104. MY-1045/BRL-029060/1 (PAR 128)		n/a	Mod.	n/a	n/a	Mod.	Mod.
105. NCT00822744 (EudraCT Number2008-001718-26)		n/a	n/a	n/a	Mod.	Mod.	Mod.
106. NCT01020799		n/a	Low	n/a	Low	n/a	Low
107. NCT01808612		Low	n/a	n/a	Low	Low	Low
108. Nemeroff 2007		n/a	Mod.	n/a	n/a	Mod.	Mod.
109. Nierenberg 2007 (F1J-MC-HMCR, NCT00073411, Pigott2007)		n/a	Low	n/a	Low	Low	Low
110. Ninan 2003 (poster SCT-MD-26)		n/a	Mod.	n/a	n/a	Mod.	Mod.
111. NKD20006 (NCT00048204)		n/a	Mod.	n/a	Mod.	Mod.	Mod.
112. Norton 1984		n/a	Low	n/a	n/a	n/a	Low
113. Olie 1997		n/a	Low	n/a	n/a	Mod.	Mod.
114. PAR 279 MDUK		n/a	Mod.	n/a	Mod.	n/a	Mod.
115. Perahia 2006 (HMAY - Study Group B)	Mild	n/a	Low	n/a	Low	Low	Low
116. PZ/109 (Hieronymus 2016)		n/a	Mod.	n/a	n/a	n/a	Mod.
117. PZ/111 (Hieronymus 2016)		n/a	Mod.	n/a	n/a	n/a	Mod.
118. Rapaport 2009 (BRL-29060/874) (NCT00067444)		Low	n/a	n/a	Mod.	Mod.	Mod.
119. Ravindran 1995		n/a	n/a	n/a	n/a	Mod.	Mod.
120. Reimherr 1990 (SER 104 - FDA)		n/a	Mod.	n/a	n/a	Mod.	Mod.
121. Rosenberg 1994		Low	n/a	n/a	n/a	n/a	Low
122. Roth 1990		n/a	Mod.	n/a	n/a	n/a	Mod.
123. Rudolph 1999		n/a	Low	n/a	n/a	Low	Low
124. Ruhe 2009		n/a	n/a	Low	n/a	n/a	Low
125. Schatzberg 2006a		n/a	n/a	n/a	n/a	Mod.	Mod.
126. Schneider 2003		n/a	n/a	n/a	n/a	Low	Low
127. Schweizer 1990		n/a	n/a	High	n/a	n/a	High

128. Schweizer 2001		n/a	n/a	Mod.	n/a	n/a	Mod.
129. SCT-MD-35 (NCT00109044)		n/a	n/a	n/a	Mod.	n/a	Mod.
130. SCT-MD-49 (NCT00668525)		Mod.	Low	n/a	Low	Mod.	Mod.
131. SER 101 (FDA)		Mod.	n/a	n/a	High	High	High
132. SER 310 (FDA)		Mod.	n/a	n/a	Mod.	Mod.	Mod.
133. SER 315 (FDA)		n/a	Mod.	n/a	n/a	Mod.	Mod.
134. Sheehan2009a		n/a	Mod.	n/a	n/a	n/a	Mod.
135. Silverstone 1999		n/a	Mod.	n/a	n/a	Mod.	Mod.
136. Sramek 1995		n/a	Low	n/a	Low	Low	Low
137. Stahl 2000		n/a	Mod.	n/a	n/a	Mod.	Mod.
138. Stark 1985 (Study 27 - FDA)		n/a	Mod.	n/a	n/a	Mod.	Mod.
139. Study 19 (Fabre 1985)		n/a	Mod.	n/a	n/a	n/a	Mod.
140. Study 25 (Rickels 1986)		n/a	Mod.	n/a	n/a	n/a	Mod.
141. Study 62a (FDA) - (Dunlop1990)	Mild	Mod.	Mod.	n/a	Mod.	Mod.	Mod.
142. Study 62b (FDA)		n/a	Mod.	n/a	Mod.	Mod.	Mod.
143. Study 89306 (FDA)		Mod.	Mod.	n/a	Mod.	Mod.	Mod.
144. Study F1J-MC-HMAQ - Study Group B	Mild	n/a	Mod.	n/a	Mod.	Mod.	Mod.
145. Suri 2000		Mod.	n/a	n/a	n/a	n/a	Mod.
146. Trivedi 2004 (29060/810)		Low	Mod.	n/a	Mod.	Mod.	Mod.
147. Tural 2003		High	n/a	n/a	n/a	n/a	High
148. VEN XR 367 (FDA)		n/a	Mod.	n/a	Mod.	Mod.	Mod.
149. Wade 2002 (ESC Study 99001 - FDA)		n/a	Low	n/a	Low	Low	Low
150. Walczak 1996		Mod.	n/a	n/a	n/a	n/a	Mod.
151. Wang 2014 (EUCTR2005-005052-40, NCT00351169, D1448C00004)		n/a	Mod.	n/a	n/a	Low	Low
152. WELL AK1A4006		n/a	Mod.	n/a	n/a	Mod.	Mod.
153. Wernicke 1987		Mod.	n/a	n/a	n/a	n/a	Mod.
154. Wernicke 1988		Mod.	n/a	n/a	Mod.	Mod.	Mod.
155. Yevtushenko 2007		Low	n/a	n/a	Low	n/a	Low
156. 003-048		n/a	Mod.	n/a	Low	n/a	Mod.
157. 244 (EMD 68 843-009) (FDA)		n/a	Mod.	n/a	n/a	Mod.	Mod.
158. 245 (EMD 68 843-010) (FDA)		Mod.	Mod.	n/a	Mod.	Mod.	Mod.
159. 246 (SB 659746-003) (FDA)		Mod.	Mod.	n/a	Mod.	Mod.	Mod.
160. 29060/07/01		n/a	Mod.	n/a	n/a	n/a	Mod.

