Adherence to antidepressant medicines in people living with unipolar depression

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DECLARATION

This thesis describes research carried out in the Faculty of Pharmacy, The University of Sydney, under the supervision of Professor Timothy F. Chen and Professor Parisa Aslani, and with the permission of the Head of School and Dean, Sydney Pharmacy School, Professor Andrew McLachlan.

The work presented in this thesis is, to the best of my knowledge, original except as acknowledged in the text. This work has not been submitted for the award of a degree at this or any other institution. Full acknowledgement has been provided where the work of others has been cited or used.

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'Increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatments'.[1]

Haynes RB et al, 2002

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LIST OF ABBREVIATIONS

ABC	Ascertaining Barriers to Compliance project
YLDs	Years Lived with Disability
SSRIs	Selective Serotonin Reuptake Inhibitors
SNRIs	Serotonin Noradrenaline Reuptake Inhibitors
SSNRIs	Selective Serotonin Noradrenaline Reuptake Inhibitors
MGLS	Morisky, Green, and Levine Self-Reported Medication Taking Scale
WHO	World Health Organization
MEMS	Medication Event Monitoring System
ADRs	Adverse Drug Reactions
HCPs	Health Care Professionals
GPs	General Practitioners
CVI	Content Validity Index
I-CVI	Content Validity of Individual Items
S-CVI	Content Validity of the overall Scale
S-CVI/Ave	the Average of Content Validity of the overall Scale
BMQ by Horne	Beliefs about Medicines Questionnaire
BMQ by Svarstad	Brief Medication Questionnaire
MAQ	Medication Adherence Questionnaire
SMTS	Self-reported Medication Taking Scale
AAS	Antidepressant Adherence Scale
ADHD	Attention Deficit Hyperactivity Disorder
NCF	Necessity and Concerns Framework
HCS	Healthcare System
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
COREQ	Consolidated criteria for Reporting Qualitative research

LIST OF PUBLICATIONS

Original Peer-Reviewed Publications

This thesis comprises the following peer-reviewed journal publications. A short description of each journal is included in Appendix One

1. Srimongkon P, Aslani P, Chen TF. A systematic review of measures of medication adherence in consumers with unipolar depression. *Res Social Adm Pharm*. Published online 20 Feb 2018. doi: 10.1016/j.sapharm.2018.02.008.
2. Srimongkon P, Aslani P, Chen TF. Consumer related factors influencing antidepressant adherence in unipolar depression: A qualitative study. *Patient Preference and Adherence.* Published online 19 Sep 2018. https://doi.org/10.2147/PPA.S160728
3. Srimongkon P, Aslani P, Chen TF. The influence of society and the healthcare system on adherence to antidepressants: consumer perspective. A manuscript in preparation.
4. Srimongkon P, Aslani P, Chen TF. The development and validation of medication adherence conceptual framework in people with unipolar depression. A manuscript in preparation.

Peer-Reviewed Scientific Conference Presentations

The following abstracts resulted from the work described in this thesis and were presented at scientific conferences in Australia and internationally:

1. Srimongkon P, Aslani P, Chen TF. A systematic review of medication adherence measurements in unipolar depression. Presented at 74th FIP

World congress of Pharmacy and Pharmaceutical Sciences 2014 Conference; Bangkok, Thailand, 31 August - 4 September 2014.

2. Srimongkon P, Aslani P, Chen TF. Factors influencing patients' adherence to antidepressant medicines in unipolar depression: A qualitative study. Presented at the Australian Pharmaceutical Science Association (APSA) Conference; Hobart, Australia, 29 November - 2 December 2015.
3. Srimongkon P, Aslani P, Chen TF. A qualitative investigation of factors influencing adherence to antidepressants in unipolar depression. Presented at the International Social Pharmacy Workshop (ISPW) Conference; Aberdeen, Scotland, 19 - 22 July 2016.
4. Srimongkon P, Aslani P, Chen TF. Factors influencing medication adherence in unipolar depression: Exploring patients' views. Presented at the Pharmaceutical Care Network Europe (PCNE), 10th PCNE Working Conference; Bled, Slovenia, 1 – 4 February 2017.

Published abstracts

1. Srimongkon P, Aslani P, Chen TF. Factors influencing patients' adherence to antidepressant medicines in unipolar depression: A qualitative study. *Research in Social and Administrative Pharmacy.* 12:e24. DOI: https://doi.org/10.1016/j.sapharm.2016.05.061

ABSTRACT

Unipolar depression is a common mental disorder and is the leading cause of mental disability worldwide. Medication adherence is a complex process, particularly in people with unipolar depression. The signs and symptoms of depression can also contribute to non-adherence and it is a risk factor for non-adherence in other chronic conditions such as diabetes and HIV. The overall aim of the research presented in this thesis was to explore and examine issues pertaining to medication adherence in people with unipolar depression. To address the overall aim, the methods used in this research included a systematic review of published literature, semi-structured interviews with consumers, and a content validation study involving health care professionals. The ABC taxonomy which conceptualises adherence into three components—initiation, implementation, and discontinuation—was used as the framework for this research.

The major outcome for this research was the development and content validation of a depression-specific medication adherence framework, based on the literature, qualitative findings, and experience of the research team. It was designed as a guide for health care professionals to better understand the adherence process from the consumer perspective and to inform tailored interventions to facilitate adherence. The framework acknowledges the different nature of potential factors influencing medication adherence at the specific phases of medication taking. Key considerations included individual perceptions, personal experience/s, and the influence of people around them. The findings also highlighted the need for valid measures to evaluate adherence across the three phases of adherence. A standout measure with strong reliability and validity was not apparent. Hence, a range of different subjective and objective measures is recommended to assess medication adherence across the different phases of medication taking. The overall findings of this thesis can be applied in everyday practice to enhance medication adherence in people with unipolar depression.

THESIS OVERVIEW

This thesis is divided into five parts (A–E). An overview of the relationship between each of the parts is presented in Figure 1.

Part A of the thesis (Chapters One and Two) provides the background and overview of the concepts discussed in this thesis, including detailed methods of the research described in this thesis. Chapter One contains the overall framework of the thesis. It also provides a brief overview of the burden, scope, and consequences of medication non-adherence in unipolar depression, definition of adherence, adherence measures, factors influencing medication adherence in unipolar depression, and a medication adherence framework. Chapter Two describes the methods used in this thesis.

Part B of the thesis (Chapter Three) presents a systematic review of the measures of medication adherence in consumers taking antidepressant medicines for unipolar depression. This part identifies and evaluates the range of measures that have been used to assess medication adherence in the past two decades. These measures were investigated and categorized under the Ascertaining Barriers to Compliance (ABC) taxonomy or the ABC project[2], which focuses on three components of adherence: initiation, implementation, and discontinuation. This chapter also describes the evaluation of the psychometric properties of these measurements in order to facilitate selection of an appropriate measure(s) for the specific phases of adherence.

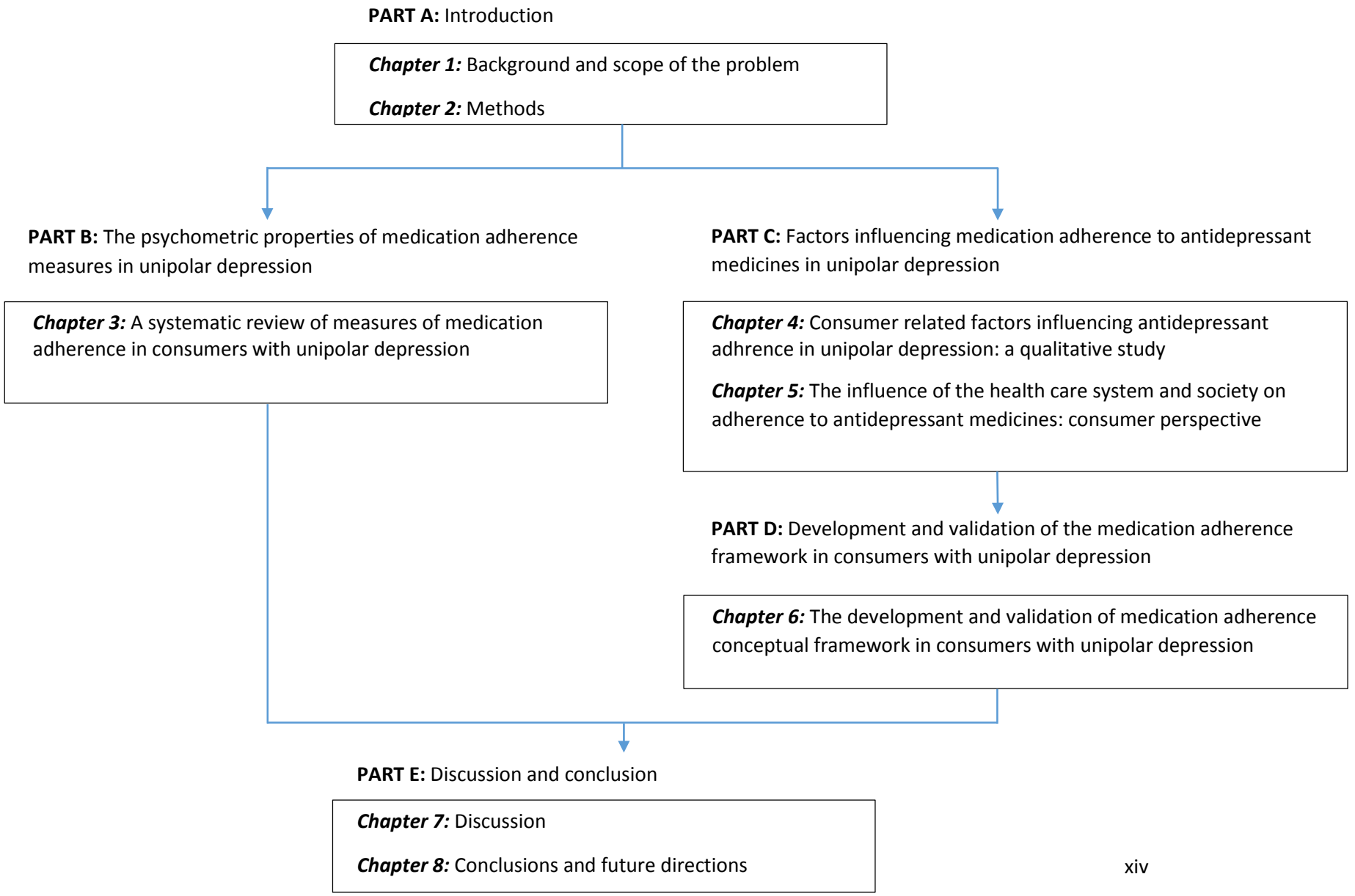
Part C of the thesis comprises two chapters (Chapters Four and Five) and investigates both facilitators of and barriers to medication adherence at specified phases from initiation to discontinuation, focusing on the consumer perspective. A qualitative approach was applied in order to elicit the consumers' experiences as well as their perceptions of antidepressant-taking behaviour. Themes were divided into four main categories: 1) consumer, 2) health care professionals, 3) health care system, 4) family and social-related factors. Part C elucidates potential factors which may influence medication-taking behaviour in individuals. The findings were used as the basis for

the next phase, that is, to create a medication adherence framework in consumers living with unipolar depression.

Part D of the thesis (Chapter Six) presents and content validates a new medication adherence framework for consumers with unipolar depression. It encompasses the entire process of adherence, including potential factors that influence medication-taking behaviour in unipolar depression from the initiation to the discontinuation phase. This framework will allow health care professionals to better understand antidepressant medication adherence in people living with unipolar depression. Hence, health care professionals can select specific strategies to address medication adherence at specific phases of medication adherence, to aid their patients in reaching their treatment goal. As previously mentioned, the proposed framework was created based on the findings from previous qualitative study (Chapters Four and Five), systematic review of the literature (Chapter Three), and the collective experience of the research team. A content validation using an expert panel was applied in order to evaluate face and content validity of the framework components.

Part E of the thesis (Chapters Seven and Eight) provides a general discussion of the overall findings of the studies described in this thesis. Chapter Seven discusses the main findings of the entire thesis, including study implications, strengths, and limitations. Lastly, Chapter Eight reports the conclusions for this research and provides a guide for future studies.