A3.9 Primary studies references, from low risk of bias reviews

160 primary studies from the 5 reviews assessed as being at low risk of bias

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160. 29060 07 001
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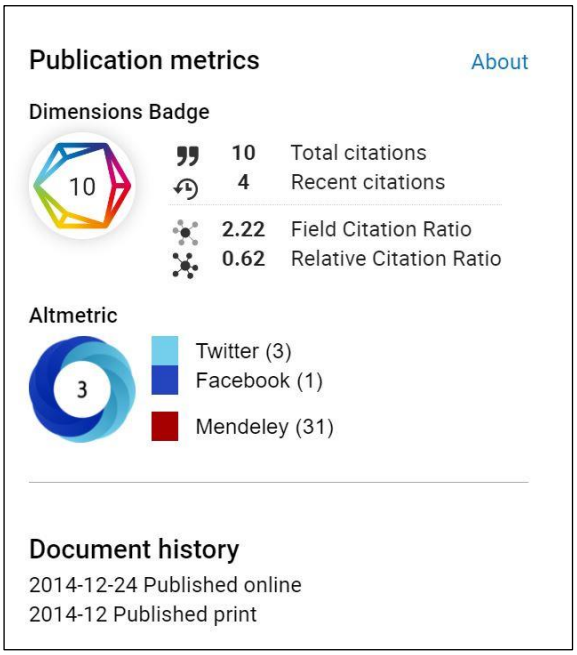
Appendix 4 – Dissemination and impact

The regression analysis and qualitative study were published in BMC Family Practice. This journal is an open access peer reviewed journal, that has a special focus on clinical practice and decision-making, continuing professional education, eHealth, health services research in primary care settings, and health promotion.

BMC Family Practice's Impact Factor was 2.24 and 2.17 respectively for 2014 and 2017 [link].

A4.1 Cross-sectional study – Dissemination

Johnson CF, Dougall NJ, Williams B, MacGillivray, SA, Buchanan AI, & Hassett RD. (2014). Patient factors associated with SSRI dose for depression treatment in general practice: A primary care cross sectional study. BMC Family Practice, 15, 210. [link]



This article is in the 61st percentile (ranked 104,223rd) of the 278,309 tracked articles of a similar age in all journals and the 50th percentile (ranked 1st) of the 2 tracked articles of a similar age in BMC Family Practice.

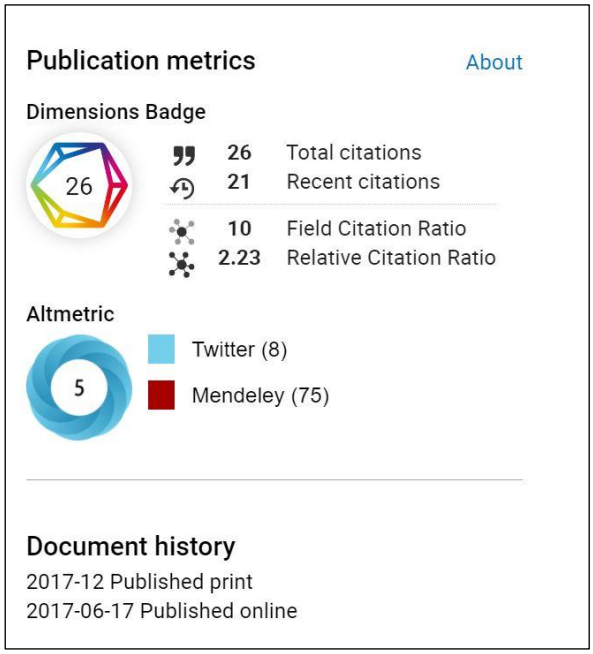
Authors' contributions: CFJ identified the evidence gap in the literature, conceptualised the study, designed and piloted data extraction tools (jointly with AIB and RDH), recruited practices and extracted patient-level data from individual practices. CFJ and NJD worked jointly on data analysis, with NJD making significant contributions to regression modelling. CFJ primarily wrote the manuscript with input from NJD, BW, SAM, AIB and RDH. All authors read and approved the final manuscript.

Oral presentations

	Venue	Year
NHS Education Scotland, continuing professional development education webinar. Depression: bringing the black dog to heal	Scotland	Dec 2019
Pharmacy Management Conference, Mental Health in Scotland	Stirling	Jan 2018
Royal College of Psychiatrist (Scotland), Annual Meeting	Glasgow	Jan 2016
Farr Institute Conference	St Andrews	Aug 2015
Scottish School of Primary Care, Conference	Cumbernauld	May 2015

A4.2 Qualitative study – Dissemination

Johnson CF, Williams B, MacGillivray SA, Dougall NJ, Maxwell M. (2017). 'Doing the right thing': Factors influencing GP prescribing of antidepressants and prescribed doses. *BMC Family Practice,* 18(1), 72. [link]



This article is in the 70th percentile (ranked 81,968th) of the 276,366 tracked articles of a similar age in all journals and the 1st percentile (ranked 1st) of the 1 tracked articles of a similar age in BMC Family Practice.

Authors' contributions: CFJ identified the evidence gap in the literature, conceptualised the study, recruited and interviewed GPs. CFJ, BW, SAM, and MM worked jointly on data analysis. CFJ primarily wrote the manuscript with input from BW, SAM, NJD and MM. All authors read and approved the final manuscript

Oral presentations

Conferences	Venue	Year
Scottish School of Primary Care	Edinburgh	May 2018
Pharmacy Management Conference, Mental Health in Scotland	Stirling	Jan 2018
European Drug Utilization Research Group Conference	Glasgow	Nov 2017
Royal College of Psychiatrist (Scotland)	Glasgow	Jan 2016

A4.3 Systematic review of review – Dissemination plan

As already acknowledge in Section 8.4, the unpublished findings of this study have and are being used to inform the development of a range of regional health board and national initiatives.

The key audience for dissemination, in the following order, are: GPs and the general practice multidisciplinary team, pharmacists, psychiatrists, and community psychiatric nurses. Findings will be shared via a range of activities:

- Publication in a peer review journal. First, British Medical Journal, and if unsuccessful submit to BMJ Open.
- Face-to-face.
    - Educational. Within NHSGGC as part of my specialist mental health pharmacist and advanced general practice clinical pharmacist role: general practice multidisciplinary team updates, general practice clinical pharmacist training. Pharmacy undergraduate experiential learning (Robert Gordon University and University of Strathclyde).
    - As part of routine practice via general practice clinical pharmacists.
- Local publications: NHSGGC Medicines Update blog.
- Conferences
    - College of Mental Health Pharmacy, International Conference
    - Scottish Practice Pharmacy & Prescribing Advisers Association
    - European Drug Utilization Research Group
- Key stakeholders and opinion leaders:
    - REDUCE team Southampton University: Tony Kendrick, Michael Moore, Joanna Moncrief, etc.
    - Effective Prescribing & Therapeutics Branch Scottish Government.