Figure 1: The overall view of thesis



PART A - INTRODUCTION

CHAPTER ONE: Background

1.1 Introduction

Poor adherence to medicines for the treatment of chronic conditions is a worldwide problem of striking magnitude, particularly as the burden of chronic conditions increases.[3] Non-adherence to prescribed medicines is recognised as a major barrier to successful treatment outcomes in people living with chronic conditions. Major consequences of non-adherence to long-term therapies are poorer health outcomes and increased health care costs.[3, 4] The enhancement of adherence to long-term therapies is one of the main strategies adopted by the World Health Organisation (WHO) towards the management of chronic conditions (particularly focusing on diabetes, depression, and HIV/AIDS) and health promotion worldwide.[5]

Unipolar depression or major depression is a well-established risk factor for non-adherence to medicines.[6, 7] Both current and remitted depression disorders have been proven as risk factors for medication non-adherence.[7] Consequently, poor adherence to antidepressant medicines among people with unipolar depression is relatively high.[6-10]

Depression is a common mental disorder that affects many people around the world and is a leading cause of work absence, poor health in general, and suicidal ideation.[11] It is a chronic condition which may require long-term treatment, and most treatment guidelines recommend a minimum course of antidepressant treatment for 6–9 months after the alleviation of depressive symptoms.[12-16] However, studies have shown the average length of antidepressant medicine to be less than 6 months with approximately 50–60% of patients ceasing their antidepressant medicine dosage within the first four months.[17-19] In certain cases, for example, people who have had three or more prior major depressive episodes or who have chronic major depressive disorder may require longer treatment periods or, occasionally, maintenance therapy to reduce the risk of recurrent depressive episodes.[12, 16] Non-adherence frequently

results in an increase in the dosage of medicines, which contributes to higher medical costs as well as increased risk of adverse drug events, misdiagnoses, unnecessary treatment, increased severity of disease, and death.[20, 21] The consequences of non-adherence are significant not only for individuals, but also in terms of the impact on the health system, such as overall health care costs.[21] Therefore, adhering to antidepressant therapy is a key solution to tackle and prevent these problems; it is also an important strategy to achieve desired therapeutic effects and potentially improve overall outcomes for patients with unipolar depression.[22]

Non-adherence to antidepressant medicines in people living with unipolar depression is complex and multifactorial. The symptoms of depression, such as lowered mood, excessive sadness, feelings of guilt or low self-worth, and pessimism, negatively impact adherence to antidepressant treatment. In addition, negative consequences in relation to antidepressant medicine consumption are frequently reported and can significantly decrease medication adherence. Adherence is a dynamic process and is influenced by numerous factors. Furthermore, medication adherence generally decreases as the duration of therapy lengthens.[23] Therefore, comprehensive strategies to address non-adherence to antidepressant medicines are important, particularly from the consumer perspective on taking medicines. Accurate evaluation of medication adherence is also critical. This requires precise measure(s) to assess medication adherence in order to assess medication-taking behaviour. The series of research studies described in this thesis focuses on the above-mentioned issues in accordance with the ABC taxonomy in which medication adherence is divided into three components: initiation, implementation, and discontinuation of medicines.[2]

1.2 Unipolar depression

Unipolar depression is a common mental illness that affects people around the world with unique symptoms which directly impact the mood or feelings of the affected persons; it is characterised by abnormal and persistent low mood, such as sadness, loss of interest or pleasure, feelings of guilt or low self-worth, pessimism, disturbed sleep or appetite, feelings of tiredness, and poor concentration and attention.[3, 24] Depending on the severity, depression may be categorised as mild, moderate, or severe.[12-16, 25] It can be long-lasting, ranging from months to years, and recurrent, substantially impairing an individual's ability to function at work or school or cope with daily life.[11, 24] In severe cases, depression can lead to suicide.[11, 24] The risk of becoming depressed is increased by poverty, unemployment, life events such as the death of a loved one or break up of a relationship, physical illness, and problems caused by alcohol and drug use.[11]

1.2.1 Epidemiology and burden of illness

Depression is a high prevalent chronic condition worldwide. In 2017, 322 million people globally were living with depression, which is approximately 4.4% of the world population.[11] Globally, the number of people with depression has increased by 18.4% over the period 2005–2015. It is twice as common among females (5.1%), compared to males (3.6%).[11] Depression is the single largest contributor to global disability, with 7.5% of years lived with disability (YLDs), and is ranked as the major contributor to death by suicide.[11] The consequences of depression are significant in terms of personal, clinical, social, and economic burden.[4] A 2016 systematic review indicated that people who were non-adherent to antidepressant medicines were more likely to experience increased risk of relapse and/or recurrence, emergency department visits, and hospitalisation rates, increased severity of depression, a decrease in response and remission rates, and an increase in healthcare utilisation and charges.[4]

In Australia, mental disorders, including depression, are the third largest disease group, after cancer and cardiovascular diseases. Mental health contributed an

estimated 12.1% of the total burden of disease in 2011, resulting in significant disability and morbidity.[26] The National Survey of Mental Health and Wellbeing reported that almost half the Australian population aged 16–85 years (45%, which equates to 8.5 million people based on population data in 2015) experience at least one mental health condition, including unipolar depression, at least once in their lifetime.[27] The mean age of diagnosis of unipolar depression is 27 years, but 40% have first episode by the age of 20 years.[25] Over 80% of those affected by depression experience at least two episodes in their lifetime.[25]

1.2.2 Antidepressant treatment in unipolar depression

Antidepressant medicines are often considered the best treatment option for unipolar depression, particularly in moderate to severe depression, and are recommended as an initial treatment choice for patients with mild to moderate depression.[12, 13, 24, 28] The goal of achieving adherence with antidepressants is to treat depressive episodes with full functional recovery, prevent relapse, and decrease risk of suicide.[25, 29] Some clinical practice guidelines recommend the following three phases of antidepressant treatment: acute, continuous, and maintenance.[12, 13, 16, 30-32]

For the acute phase, the aim of treatment is to induce remission of the major depressive episode and achieve full recovery to the patient's baseline level of functioning.[12, 13] In this phase, a range of treatment options are available, such as pharmacotherapy, depression-focused psychotherapy, a combination of medicines and psychotherapy, or other somatic therapies such as electroconvulsive therapy[2], transcranial magnetic stimulation (TMS), or light therapy.[12, 25] The selection of treatment is influenced by clinical features (e.g. severity of symptoms, presence of co-occurring disorders, or psychosocial stressors) as well as other factors (e.g. patient preference and prior treatment experiences).[12, 25] The first-line antidepressants recommended for the acute phase of the treatment in Australia are selective serotonin reuptake inhibitors (SSRIs) such as citalopram, escitalopram, fluvoxamine, and fluoxetine), noradrenergic and specific serotonergic antidepressants (NaSSAs)

such as mirtazapine, mianserin, noradrenaline -dopamine reuptake inhibitors (NDRIs) such as bupropion, noradrenaline reuptake inhibitors (NARIs) such as reboxetine, and melatonin agonist (agomelatine). The second-line treatments include tricyclic antidepressants (TCA) such as amitriptyline, clomipramine or serotonin norepinephrine reuptake inhibitors (SNRIs) such as desvenlafaxine and venlafaxine are suggested.[25]

The other treatment guidelines such as the American Psychiatric Association guideline (APA guidelines 2010)[12] and the American College of Physicians guidelines (ACP clinical practice guidelines 2008)[16] recommend SSRIs, SNRIs, and selective serotonin and noradrenaline reuptake inhibitors (SSNRIs) as the first-line medicines owing to their similar efficacy with lower toxicity in overdose when compared to tricyclic antidepressants and monoamine oxidase inhibitors. However, other factors such as adverse effect profiles, cost, safety profile, history of prior medication treatment, and patient preference are important in the initial selection of antidepressant medicines, which health care professionals must consider.[12, 16]

During the acute phase, at least 4–8 weeks of treatment is needed in order to evaluate adequate response to antidepressant therapy.[12, 13] In cases of minimal or no improvement in symptoms, an additional 4–8 weeks of treatment is recommended for investigation and changes to the treatment plan.[12, 13]

In the continuous phase, the aim is to reduce the risk of relapse, with people who have been treated successfully during the acute phase recommended to continue treatment for 6–9 months.[12, 13, 16, 30-32] In this phase, systematic assessment of symptoms, adverse drug reactions (ADRs), adherence, and functional status is essential.[12] In addition, it is crucial to monitor both remission and signs of possible relapse.[12, 16]

Lastly, for the maintenance phase, in certain cases, people with two or more previous episodes of depression, longer treatment (one or more years or even for lifetime) may be required in order to reduce the risk of early relapse.[16, 32, 33] One study

reported a relapse risk of 25% in the first year after remission, 42% after 2 years, 60% after 5 years and 50–85% after 15 years.[33] Hence, regular consumption of antidepressant medicines is crucial for both successful treatment and prevention of recurrent episodes. Maintenance therapy is recommended in people with additional risk factors for recurrence, such as the presence of residual symptoms, ongoing psychosocial stressors, early age at onset, and family history of mood disorder.[12] A full therapeutic dose of antidepressant medicine which produces symptoms remission in the acute and continuation phases should be continued throughout the maintenance phase.[12]

Although generally well tolerated, all antidepressant medicines have been known to have negative consequences, including intolerable adverse events which are well-known leading causes of non-adherence.[34-39] A recent systematic review and network meta-analysis (2018), which included 522 trials comprising 116,477 participants, reported that all antidepressants were more effective than placebo.[40] Agomelatine, amitriptyline, escitalopram, mirtazapine, paroxetine, venlafaxine, and vortioxetine were more effective than other antidepressants; whereas fluoxetine, fluvoxamine, reboxetine, and trazodone were the least efficacious antidepressants.[40] For acceptability (treatment discontinuations due to any cause), agomelatine and fluoxetine were associated with fewer dropouts than placebo, while clomipramine was worse than placebo.[40]

1.3 Medication adherence in the treatment of unipolar depression

1.3.1 Overview of adherence terminology and definitions

Over the past four decades, a variety of terms have been used interchangeably to describe medication-taking behaviour among patients, such as *'compliance'*, *'adherence'*, *'persistence'*, and *'concordance'*.[2, 41, 42] Although it is noteworthy that these terms have occasionally been used with slightly or significantly different meanings, particularly when considering the nature of professional relationships

between patients and health care professionals,[42] this has contributed to much confusion and misunderstanding in the literature.

In general, *compliance* refers to the notion of the patient being passively obedient to the physician's instruction, while *adherence* has a greater sense of cooperation between the prescriber and patient.[2, 41-45] *Concordance* focuses more on the therapeutic alliance between the physician and patient in negotiating a process, with equal respect, and is occasionally incorrectly used as a synonym for compliance and or adherence.[42, 43, 45] *Persistence* reflects the duration of time from initiation to discontinuation of therapy.[41]

'*Medication adherence*' is the most widely used term that refers to medication-taking behaviour. It is often a key to successful treatment, particularly in chronic conditions. The most cited definition of adherence, proposed by the WHO, defines it as '*the extent to which a person's behaviour—taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider'.*[3]

Many patterns of non-adherence have been documented. The WHO classifies non-adherence to medicine into two main types: *'primary non-adherence'* and *'secondary non-adherence'*.[3] *Primary non-adherence* refers to patients who fail to fill the prescription. *Secondary non-adherence* refers to patients not taking their medicines as intended after they have had their prescriptions dispensed; this behaviour can range from not following the frequency or dose instructions of the prescription (e.g. skipping doses, taking medications at incorrect times or in incorrect doses, taking more than prescribed), forgetfulness, errors of purpose, or use of inadvertent combinations.[3, 8, 46-49]

Secondary non-adherence can be categorised into many other types, such as non-persistence or non-conformance, and intentional and unintentional non-adherence. Non-persistence or non-conformance occurs when a person decides to stop taking a medication after starting it, without being advised by a health care professional to do

so.[8, 46] Intentional non-adherence can be considered as a process in which the person actively decides not to use the treatment or follow treatment recommendations.[42] It is usually related to a personal decision-making process, in which people with depression weigh the pros and cons of their treatment plan.[42] Intentional non-adherence arises from the beliefs, attitudes, and expectations that influence peoples' motivation to begin and persist with the treatment regimen.[42, 45] On the other hand, unintentional non-adherence refers to unplanned behaviour which is less associated with beliefs and level of cognition when compared with intentional non-adherence.[42] Unintentional non-adherence can occur due to capacity and resource limitations which prevent people from implementing their decision to follow treatment recommendations (e.g. problems of accessing prescriptions, cost, competing demands, etc.) and occasionally involves individual constraints (e.g. problems remembering doses etc.).[48]

In 2012, a European consortium of researchers in the field of medication adherence conducted the ABC project which proposed a new taxonomy on medication adherence in order to identify the different conceptual approaches to adherence research.[2] They reported *'adherence to medication'* as '*the process by which patients take their medications as prescribed, composed of initiation, implementation and discontinuation. Initiation occurs when the patient takes the first dose of a prescribed medication. Implementation is the extent to which a patient's actual dosing corresponds to the prescribed dosing regimen, from initiation until the last dose. Discontinuation marks the end of therapy, when the next dose to be taken is omitted and no more doses are taken therafter'.*[2] Figure 2 illustrates the definition of the adherence process endorsed by the ABC project.[2]

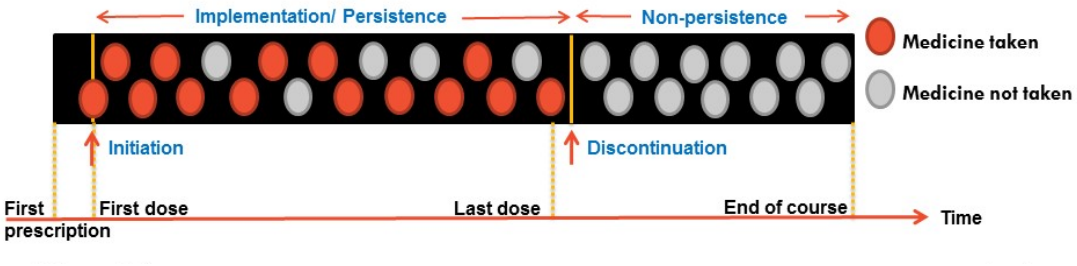


Figure 2: The process of adherence to medication and definition of medication adherence endorsed by the ABC project (2012),[2] adapted from the original article.

The ABC framework is the first taxonomy that endorses the conceptual foundation of medication adherence based on behavioural and pharmacological science which supports quantifiable parameters.[2] The framework is suitable for our research, as it provides a transparent taxonomy which makes a clear distinction between processes that describe actions through established routines. Therefore, it was adopted as the main conceptual framework for studies conducted in this thesis. Specifically, this framework provides a clear delineation for a more detailed and nuanced understanding of consumers' medication-taking process. This framework may enable a better and more detailed understanding of medication-taking in consumers with depression from the consumer's perspective, a necessary consideration when strategies to improve medication adherence are being implemented.

1.3.2 Scope of non-adherence to antidepressants in unipolar depression

Low adherence and persistence to antidepressant medicines in people with unipolar depression are commonly reported. At the initiation of treatment, only a limited number of studies pertaining to antidepressant adherence was found. One study in the United States reported that 5% of participants (40 of 765 patients) have filled but never initiated antidepressant medicine.[38] Another study reported that one-third of patients did not fill their antidepressant prescription for six months following the receipt of their first prescription (approximately 1,620 of 4,860 patients), with the

rates being higher among those prescribed tricyclic antidepressants compared with newer generation antidepressant medicines.[50] A US database study has also shown that adherence to antidepressant medicines has decreased over time (41% at 3 months, 31% at 6 months, 24% at 9 months, and 21% at 12 months respectively).[22] For the maintenance phase of recurrent depression, adherence rates have been reported to be between 39.7% to 52.7%, when assessed with the Morisky, Green, and Levine Self-reported Medication-taking Scale (MGLS).[51]

Early discontinuation rates occur during the first month of therapy, with approximately 25% of people with unipolar depression ceasing their antidepressant medicine without informing their physician.[17, 52] A recent study stated that 28% of patients (6,952 of 24,817 patients) discontinued their antidepressant medicine after receiving their first prescription.[53] Overall, approximately 50–60% of patients discontinued their antidepressant medicine within the first 10–24 weeks of treatment, while the average length of treatment is commonly reported as less than six months.[17-19, 54, 55] Non-adherence to antidepressant medicine was varied among different types of antidepressant medicines (according to their pharmacological properties), severity of depressive symptoms, duration of episode, as well as the inconsistency of adherence/non-adherence rate obtained from using different measures of medication adherence.[35, 56-66]

Depression is a well-known risk factor to non-adherence.[6, 7] People with depression reported three times greater non-adherence (odds ratio) than non-depressed patients, and 1.76 times higher than those with asthma, coronary heart disease, diabetes, hyperlipidaemia, or hypertension.[6, 67] Being depressed impacts adherence to chronic treatment regimens irrespective of disease and, therefore, depression can have an added impact on non-adherence to antidepressant medicines. Furthermore, worsening adherence can worsen depression, which in turn can worsen adherence, and then the cycle repeats itself.

The consequences of non-adherence to long-term therapy include poorer health outcomes and increased healthcare utilisation and charges.[3, 4] Medication non-

adherence in depression has led to unnecessary switches in antidepressant medicine, unnecessary instructions to increase doses, initiation of unwarranted adjuvant treatments, increased risk of relapse and/or recurrence, and misclassification of treatment resistance.[68] In addition, it is associated with an increase in emergency department visits and hospitalisation.[4]

1.4 Measures of medication adherence in unipolar depression

In order to evaluate medication adherence in people with unipolar depression, the percentage of prescribed doses of the medicine actually taken by the person over a specified period (adherence rate) is usually reported.[10] In general, good adherence has been defined as an adherence rate greater than or equal to 80%.[69, 70] It may be estimated by the objective measure of pill counts: [No. of pills absent in time X/ No. of pills prescribed for time X] x 100].[70]

The methods available to assess medication adherence can be categorised into 1) direct or indirect measures[44, 71] and 2) objective or subjective measures.[72, 73] Direct measures include measurement of the medicine or its metabolite concentration in body fluids, such as blood or urine and the presence of biological markers which indicate a patient's medication taking behaviour.[73] Although direct approaches are one of the most accurate measures of medication adherence, they are less useful in practice due to their cost, their intrusive nature, and because they may be technically demanding, time consuming, and impractical.[17] Most of the currently available tools to evaluate medication adherence in clinical settings are indirect measures of adherence (e.g. pill counts, patient self-report, clinical response, Medication Event Monitoring System (MEMS), and medical record or prescription refill records).[71] Indirect measures like specifically standardized adherence questionnaires are generally considered more practical due to their ease of administration, affordability, and relatively unobtrusive approach.[74, 75] Furthermore, a number of patient self-reported measures include specific advantages such as the ability to provide information on attitudes and beliefs regarding medications (Beliefs about Medicines Questionnaire or BMQ by Horne[76]) and the ability to distinguish between intentional and unintentional non-adherence (the MGLS[77]).[74, 75] As beliefs regarding particular health conditions and its treatment are closely linked to medication-taking behaviour,[76] the identification of the intention to take medicines can differentiate causes of non-adherence and, therefore, inform the use of different interventions.[74] For this reason, apart from the validity and reliability of the tools, the selection of an

appropriate type of adherence measure is another important consideration. At the same time, 'questioning' the patient can be susceptible to misrepresentation, depending on the willingness to disclose information, which can influence response accuracy as well as validity.[44, 75] Further, it can also overestimate a patient's medication adherence as well as the overestimation from patient self-report.[44]

Objective measures of medication adherence may provide a higher level of reliability when compared to subjective measures. Objective measurements include drug metabolite and biological markers, MEMS, pill counts, prescription refill, and data from claims databases, although each type of measure has both pros and cons. MEMS is often accepted as an accurate measurement; however, the system is expensive and impractical for everyday use. It requires device installation, connection, and data processing. In addition, it is generally only used for selected dosage forms and not for others such as patches, drops, creams, etc. Pill counts do not provide important information on dose timing and patterns of missed dosages or drug holidays.[3, 44] Further, pill counts are time-consuming, labour-intensive, and less accurate when compared with other measures.[58] Pill counts may not reflect adherence if a patient suspects that they are being monitored, as they may simply throw the pills away to lower the pill count. However, pill counts are useful, particularly if an "unannounced" home visit is made. Prescription refill and claims data provide accurate measures of dispensing in a closed pharmacy system (e.g. a health maintenance organization or countries with universal drug coverage and linked dispensing systems) and are useful for long-term investigations.[44] They can be used to check when prescriptions are initially filled, refilled over time, and prematurely discontinued. Inaccuracies clearly occur when databases are incomplete. Prescription refill and claims data do not directly reflect whether or not a medicine has been used, rather, they indicate whether or not a medicine has been dispensed.[44]

Despite the various methods used to evaluate medication adherence, there is no universally accepted gold standard measure.[3] Ideally, a *'gold standard'* measure would be 1) direct, 2) objective, and 3) unobtrusive.[3] Currently, MEMS, is recognised

as a more sensitive measure; however, it cannot be 'proven' that the patient has taken the medicine with the correct dose or at the correct time.[44] Consequently, multiple measures are typically recommended to evaluate medication adherence in practice.

To sum up, measurement of medication adherence provides useful information regarding the estimation of a patient's actual medication-taking behaviour and is beneficial to health care professionals when monitoring treatment outcomes and developing and modifying treatment plans. In order to assess accurate adherence rate, health professionals should select measurement(s) with good reliability and validity to ensure the precision and accuracy of obtained results. In addition, adherence measures may be better suited to measure a particular phase or phases of adherence (e.g. initiation, discontinuation).[71]

1.5 Factors influencing medication adherence in unipolar depression

Numerous factors, both positive and negative, influence medication adherence in people with unipolar depression. The WHO (2003) classified these factors into five dimensions: social and economic factors, health care team and system-related factors, condition-related factors, therapy-related factors, and patient-related factors.[3] Since the ability of people to follow their treatment plan is frequently compromised by multiple factors, tailored-interventions with multidimensional aspects should be implemented in order to address non-adherence problems to enhance adherence to medicines.[3]

While the complexity associated with taking medicines on a routine basis by people with depression represents a good starting point, other factors should also be considered. These include the influence of health care professionals, carers, and society in general as well as the consequences of antidepressant use (e.g. potential adverse effects and the effectiveness of the selected treatment). Furthermore, it is

noteworthy that some factors may have a positive influence on adherence in certain individuals but a negative influence on others and vice versa.

1.5.1 Facilitators of medication adherence in unipolar depression

Common factors associated with good adherence include a positive attitude towards antidepressant medicine, previous experiences, and vicarious experiences of depression or treatment, and welcoming positive effects of antidepressant medicines (i.e. effectiveness of antidepressant medicines).[20, 35, 55, 62, 78, 79] Other factors which are associated with increased adherence in unipolar depression are sufficient information and knowledge of depression and antidepressant medicines provided by health care professionals, accessible health care professionals, and family support with positive attitude towards antidepressant treatment.[38, 61, 62, 80 36, 37, 60, 81] These factors are depicted in Table 1.

1.5.2 Barriers to medication adherence in unipolar depression

Many studies have reported that feeling better and unbearable ADRs are the two most common barriers to ongoing adherence, thereby contributing to early discontinuation of antidepressant use.[17, 39 35-39, 55, 64, 78, 81, 82] Sexual dysfunction, sleep disturbances, and weight gain were perceived to be of most concern.[82] In addition, forgetfulness, a common unintentional reason for non-adherence, was also found to lead to omission of doses.[29, 39, 83] Self-stigma, a well-known barrier to medication adherence, is a significant factor with negative correlation to good adherence.[65, 84-86] From the long-term viewpoint, inadequate adherence to treatment may be related to beliefs and perceptions regarding antidepressant medicines rather than its undesirable effects.[23]

Unsatisfactory interactions between health care professionals and people with unipolar depression, including a lack of health care professional attention to the consumer's concerns, may also decrease adherence to antidepressant medicines.[66, 78, 80] Difficult access to physicians or to having medicines dispensed, over-prescribing on the part of the physician, dissatisfaction with treatment, low income, low

socioeconomic status, and severity of depression were also found to be associated with poorer adherence or persistence.[23, 35, 39]

In terms of early discontinuation of antidepressant treatment, one significant reason perceived by people with unipolar depression was the lack of perceived need for antidepressant medicines once they felt better.[39, 82] The absence of a support network, particularly family support, was perceived to be a potential factor to non-adherence as well as poor lifestyle factors and unstable living conditions.[61, 82] A summary of factors influencing non-adherence are presented in Table 1.

Table 1 Facilitators of and barriers to antidepressant adherence in unipolar depression

Dimensions	**Facilitators of antidepressant adherence**	**Barriers to antidepressant adherence**
1. Factors relating to health care professionals and health care system		
1) Health care professionals (HCPs) influence on medication adherence	• HCPs role as a facilitator[87]	• Multiple prescribers[36]
2) Relationships between HCPs and patients	• Good relationship[17, 35, 62, 78, 80, 81] • Rapport established[80] • Positive HCP-patient interaction[66]	• Lack of attention to the patient[80] • Apparent dismissive reaction[80] • Superficial or glib responses from doctors to patients[80] • Unsatisfactory interaction with HCPs[78] • Disconnected relationship[78] • Patient fear of HCPs[36] • Negative HCP-patient interaction[66]
3) Support from HCPs/ helpfulness of HCPs visits	• Rating general practitioners (GPs) visits as moderately to extremely helpful[60] • Good support from HCPs[37, 80]	
4) Interactive communication and open dialogue between HCPs and patients	• Communication[60, 78, 88] • Two-way communication/ being listened too[80] • Shared decision-making[80] • Early discussion[62]	• Problems communicating with HCPs[36] • Poor provider-patient communication[44] • Patient-physician discordance[44]
5) Adequate information about depressive treatment from HCPs	• Adequate information[38, 62, 80] • Patients are expected to be informed about medicines before treatment initiation[78]	• Required more information from their doctors before taking the first dose[80] • Inadequate knowledge about antidepressant medicine and its use[44]

Dimensions	Facilitators of antidepressant adherence	Barriers to antidepressant adherence
	• Sufficient information form HCPs[37, 81] • Knowledge about the causes of depression and mechanism of antidepressant medicines[37] (and other relevant issues[51])	
6) Adequate time to see the doctor/ length of GPs visit	• GP visits longer than 20 mins[60] • Sufficient time during the consultation[17, 78, 80] • No obligation to rush[62]	• Insufficient time to see the doctor/ in a rush[60]
2. Factors relating to the health care system		
1) Accessibility to HCPs/ Access to practice	• Accessible[36, 60]	• Difficult access[44, 61, 82]
2) The continuity of care in public system/ health system	• Continuity of care[60]	• Lack of continuity of care[60]
3) Management issue	• Frequent clinic visits[36]	• Long waiting time at the clinic[36] • Frequent medication refills[36] • No supply of medications[36]
3. Factors relating to patients and carers		
1) Patient self-motivation	• 'will power'[62] • Wish for complete recovery[36] • Fear of relapse[36] • The ownership of the decision[37]	
2) Acknowledgement of their depression condition	• Accepted their health conditions[78]/diagnosis[62]	• Non-acceptance of the diagnosis[78]
3) Previous experience of antidepressant treatment	• Previous experience of antidepressant treatment[35, 39, 78]	• Unfavourable experiences towards antidepressant treatment*

Dimensions	**Facilitators of antidepressant adherence**	**Barriers to antidepressant adherence**
	• Personal or family experience of antidepressant medicine, frequently negative[62]	
4) Family support	• Family's positive attitude toward medication[61] • Family support (family/spouse)[36] • Cultural beliefs[36]	• Family's negative attitude toward medication[61] • Cultural beliefs[36] • Lack of family support[61, 82]
5) Peer support	• Support from friends[36] • Trusted friends[62] • Social support[36, 81, 89] • Similar experience sharing/ support from people with depression[79]	
6) Patient regular activities	• Habit such as taking with a meal[36]	
7) Stigma about depression/ antidepressant medicines		• Stigma related to perceived drug dependency[80] • Strong self-stigma attached[80] • 'Felt' Stigma[79]; refers principally to the fear of discrimination on the basis of perceived unacceptability or inferiority, as opposed to actual instances of discrimination. • Self-stigma[35, 65, 85] • Stigma associated with both having depression and taking antidepressant medications[82]
8) Stigma in society		• Societal stigma[36, 39] • This type of stigma was connected to the view that psychotropic medications would affect cognitive functions. It was

Dimensions	Facilitators of antidepressant adherence	Barriers to antidepressant adherence
		based on actual discriminatory remarks by others and can therefore be interpreted as 'enacted' stigma.[79] • Public opinion about depression and its treatment reveals reluctance to consult practitioners about depressive symptoms, and evidence that counselling is favoured over antidepressant treatment.[62]
9) The ability to self-manage on medication taking	• Self-help practices[60]	
10) Concern about the effect of stopping antidepressant therapy	• Experiencing symptoms worsening when they weren't regularly taking antidepressant[39] • Fear of withdrawal symptoms[87] • Fear of relapse[87] • Uncertainty about what would be like without antidepressants[87]	
11) Clinical improvement/ feeling better	• Welcoming effects of antidepressant[78] • Recovery[62, 79] and positive treatment outcome[35] • Early treatment response[81] • Feeling better[55]	• Lack of therapeutic response[38] • Lack of efficacy[36, 37, 39, 55, 66] • Feeling better[17]
12) Patients who have trust in their HCPs	• Trust in HCPs[36, 78, 80] , Trust in GPs[60] • They believe that 'doctor knows best'[80]	
13) Knowledge about depression and	• Knowledge[78, 80]	• Lack of knowledge about the use of antidepressant,

Dimensions	Facilitators of antidepressant adherence	Barriers to antidepressant adherence
antidepressant medicine		the effect of antidepressant[36, 82]
14) Forgetfulness		• Forgetfulness[29, 36, 39, 83] • Including: having a busy schedule, being away from home, simply forgetting to take their antidepressant[36]
15) Perceive drug dependency and addiction		• Fear of drug dependency and/or addiction[80] • Fear of drug dependence[36, 55] (erroneous belief, misconceptions about depression and/or antidepressant)[36]
16) Patient perceptions and beliefs about depression	• Positive perceptions and beliefs about depression[78, 80]	• Negative perceptions and beliefs about depression[78, 80]
17) Patient concerns about sense of self while using antidepressant medicines		• Sense of self,[80] not feeling like oneself[39] • Worries about the feeling 'fluffy' or 'out of control' when using antidepressant[80] • Sense of self control[55] • Self-reliance[39]
18) Patient beliefs about the need for antidepressant	• Beliefs about the need for antidepressant[66, 78, 80] • Awareness about the need to take antidepressant[36]	• Uncertainty about the benefits of and the need for antidepressant[87]
19) Attitudes towards antidepressant	• Positive attitudes towards antidepressant[37] • Beliefs about efficacy of antidepressant[78] • Belief/ perception[16, 36, 62, 63, 90] • Faith[81]	• Negative attitudes such as a dislike for the pill[36, 37]

Dimensions	Facilitators of antidepressant adherence	Barriers to antidepressant adherence
	• Beliefs and attitudes towards depression and antidepressant[35] • Attitudes toward antidepressant[35, 78, 81]	
20) Reminders	• Such as using pillboxes, reminder form family members, keeping medications in visible places[36]	
4. Demographic and socioeconomic factors		
1) Level of education	• Higher level of education predicted the correct intake of antidepressant[81] • Education level[61]	
2) Cost of antidepressant medicines		• Cost of antidepressant[36, 44]
3) Benefits as main source of income	• Benefits as main source of income[60]	
4) Family income		• Low family income[35]
5. Disease and medicine factors		
1) The severity of depressive symptoms	• Severity of depression[60, 62-66]	• Severity of depression[60, 62-66]
2) Inherent of depressive symptoms	• Diagnosis of depression[69] • Clinical features of depression[35]	• Clinical features of depression[6, 7, 9, 35, 82]
3) Chronic conditions that require long-term treatment		• Chronic condition of depression which requires long-term treatment[60, 78]
4) Recurrent episode		• Recurrent depressive episode[60, 61]
5) Comorbidity		• Comorbidity[35, 36, 60, 65, 80, 90-92] • Including alcohol dependence[7, 36] and substance abuse[90]
6) Length of depressive illness		• Length of previous illness[62]

Dimensions	**Facilitators of antidepressant adherence**	**Barriers to antidepressant adherence**
		• Longer onset of depression[81]
7) Category of antidepressant used	• Category of antidepressant used[60]	• Category of antidepressant used[60]
8) Other medicines used	• Polypharmacy[69]	• Pill burden[36]
9) ADRs		• Experiencing ADRs[17, 35-39, 55, 64, 78, 81, 82] • Concern about the potential ADRs[39, 78, 80] • Fear of ADRs[44]
10) Medication duration of treatment		• Medication duration of treatment[36, 61] • Long term drug regimens[44]
11) Medication onset	• Pharmacological factors[35]	• Pharmacological factors[35]
12) Complex regimen		• Complex regimen[44]
13) The absence of pathology		• Absence of personality pathology[65]

1.6 Medication adherence frameworks

In the past two decades, many strategies have been implemented to improve medication adherence in people living with unipolar depression, such as behavioural interventions, educational interventions, and multifaceted interventions.[93] In order to develop effective approaches, there is a need for clear understanding of the entire process of adherence/non-adherence to antidepressant medicine. A conceptual framework is a tool that has been extensively used to explain the phenomena that are linked to multidisciplinary bodies of knowledge, and has been adopted to better understand and enhance adherence to medicine in many conditions such as diabetes and heart failure.[94, 95] A few frameworks have been developed for unipolar depression, but none of them has been specific to medication adherence.[96-103]

1.6.1 Conceptual frameworks and theoretical models

The current usage of the terms '*conceptual framework'* is not precise and occasionally has been used erroneously.[104] A conceptual framework is a logical structure of a theory or model in a discipline.[105, 106] Jabareen (2009) has defined a conceptual framework as '*a network or a plane of interlinked concepts that together provide a comprehensive understanding of a phenomenon or phenomena'.*[104] The concepts that constitute a conceptual framework support one another, articulate their respective phenomena, and establish a framework-specific philosophy.[104] Conceptual frameworks usually denote a structure, overview, outline, system, or plan comprising various descriptive categories.[107] The relationships among these categories are presumed to account for the phenomenon.[107] Generally, the framework describes the phenomena by fitting them into a set of categories.[107] Consequently, conceptual frameworks have been extensively implemented in various disciplines to elucidate relationships between concepts of interest (such as in business and marketing, politics, tourism management) as well as in health sciences, including medication adherence in specific conditions.[94, 95, 108-114] For unipolar depression, conceptual frameworks have been applied to improve the quality of treatment.[96, 98, 99, 101-103, 115]

However, no framework has been specifically created to address the non-adherence problem in people with depression.

A model typically involves a deliberate simplification of a phenomenon or a specific aspect of a phenomenon.[107] It is closely related to theory and can be described as theory with a more narrowly defined scope of explanation.[107] Many theoretical models are commonly implemented to explain health behaviours, including adherence to medicines. For example, the Health Belief Model (HBM), theory of planned behaviour, transtheoretical model of behaviour change etc.[47, 109, 116-118] However, none of the existing conceptual frameworks or behavioural models are specifically focused on depression. The strengths and limitations of these models when they were employed to enhance medication adherence is presented in Table 2.

Table 2 Strengths and limitations of the theoretical behavioural models that have been commonly applied to improve medication adherence in chronic diseases.[118-122]

Model	Strengths	Limitations
Health Belief Model (HBM)	It is able to explain why people fail to undertake preventive health behaviour, investigating based on the assumption that patients weigh the benefits versus the barriers to treatment when deciding whether or not to adhere to medications. Six components were conceptualized: perceived barriers, perceived benefits, perceived susceptibility, perceived severity, cues to action, and self-efficacy.[118, 119]	This model is limited to health-risk behaviours and as such cannot help the researchers understand the environmental, social and personal factors that influence specific health conditions.[118] Also, it has low predictive capacity of the variables.[120] Lack of clear rules of combination and relationship between the individual variables is indicated.[120]
Theory of planned behaviour	The efficacy in explaining substantial amounts of variance in both intentions and behaviour in health domains from a relatively parsimonious set of predictors.[122]	The manipulations based on the theory lead to substantial changes in behaviour and the gap between intentions and behaviour.[122]
Self-regulatory model	It accounts for both emotional and cognitive influences in explaining patient's behaviour.[119]	Little supporting data and difficult to use in studies because of multivariate nature.[119, 121]
The transtheoretical	It presents behaviour change as a series of stages, therefore, it is	It ignores social context of change, i.e., socioeconomic

Model	Strengths	Limitations
model of behaviour change	important to tailor approach to behaviour change by first identifying an individual's stage.[119, 123]	status differentiation between the stages can be arbitrary, because there are no set criteria to determine an individual's stage of change.[119]
The cognitive model	Adherence is directly related to an individual's attitudes, beliefs, and expectations regarding treatment. This model focuses on the conscious, intentional decision-making.[119, 121]	It does not adequately address the automatic, habitual behaviours.[119, 121]

1.6.2 Conceptual framework and theoretical model used in medication adherence

Current frameworks pertaining to medication adherence have been designed to address non-adherence problems in non-specific conditions. Some of them have been adopted to explain non-adherence to antidepressant medicines in unipolar depression such as the Capability, Opportunity, and Motivation (COM-B) model of behaviour and the necessity-concerns framework (NCF).[110, 116, 124, 125]

The COM-B is a comprehensive framework that focuses on behaviour change; therefore, it is applicable in medication-taking behaviour. The framework comprises three main components—capability, opportunity, and motivation—which impact the performance of the behaviour and, hence, can provide explanations for why a recommended behaviour has not been implemented.[116, 126] In light of medication non-adherence, the COM-B framework helps to describe a wide range of factors which have been identified to explain non-adherence to medication as well as identify appropriate change techniques to improve adherence.[116] However, because of the complexity of the non-adherence process, the COM-B framework does not clearly explain or classify all factors pertaining to non-adherence in certain circumstances such as depression and substance abuse.[116] This indicates the need for a more specific framework for people with depression.

The approach to medication adherence has shifted over recent years, from a focus on the role of the doctor to patients' beliefs, motivation, and planning abilities.[116, 127] Consequently, there is a need for a nuanced medication adherence framework for use in practice: in other words, a medication adherence framework that can be adopted to everyday practice which adopts a patient-centred approach.[116, 128] One such approach is the NCF. The NCF has been used extensively and has proved to provide a conceptual framework for understanding patients' perspectives on prescribed medicines.[110, 124, 125, 129] The NCF highlights patients' beliefs regarding medicines which influence medication adherence.[110, 125, 129] It indicates that patients

weigh up their perceived personal need for treatment against their concerns regarding negative consequences. Essentially, patients are more likely to adhere to their treatment when perceived need exceeds perceived harm. In other words, people who were less sceptical (high necessity and low concerns) were more likely to adhere to antidepressant medicines.[110, 125]

Although the NCF has been widely used, its focus is on the belief aspect. As previously mentioned, medication adherence is a multidimensional behaviour which requires a multifaceted approach, hence the adoption of a single concept may not be adequate to address other aspects of medication non-adherence for the entire process of adherence.

Although existing frameworks have been created to address medication non-adherence, they do not necessarily directly map to conditions such as depression. Nor do they directly consider the dynamic nature of medication-taking, which can change over time.[116, 130-136] Even though some frameworks have identified a range of explanatory factors pertaining to medication-taking behaviour, they do not explicitly identify relevant details in the adherence process, which is crucial for health care professionals when creating tailored interventions as the most effective strategy to enhance medication adherence in chronic diseases, including unipolar depression.[93]

1.7 Aims and objectives

In order to achieve a successful treatment outcome in unipolar depression, it is crucial to ensure that consumers are constantly and correctly taking their antidepressant medicines. Because adherence is a multidimensional process in which various factors may influence an individual's medication taking behaviour, it is important to provide a framework for health care professionals to better understand medication-taking behaviour in consumers with depression.

The overall aim of the research described in this thesis was to explore and examine issues pertaining to medication adherence in people living with unipolar depression.

To address these research aims, three key steps of investigation were conducted (Figure 1: The overview of the thesis). The specific objectives of each step are reported below:

Part B: The psychometric property of medication adherence measures in unipolar depression.

1) To systematically identify and evaluate the range of medication adherence measures used to assess medication adherence in a specific phase (i.e. initiation, implementation, and discontinuation), in consumers taking antidepressant medicines for unipolar depression.
2) To evaluate the psychometric property of adherence measures used in unipolar depression.

Part C: Factors influencing medication adherence to antidepressant medicine in unipolar depression.

1) To explore the strategies or positive influencing factors which promote medication adherence in three phases of adherence (i.e. initiation, implementation, and discontinuation) in unipolar depression from the consumer perspective.

2) To explore the barriers or negative influencing factors which reduce medication adherence at three phases of adherence (i.e. initiation, implementation, and discontinuation) in unipolar depression from the consumer perspective.

Part D: Development and validation of the medication adherence framework in consumers with unipolar depression.

1) To develop and propose the conceptual framework that illustrates potential factors influencing medication-taking behaviour in consumers with unipolar depression.
2) To evaluate face and content validity of the proposed framework.

CHAPTER TWO: Methods

This chapter provides detailed information pertaining to the rationale of the methods used in conducting the research presented in this thesis. The overall aim of the research described in this thesis was to explore and examine issues pertaining to medication adherence in people living with unipolar depression, using the ABC taxonomy as a framework. The specific objectives are reported in Chapter One, section 1.7. This thesis comprises four main parts (Parts A–D).

Part A of this thesis presents the thesis overview, including the background and scope of the problems of the research as well as the aims and objectives of the research included in this thesis.

Part B of this thesis involves a systematic review of the literature. This part employs a standard approach for conducting systematic reviews, the Preferred Reporting Items for Systematic Reviews, and Meta-Analyses (the PRISMA statement).[137] Specifically, the aim was to systematically identify and evaluate the range of medication adherence measures used at specific phases of adherence in accordance with the ABC taxonomy (initiation, implementation, and discontinuation) and then evaluate the psychometric properties of these measures of adherence.

Part C of this thesis explores the factors influencing medication adherence at each phase of adherence in accordance with the ABC taxonomy, elicited from people living with unipolar depression. For this stage, a qualitative approach informed by phenomenology was adopted. This approach was considered appropriate as it can be used to obtain a profound understanding of a particular issue or phenomenon (i.e. factors influencing medication adherence at specific phase of adherence) based on the lived experiences of consumer perspectives.[138-142] Both facilitators of and barriers to medication adherence were identified for each phase of medication-taking. This approach allows an in-depth exploration of 'what influences medication adherence',

'how adherence is facilitated' or 'why medication adherence or non-adherence occur', rather than just measuring the phenomenon.[138] Due to the complexity of the behaviour (phenomenon of interest), a qualitative approach was deemed appropriate, as it allows for a detailed understanding of concepts and generates hypotheses on the phenomenon of interest. Thereafter, the obtained information could be further generated for the next step of framework development (Part D).[143] Part C is informed by the consolidated criteria for reporting qualitative research (COREQ) in order to ensure the comprehensiveness of the procedure.[144]

Part D of this thesis comprised the development and validation of the medication adherence framework for people with unipolar depression. This framework was informed by the findings of qualitative study (Part C), review literature, and the experience of the research team. The aim of this part was to develop and content validate this adherence framework. A content validation method using an expert panel was employed for the validation process of the framework. This approach is common for framework evaluation.

The chapters in this thesis have been presented in the form of research manuscripts and in accordance with journal word counts. Although, each manuscript includes a section on methods, due to word limits, a detailed explanation of the rationale behind the methods used was not included. Therefore, in order to address this, this chapter further describes the methods used. It also includes supportive principles employed in the research included in this thesis. It should be noted that the information written in journal formats are not presented in this chapter in order to avoid repetition.

This chapter contains three main sections on methods employed: 1) psychometric properties of adherence measures, 2) qualitative methods, and 3) the development and validation of the conceptual framework.

2.1 Psychometric properties of adherence measures

The precise and accurate measurement of medication adherence is critical to any study of medication adherence. No previous research has documented the psychometric properties of the measures of medication adherence used by consumers who were prescribed antidepressant medicines for the management of depression. Part B (Chapter Three) of this thesis focused on an appraisal of the psychometric properties of adherence measures used to evaluate medication adherence to antidepressant medicines for the management of depression in accordance with the ABC framework. The PRISMA statement was adopted to systematically search and analyse the obtained information in the systematic review. This section expands critical areas of the method employed for the systematic review to underpin the underlying rationale. This section contains three main aspects. The first part contains detailed information on the systematic review process. The second part focuses on the issues relevant to the psychometric properties of the measurements. The third part provides key information pertaining to the adoption of the ABC framework in the analysis process.

2.1.1 The systematic review process

A systematic review was conducted as it provides both reliable and defensible findings due to the rigorous procedure, when compared to other types of reviews.[137, 145-148] Although systematic reviews of the measurement of medication adherence and its psychometric properties have been conducted in certain conditions such as HIV and adult transplant patients,[149, 150] no previous study has been conducted among people with unipolar depression. Our focus for this study was to robustly evaluate the psychometric properties of tools used to evaluate medication adherence in people with unipolar depression. Consequently, we needed to make precise assessments and to comprehensively understand the psychometric properties of adherence measures. Strict inclusion and exclusion criteria for included papers were applied. This helped to maximise the internal validity of our findings, potentially trading off with external validity. In addition, in order to strengthen the internal

validity of the study, we excluded people over 60 years of age. Although we acknowledge that there is no clear cut-off for memory (which can influence adherence) and aging, we chose a conservative cut-off value for this study.[151] Similarly, children and pregnant women were also excluded as the consumption of medicines in children is usually administered by carers and depression during pregnancy is very specific condition. That is, the inclusion of potential confounding comorbidities might impair the internal validity of our findings.

During the search procedure, the timeframe for searching was set for the last two decades (1994–2015), because this period captures a time in the literature where the term 'compliance' shifted to 'adherence'. Conceptually, this change reflects a shift from the notion of 'obedience' to the notion of 'cooperation'.[2] The period also allowed for adequate time to obtain a comprehensive answer to our research questions. Importantly, this period also included the development of several well-known and used self-report measures of adherence (e.g. MGLS and BMQ).[76, 77]

2.1.2 Psychometric properties of the measurements

Despite the range of surrogate measures which have been developed to assess medication adherence in unipolar depression, there is no a recognised standard measure which provides an accurate and precise measurement of adherence. In general, the selection of an 'appropriate' measurement should consider the specific propose of the measure, population and settings, and the accuracy of the tool. Because the accuracy of the measure is key to obtain credible findings, there is a need to evaluate psychometric properties of the measure. When evaluating psychometric properties, the key concepts are reliability and validity, as provided in the definitions used in the manuscript (Table 1).

With regard to the evaluation and data analysis process, a number of measurement properties were reported, such as reliability and validity of the measure, correlation between measures, agreement between measures, correlation between clinical outcome (depressive symptomatology scores) and adherence scores, and

concordance between measures. Many studies did not clearly specify the type of psychometric tests performed; therefore, the researchers categorised measures based on the definitions presented in Table 1 (page xx). For example, we categorised validity tests into different types such as 'concurrent validity', which occurs when medication adherence is assessed simultaneously using two different measures. In the absence of a universally accepted gold standard measure for adherence, we used the MEMS, as it is widely accepted as one of the most accurate tools.

The reliability of medication adherence measures was predominantly reported when consumer self-report measures were used both for the researcher developed self-report scales and standardised self-report scales. Therefore, the main type of reliability test provided was that for internal consistency reliability, reported as Cronbach's alpha. The interpretation of Cronbach's alpha values were made in accordance with ranges reported in the literature.[152, 153] For example, in general, the minimum acceptable level of Cronbach's alpha varies between 0.60–0.80, while the value 0.70 is more commonly accepted.[152, 153] In addition, considering another study, the range of the Cronbach's alpha value of the Antidepressant Adherence Scale (ASS) was reported from 0.60-0.86 in a different time frame during the first 12 weeks of treatment.[83] Consequently, we concluded that the AAS represents acceptable reliability. For the MGLS, a range of values for Cronbach alpha between 0.62-0.70 have been reported in the text and we have described this appropriately as demonstrating 'adequate reliability', as that value was within the range of the minimum accepted value.[152]

The evaluation of agreement between measures was also commonly reported as a form of assessment. To a certain extent, this may indicate consistency between measures. However, this does not fit the standard classification of reliability testing.[154-158] Therefore, we separately categorised these evaluations as 'agreement between measures' (Table 2 in the manuscript, page xx).

In terms of researcher-developed self-report scales, these were seldom used in multiple studies reported during the period 1994–2004, before a standardised

measure such as the MGLS became widely used. Prior to 2004, the majority of researchers who developed their own tools validated their self-report measures against existing objective measures, mainly pharmacy dispensing records.[57, 159]

2.1.3 The adoption of the ABC framework in the analysis process

There is no universally accepted conceptual framework for medication adherence that includes all major components of medication-taking behaviour. Despite the fact that several medication adherence frameworks have previously been established,[94, 95, 98, 99, 101, 103, 116, 160] none have provided full coverage of the major components of medication-taking behaviour. The ABC framework was employed in this study because it provides a transparent taxonomy which makes a clear distinction between different phases of medication-taking behaviour from the initiation of the medicine right through to the discontinuation of the medicine.[2] Therefore, this framework was considered well-suited for the main purpose of our systematic review and subsequent studies.

Because the ABC framework was proposed in 2012, there were relatively few included studies which have already employed this framework in their studies. Most studies focused on the implementation phase of medication adherence. For the studies which recruited newly diagnosed patients or patients who received their first prescription for an antidepressant medicine, we classified participants as being in the initiation phase. However, it appeared that measurements and their psychometric properties were applied across the initiation and implementation phases without specifically examining initiation of therapy and, therefore, measuring initiation of therapy. That is, adherence was assessed at some point between initiation and implementation and/or between implementation and discontinuation. Therefore, no measure was used exclusively to evaluate the initiation phase of medication adherence. Similarly, for the assessment of adherence at the discontinuation phase, adherence between the two phases of implementation and discontinuation was evaluated.

2.2 Qualitative study

Adherence is a sophisticated process and is simultaneously influenced by multiple factors. The ability of people with unipolar depression to follow their treatment plan may be influenced by different factors—those related to health care professionals, health care system, family and society, the characteristics of depression, depression therapies, and consumer-related factors. In order to effectively tackle non-adherence problems in people with unipolar depression, it is crucial for health care professionals to better understand their patients and potential factors influencing medication adherence. This part of the thesis (Part C) aimed to explore both facilitators of and barriers to medication adherence in people with unipolar depression. Therefore, detailed information and in-depth understanding of medication-taking behaviour and relevant aspects (such as personal beliefs and perceptions of depression and antidepressant medicines) were required from the consumer's perspective. In this case, a qualitative study was considered to be the most appropriate method, as it can be used to comprehensively explore experiences of interest in a particular group of people by evaluating abstractions, concepts, hypotheses, and theories from the obtained data.[143, 161] In our study, adherence to antidepressant medicine was influenced by many factors including personal beliefs, concerns, attitudes, and experiences toward the use of antidepressant medicines and unipolar condition. These are intangible and, thus, a quantitative approach was unlikely to be suitable for this study. Moreover, as medication adherence is a complex human behaviour, qualitative methods can provide a rich understanding of the behaviour, which is unlikely from a purely quantitative study.[143]

A number of qualitative inquiry frameworks may be applied in health services research, for example, grounded theory, phenomenology, ethnography, and narrative inquiry frameworks. These frameworks contain their own characteristics; therefore, the selection of a specific framework should be done in accordance with the aim of the study. In this study, we employed a phenomenological approach in the methods as it allowed for an exploration of lived experience with the phenomenon

of interest (i.e. factors influencing medication adherence to antidepressant medicine at specific phases).[142] A phenomenological approach was considered suitable for the aim of our study, to explore and better understand individual experiences pertaining to the consumption of antidepressant medicines in consumers living with unipolar depression, with a particular focus on both positive and negative influencing factors. In contrast, grounded theory is applied when researchers aim to develop the theory based purely on fieldwork data. Similarly, an ethnography framework is used when the focus is on understanding how culture explains the participant's perspectives and behaviour, while a narrative framework is used when researchers are interested in the interpretation of life story to understand and illuminate the life and culture that create it.[142]

Individual face-to-face interviews were selected as this medium aids the collection of detailed information on the participants' perspectives and experiences pertaining to medication-taking behaviours.[138, 162] In addition, semi-structured face-to-face interviews allow researchers to modify the line of questioning. They also provide a medium to discuss sensitive personal issues with skilled experienced interviewers.[141, 162] In this case, a skilled interviewer is able to discuss private matters such as personal beliefs and perceptions pertaining to the consumption of antidepressant medicines and their actual behaviour on medication-taking. Face-to-face interviews allow participants to speak freely; moreover, it allows the researcher to probe further into the responses that participants provide through both verbal and nonverbal ques (e.g. facial expressions, gestures, and body language), including emotions and behaviours during the interview. These aid the interviewer to seek further information as well clarity.[163] As it is a one-on-one method, it is also easier to gauge from the participant's non-verbal responses whether they are comfortable or uncomfortable with the questioning. It must be noted that focus groups were not considered suitable for this research because of the sensitive and very personal nature of participant experiences. In addition, we were concerned about the privacy of the participants and the stigma attached with mental illness.

Purposive sampling was selected to identify and select information-rich cases in accordance with the objectives of this study.[164, 165] In our study, a wide range of participants (in terms of their age, background, length of diagnosis, duration of using antidepressant medicines, and variety of antidepressant medicines) were expected in order to obtain a full range of different views. Further, a snowball sampling technique was not considered suitable for this research due to the inherently personal nature of experiences of depressive illnesses.[166] Theoretical sampling is recommended when the searcher applies a grounded theoretical approach owing to its principle of building interpretative theories from the emerging data and selecting a new sample to examine and elaborate on the theory.[164] Hence, theoretical sampling was not considered suitable for the purpose of our study as we did not aim to generate a theory.[164, 166] Notwithstanding the selected approach of purposive sampling, the recruitment of participants presented a challenge for this research and, hence, a broad recruitment approach was adopted which initially included recruitment through community pharmacies and a range of online platforms. However, due to the relatively slow rate of recruitment, a third approach using a market research company was added to facilitate participant recruitment until there was data saturation.

With regard to the analysis approach, inductive analysis, deductive analysis, content analysis, and thematic analysis are frequently used in qualitative studies in health services research.[142] In particular, content analysis and thematic analysis are commonly used.[161] These approaches have some elements in common and occasionally the terms are used interchangeably.[161] However, one distinction between them is that content analysis generally uses a descriptive approach in coding of the data and can include quantitative counts of the codes. In contrast, thematic analysis provides a purely qualitative, detailed, and nuanced account of data.[161] Thematic analysis was employed in this study as we attempted to generate and categorise potential factors influencing medication adherence in particular phases of adherence. This process requires narrative interpretation, and thematic analysis

assisted us to consistently extract the obtained themes and classify them in accordance with the ABC framework.

The qualitative methods employed in this research have some limitations. One particular limitation was the inability to include people (diagnosed) with unipolar depression who did not believe in the diagnosis or the use of antidepressant medicines. This group of participants may align with those categorised as displaying primary non-adherence. Primary non-adherence refers to patients who fail to fill the prescription.[3] Hence, this study focused on people who acknowledged their own experience of depression as a disease and were willing to use antidepressant medicines as a choice of treatment.

On the other hand, a strength of the employed sampling methods was the very broad range of participant experiences with the use of antidepressant medicines and their experiences within the broader healthcare system. This included the diversity of antidepressants used and the wide range of duration of antidepressant consumption (a range from the first diagnosis to recurrent depression with approximately 20 years of treatment). Therefore, the findings were assumed to encompass the main issues influencing medication adherence in the target sample.

2.3 Development and validation of the conceptual framework

A conceptual framework may serve as a helpful tool to illustrate and understand different aspects of participant behaviour and the impact of broader factors such as the influence of health care professionals, health care system, carers and views of the general public. Such an approach may provide a useful guide for health care professionals when dealing with complicated behavioural issues such as medication adherence.

Building on the findings of Part C (Chapters Four and Five) and Part D (Chapter Six) of this thesis, the main purpose was to develop and propose a framework to aid medication adherence in people with unipolar depression. The ABC taxonomy was adopted for the framework in order to obtain a detailed understanding of the adherence process.

This section comprises two main parts: 1) the rationale for developing the framework and 2) the validation of the proposed framework. This conceptual framework elucidates the entire process of medication adherence and its components, including potential factors that influence medication-taking behaviour at each phase of adherence, from the initial diagnosis to the discontinuation of antidepressant medicines. Therefore, this framework provides a clear and comprehensive disease-specific framework that captures factors which may influence medication adherence at specific phases of medication-taking behaviour.

2.3.1 Rationale for developing the conceptual framework

Although a number of conceptual frameworks have previously been proposed to answer a range of research questions in unipolar depression, they have not been related to medication adherence but instead have generally had a focus on the etiology and treatment of depression.[96, 98, 99, 101-103, 115] Currently, there is no framework which aims to comprehensively understand medication-taking behaviour in people with unipolar depression. Therefore, this proposed framework was developed with the aim of providing an overall view of the adherence process and

potential factors influencing medication-taking behaviour for individuals with unipolar depression.

Initially, a preliminary framework and its components were created by the researchers, based on multiple resources that included a review of the published literature and the findings of the qualitative studies (Part C, Chapters Four and Five). These concepts were combined with the clinical and research experiences of the researchers. Accordingly, item generation of factors influencing medication adherence at each phase of medication-taking were generated. As the proposed framework adopted the key concepts of the ABC taxonomy to explain the adherence process, potential factors were categorised into five dimensions (factors relating to health care professionals; factors relating to consumers; factors relating to health care system; factors relating to family, society, and economy; and factors relating to depression) and then mapped to each phase of medication adherence (i.e. initiation, implementation, and discontinuation).[2] The initial generation of factors influencing medication adherence at each adherence phase are presented in Appendix Four (Table A—Initial items generated from previous qualitative research study and review literature).

As evident, the implementation of the proposed framework is limited to people who could not/did not want to access the health care system. This included people who acknowledged depression but did not access or were unable to access the health care system, people who acknowledged depression but preferred alternative treatment to antidepressant medicines, and people who did not acknowledge their depressive disorder at all.

2.3.2 Validation of the proposed framework

Two types of validation were conducted: face and content validity. These are common tests when creating new tools or frameworks. Whilst face validity is subjective, and non-quantifiable, and not always considered important. It is often the first step in the validation process. Content validation is a more robust process than

face validation for new tools or frameworks. It is conducted assess the development process and to determine the representativeness and importance of the tool or framework content.[167] Content validity is recommended to be assessed prior to the implementation of any new tool or framework, especially if it concerns a complex behaviour such as medication adherence. Content validation may subsequently be followed by more sophisticated quantitative processes such as construct validation and criterion validation.[167]

Content validation relies on the use of a panel of experts to evaluate the tool elements or framework. Content experts are asked to rate items in relation to a number of areas including their relevance to and representativeness of the content domain.[167] We followed a two-stage process of content validation as described by Lynn (1986). The first step is the development process followed by second step which is the judgment-quantification process.[168]

For the development stage, there are three steps: domain identification, item generation and instrument formation.[168]

In our study, the development process was accomplished via multiple inputs including a comprehensive review of the literature, the findings of our qualitative studies (Part C: Chapter 4 and 5) combined with the experiences of our research team. These multiple sources were used to inform item generation. For the next step, instrument formation, the items generated in the previous step were assembled in a usable form. Those items were refined and arranged into five main domains (i.e. health care professionals, consumer, health care system, depression, and family/ society and economy) and then mapped to specific phases of adherence in accordance with the ABC taxonomy.

For the judgment-quantification stage of content validity, there are two steps. The first involves an assessment of individual items by a specific number of experts that the items are content valid, and second involves an assessment of the entire instrument or tool.[168]

At this stage, the content validity index (CVI) was adopted in both steps of the judgement stage, item-level (content validity index of the item or I-CVI) and the entire instrument level (content validity index of the entire instrument—the averaging calculation method or Ave-CVI). The CVI is the most widely accepted index for quantifying the content validity.[167-170] Also, it is easy to compute, understand, and interpret when compare to other methods such as the Content Validity Ratio (CVR).[167, 169] The CVI is derived from the rating of the content relevance (and importance) of the individual items on an instrument generally using a 4-point ordinal rating scale, where 1 connotes an irrelevant (unimportant) item and 4 an extremely relevant (extremely important) item.[168] The actual CVI is the proportion of items that received a rating of 3 or 4 by the experts (or 4 or 5 if a 5-point scale is used).[167, 168] There are some important considerations. A four-point scale has a potential limitation as it forces the rater to make a decision about relevance (or importance). As a four-point ratings are collapsed into two dichotomous categories of 'content valid' and 'content invalid' the chance of agreement among the raters is higher. There may also be a risk of losing some critical information.[167] Hence, in our study, a five-point scale was chosen. In addition, we acknowledge the presence of a middle category (i.e. neither relevant or irrelevant; and neither important or unimportant). To overcome this a open text field was included so that expert panel members could provide comments about items including issues of clarity for each item.

In order to overcome chance agreement, Lynn (1986) recommended a minimum of five experts to limit the inflation of chance agreement when using the CVI as the index of inter-rater agreement.[167, 169, 171] An appropriate number of the panel should be between five and ten experts to yield credible results.[167] With respect to the cut-point for the CVI score, we used the standard of 80% agreement or CVI 0.8 for both I-CVI and Ave-CVI, the recommended value when the panel comprises 6-10 experts.[167, 168, 171]

The developed framework was examined for content and face validity via the internet-based survey using an expert panel. The validation process was conducted

virtually, in a confidential manner, enabling all participants to freely provide their views without the process being overtaken by dominant individuals, which can occur during face-to-face interactions. In contrast, it must be noted that the dynamics of a group discussion can be lost when the internet-based survey is performed individually without immediate group feedback. Nevertheless an internet-based survey using an expert panel method was employed for the validation process of reassuring whether the framework subcomponents (influencing factors) were relevant to and import for a specific phase of adherence.

In accordance with the purpose of the framework, experienced health care professionals were selected as panellists for the validation process. The rationale for engaging health care professionals was because they are the target people who may directly apply the framework in practice. In this respect, considerable thought was given to who both the number of panellists and their collective scope of expertise. That is, both number of panellists and their individual and collective qualifications was an important consideration.[172] In our study, a broad range of the expert panel members were recruited (GPs, pharmacists, and researchers).[168, 169, 172] Hence the expert panel in our study had an adequate number and range of expertise needed for the content validity process.

PART B - THE PSYCHOMETRIC PROPERTY OF MEDICATION ADHERENCE MEASURES IN UNIPOLAR DEPRESSION

CHAPTER THREE – A systematic review of measures of medication adherence in consumers with unipolar depression

Chapter introduction

As outlined in the introduction, non-adherence to antidepressant medicine is a hindrance to successful treatment in unipolar depression. Adherence is a dynamic process and is likely to decrease over time. Furthermore, depressive symptoms can also worsen adherence to medicines. Therefore, it is crucial that health professionals regularly monitor adherence to antidepressant medicines in consumers with depression. Unfortunately, the absence of a gold standard to measure adherence as well as the inconsistency between ranges of measures have been highlighted by a number of research studies in this area. Consequently, the actual adherence rate is not necessarily comparable or known. Therefore, in this chapter, precise measure(s) of medication adherence with acceptable psychometric properties were systematically evaluated at the specific phases categorised under the ABC taxonomy (initiation, implementation, and discontinuation). This review may aid the selection of appropriate measures of medication adherence for specific phases of adherence.

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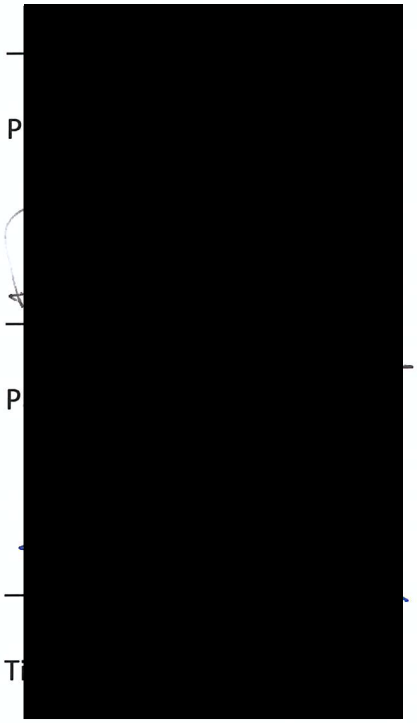
Authors' Contributions

Timothy F Chen conceptualised the study. Pornchanok Srimongkon conducted a systematic review and wrote the first draft of manuscript. Timothy F Chen and Parisa Aslani assisted in conducting the study and critically revised the manuscript.



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A systematic review of measures of medication adherence in consumers with unipolar depression

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ABSTRACT

Objective: To identify and evaluate the range of adherence measures used to assess different phases of medication adherence (initiation, implementation, and discontinuation) to antidepressants, including the psychometric properties of the measures.

Methods: This systematic review followed the PRISMA statement. Medline, Embase, International Pharmaceutical Abstracts, CINAHL and PsychINFO were searched (1994–2015) for articles which reviewed or reported the psychometric properties of adherence measures in adults with unipolar depression without comorbidity. Included articles were reviewed for the reliability and validity of their adherence measures.

Results: 26 studies met the inclusion criteria. Most assessed medication adherence at implementation and/or discontinuation phases. Self-report measures were the most frequently used, followed by electronic lid devices and pharmacy records. Standardized self-report measures such as Morisky, Green, and Levine Self-Reported Medication Taking Scale (MGLS) and Antidepressant Adherence Scale (AAS) demonstrated acceptable reliability and validity, while medication claims data showed good reliability as a long-term measure.

Conclusions: Although the psychometric properties of various measures have been evaluated across the three phases of adherence, a standout measure with strong reliability and validity was not apparent. No single measure demonstrated reliability and validity throughout the adherence process. A range of different subjective and objective adherence measures is recommended to assess medication adherence across the different phases.

1. Introduction

Medication adherence is a key to successful treatment in many chronic conditions including depression. Over the past two decades, a range of terms have been used to describe the medication taking behaviour of patients, including medication compliance, adherence, and persistence.[1] Although these terms have often been used to describe different aspects of medication taking behaviour, in many cases they have been used without a consistent understanding of what particular aspect of medication taking behaviour is being measured and described. The inconsistent use of these terms and the multitude of different definitions of medication adherence have led to difficulties in interpreting studies investigating medication taking behaviour in consumers with depression. A frequently cited definition of adherence and one endorsed by the World Health Organization is “the extent to which a person's behaviour – taking medication, following a diet, executing lifestyle changes – follows medical advice”.[2] Extending this broad definition, Vrijens et al. (2012) conceptualized a framework for describing and defining adherence to medicines. Specifically, they argued that adherence is a continuous process, but can be divided into three key phases, initiation, implementation, and discontinuation of therapy.[1] ‘Initiation’ starts when a patient take the first dose of their prescribed medicine. The process continues as the ‘implementation’ until the last dose has been taken and no further doses are taken afterwards. The stage is recognized as ‘discontinuation’.[1]

Medication adherence has become a topic of intense investigation in the management of many chronic conditions.[3] It has been reported that all current and remitted depression disorders are risk factors for medication non-adherence.[4,5] Non-adherence to antidepressant medicines is a major obstacle to the successful management of unipolar depression, a high prevalence condition which generally requires a minimum course of treatment of 6–9 months after recovery.[6] Globally, over 300 million people are estimated to suffer from depression, equivalent to 4.4% of the world's population.[7] Non-adherence in unipolar depression can lead to an unnecessary deterioration in health. It can contribute to unnecessary switches in antidepressant treatment, unneeded instructions to increase doses, initiation of unwarranted adjuvant treatments, and misclassification of treatment resistant.[8] It has been estimated that the

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odds of patients with depression being non-adherent were 1.76 times the odds of non-depressed patients with asthma, coronary heart disease, diabetes, hyperlipidaemia, or hypertension.[9] The average length of antidepressant treatment in patients with depression has been reported to be less than 6 months, and the discontinuation rate was 50–60% within 10–16 weeks.[10–12] In a European study of dispensing records, only 22% of individuals were reported as being adherent to their antidepressant medicine. In this study adherence was calculated using prescription records and defined as an adherence rate above 80%, that is, taking more than 80% of the daily dose of their medicine at 16 weeks.[11] Five percent of patients from one study in the United States reported that they never initiated therapy with their antidepressant medicine (40 of 765 patients).[13] For the maintenance phase of recurrent depression, the proportion of non-adherent consumers has been reported to vary from 39.7% to 52.7% when assessed using the four-item Morisky, Green, and Levine Self-Reported Medication Taking Scale (MGLS),[14] reported as the Medication Adherence Questionnaire.[12] Non-adherence on this scale occurs when patients miss 20% or more of their antidepressant medicine.[15] The two most common reasons for discontinuation of antidepressant medicines were feeling better (55%) and adverse events such as side effects (23%).[10] Moreover, greater than 60% of those consumers who discontinued their antidepressant medicine did not inform their general practitioner about their decision.[10]

A number of medication adherence measures have been used to evaluate medication taking behaviour in consumers with depression, however consensus on a gold standard measure or group of measures which map to the different phases of adherence (i.e. initiation, implementation, and discontinuation) has yet to be accepted. Although, electronic lid devices, such as MEMS (Medication Event Monitoring System), have been used in trials and reported as a standardized measure, they only apply if the medicine can be re-packed in a container with the electronic lid and their high cost makes them impractical for routine use in clinical practice.[16] Direct biological measurements such as drug metabolites or markers in a body fluid are invasive and have not been established for routine use with antidepressant medicines.[16] Moreover they do not show the regularity of medication taking. Individual indirect measurements such as patient self-reporting, pill counts, and pharmacy records may be readily used in clinical practice however there is significant variability in the reliability and/or validity of these measures when used alone.[17] In addition, different adherence measures can produce inconsistency in adherence reports, non-comparable adherence results, and hence increase the risk of an incorrect conclusion.[18,19]

Medication adherence is a dynamic process, which can be influenced by many factors and change over time. Particularly in unipolar depression, a unique condition, a significant impact on the mood can lower adherence at any time. Hence tailored interventions which consider specific factors, depending on the phase of adherence, are likely to facilitate improved adherence in people living with unipolar depression. Furthermore, selection and use of a medication adherence measure(s), appropriate for the phase of adherence, will provide a more accurate assessment of medication adherence, and therefore better inform the selection of tailored intervention strategies designed to improve medication adherence. The aim of this systematic review was to identify and evaluate the range of medication adherence measures used to assess different phases of medication adherence (initiation, implementation, and discontinuation), in consumers taking antidepressant medicines for unipolar depression. Specifically, the reliability and/or validity of these adherence assessments were evaluated.

2. Methods

The Preferred Items for Reporting of Systematic Reviews and Meta-Analyses[20] guideline was followed for conducting this systematic review. Five databases; Medline, Embase, International Pharmaceutical Abstracts (IPA), CINAHL and PsychINFO were searched for English language articles published from January 1994–December 2015. Search terms (MeSH) for three different concepts were combined: depression, antidepressant medicines, and adherence. Concept one included terms such as depression, major depression, and depressive disorders. Concept two included terms such as antidepressive agents, antidepressant drugs, and antidepressant agents. Concept three included terms such as patient compliance, medication adherence, treatment refusal, patient dropouts, directly observed therapy, and persistence.

2.1. Eligibility criteria

Articles were included if they met the following inclusion criteria:

1. Reviewed or evaluated antidepressant medication adherence in adult individuals with unipolar depression without co-morbidity (age ≥18 years old).
2. Reported their own statistical data on the reliability and/or validity and/or agreement of the adherence measurement/s, or referred to the primary research which had established the reliability or validity of the measurements used. In the latter case, original articles were searched and included in the study.

2.2. Articles were excluded if they

1. Reported adherence measured in depression with comorbidity
2. Included participants who were children, adolescents, pregnant women or elderly (age ≥ 60 years) persons with depression.
3. Did not report an adherence measure in the study.
4. Did not report on the reliability and/or validity and/or agreement of adherence measures in the study.
5. Were reported as book chapters, conference proceedings, dissertations, commentaries, editorials letters or reviews.

2.3. Selection process

The first author (P.S.) conducted a systematic search following the PRISMA guidelines. Firstly, all retrieved articles were screened based on titles. If the titles indicated the information relevant to the aim of the study, the abstracts were then screened and reviewed for more details. If the abstracts indicated that the studies fulfilled the eligibility criteria, full papers were then searched to extract the essential information. All duplicates were removed. The bibliographies of included articles and relevant review articles were also iteratively searched for additional articles which met the specific inclusion criteria. Primary data extraction was conducted by P.S. Then, the second researcher cross-checked 20% of the eligible articles. The inconsistencies were then discussed and resolved if required.

2.4. Data extraction and evaluation

Data extracted from studies included: country in which the study was conducted, study setting, study design (e.g. randomized controlled trial), study time frame, length of subject follow up, medication of interest, medication adherence measure(s), reliability and/or validity and/or agreement of measure/s, adherence outcome, definition of adherence and/or non-adherence, number of participants, age group, gender, diagnosis, severity of depression, new or continuing treatment, and the phase of medication adherence assessed (i.e. initiation, implementation or discontinuation). Researchers evaluated adherence phases according to the ABC framework.

The ABC conceptual framework proposed by Vrijens et al. was used for this systematic review as follows, "*adherence process starts with initiation, when patients start the first dose of medicines. Following by the implementation which referred to the extent to which a patient's actual dosing corresponds to the regimen from the first to the last dose. Discontinuation is considered where no more doses are taken thereafter.*"[1]

Table 1
The definitions of reliability and validity of adherence measures used in this study.[22,59–62]

Types of reliability and validity		Definitions
Reliability	*Internal consistency reliability/ Coefficient alpha*	Internal consistency reflects the coherence of the components of a scale. It shows the equivalence reliability. Cronbach's alpha coefficient is the most frequently used statistic to show internal consistency reliability.[22] Commonly accepted minimum values for reliability coefficients are 0.70 for group comparisons and 0.90–0.95 for individual comparisons.[59]
	Test-retest reliability	Test-retest reliability is estimated by administering the same test to the same group of respondents at different times. The correlation between the two scores, and often between individual questions, indicates the stability of the instrument.[22]
Validity	*Face validity*	Face validity is a subjective assessment. An instrument is face valid if it appears to measure the construct/s of interest.[22]
	Content validity	Content validity refers to the extent to which an empirical measurement reflects a specific domain of content.[60]
	Criterion-related validity	Criterion-related validity pertains to evidence of a relationship between the attributes in a measurement tool with its performance on some other variable. Cohen's kappa above 0.61 was considered as acceptable if at least one relationship was found.[22]
	- *Concurrent validity*	Concurrent validity is confirmed when scores on a measure are correlated to a related criterion (ideally, a gold standard criterion) at the same point in time.[60]
	- *Predictive validity*	Predictive validity is confirmed when there is evidence that the scale predicts a gold-standard criterion that is measured at some time in the future.[60]
	Construct validity	Construct validity refers to the degree to which an instrument measures the construct it is intended to measure.[61]
	- *Convergent validity*	Convergent validity occurs when there is correspondence or convergence between constructs that are theoretically similar.[22]
	- *Discriminant validity*	Discriminant validity occurs when there is differentiation or discrimination between constructs that are theoretically different.[22]

Therefore, we categorized studies as the 'initiation phase of the adherence process' when participants with new prescriptions for antidepressant medicines were recruited to the study or if the study stated that participants were commencing therapy with antidepressant medicines for the first time. Studies which evaluated antidepressant medication adherence, following participants who had commenced therapy were classified as 'implementation phase of adherence'. Studied which assessed medication adherence when patients ceased taking antidepressant medicines were classified as the 'discontinuation phase of adherence'. This process was conducted by one researcher, however, 20% of results were rechecked by the second researcher. The inconsistencies were then discussed and finalized.

2.5. Outcome of interest

The psychometric properties of the medication adherence measures were assessed in accordance with the definitions in Table 1. In general, validity refers to the extent to which any instrument measures what it is intended to measure.[21,22] Reliability concerns the extent to which an experiment, test, or any measuring procedure yields the same results on repeated trials.[21,22] Relevant measures of reliability were: internal consistency and test-retest reliability. Relevant measures of validity were: content, criterion-related, construct, convergent and face validity. In some studies, other types of psychometric properties were evaluated, including the correlation or agreement between different measures of adherence. As there is no universally accepted gold standard measure for medication adherence, MEMS was selected as the criterion measure for the purpose of this review.

The results were presented under the following structure, 1) an overview of findings 2) psychometric properties of the measures. The latter section contained data on the frequency of use of each measure to assess adherence in unipolar depression, how it was used in unipolar depression, and the psychometric properties of each measure among samples of patients with unipolar depression.

3. Results

The search following PRISMA guidelines resulted in 26 records (Fig. 1). Most of them were conducted in primary care settings or outpatient settings in the United States of America. More than half (15 of 24) of them used 2 or more adherence measures to assess antidepressant medication adherence in consumers with unipolar depression.[23–37] Twelve studies used both subjective and objective adherence measures to assess antidepressant adherence.[23–30,33,35–37] All studies focused on medication adherence at the implementation phase, and most of them assessed adherence from implementation to discontinuation. The reliability of adherence measures was assessed by researchers in 5 studies[23,32,35,38,39] while the validity of adherence measures was assessed in 12 studies.[24–28,30–33,35,36,39] Some studies cited previously reported reliability and/or validity testing of adherence measures.[12,15,29,30,32,34,37,40–44] Characteristics of the included studies are reported in Table 1A, in the appendix. A summary of adherence measures identified from this systematic review is presented in Table 2. The psychometric properties (e.g. reliability, validity) of medication adherence measures are reported in Table 3.

3.1. Adherence measures

Different types of adherence measures have been used to evaluate antidepressant adherence in consumers with unipolar depression. Self-report measures of adherence were the most commonly used type of measure and covered initiation, implementation, and discontinuation of therapy. MEMS (Medication Event Monitoring System) was the second most commonly used measure. Researcher developed measures were commonly used prior to 2004. After that time, validated self-report measures (e.g. the four-item Morisky, Green, and Levine Self-Reported Medication Taking Scale (MGLS),[14] and the Beliefs about Medicines Questionnaire[45]) became more widely used.[12,15,30,32,34,35,37]

Although ten studies assessed medication adherence at the initiation phase, none of the included studies specifically reported about the initiation phase of antidepressant medication adherence. Most studies focused on assessing medication adherence during the implementation to the discontinuation phase of therapy. Therefore, all psychometric properties of adherence measures reported in this systematic review were evaluated during implementation and discontinuation phases.

3.2. Reliability and validity of adherence measures

Different types of reliability and validity tests were used to evaluate the psychometric properties of individual measures of medication adherence. The most common assessment of reliability used was Cronbach's alpha coefficient, a measure of internal consistency.[32,35,39] Some studies reported agreement between different measures as a form of reliability assessment.[23,24] Various types of validity tests were presented, including concurrent, construct and face validity. Most assessments of validity involved concurrent validity in which different adherence measures were evaluated against the selected criterion measure (MEMS) at the same time.[25,26,31,32,35]

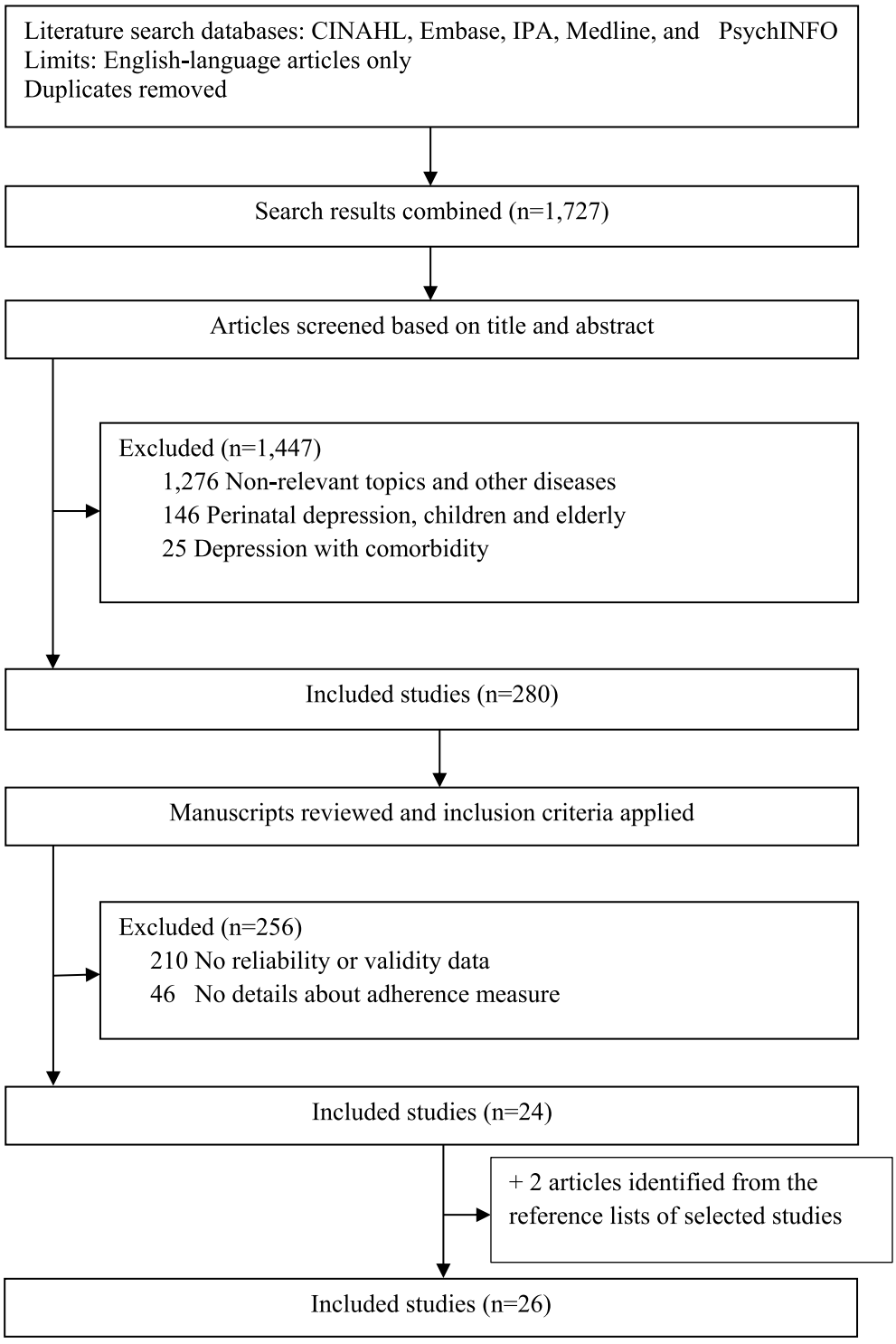

Fig. 1. Search flow diagram.

3.3. Objective adherence measures

1) **MEMS (Medication Event Monitoring System)**

MEMS was the most commonly used objective adherence measure in this systematic review (7 studies).[25,26,31,35–37,40] It has been reported to be the "gold-standard" for criterion-related validity testing against other measures such as pill counts, self-report adherence measures and pharmacy records.[25,26,31,35]

2) **Pharmacy records, prescription refill, and claims data**

Pharmacy records and prescription refill were used in 6 studies[23,24,30,31,33,42] and claims data were used in 2 studies.[29,33] Pharmacy records revealed acceptable validity when compared with MEMS. Brook et al. reported 5% underestimation of medication adherence by pharmacy records when compared with MEMS.[31] Rickles et al. reported fair consistency between claims data and MEMS.[33] Pharmacy records, prescription refill, and claims data were useful measures for long-term adherence assessment in consumers with depression.

Table 2
Summary of adherence measures used in the systematic review.

No	Authors, year	Objective data						Subjective data				
								Self-report				
		Pharmacy records/ prescription refill	Claims data	Appointment kept	Plasma/ Serum level/ blood conc.	Pill counts	MEMS	Patient report/ interview	MGLS	BMQ (Horne)	BMQ (Svarstad)	MARS
1	Katon et al.,[38] 1994							✓				
2	Katon et al.,[23] 1996	✓						✓				
3	Saunders K.,[24] 1998	✓						✓				
4	Peveler et al.,[25] 1999						✓	✓				
5	Bultman and Svarstad,[43] 2000										✓	
6	Claxton et al.,[40] 2000						✓					
7	George et al.,[26] 2000				✓	✓	✓		✓			
8	Sirey J.A.,[27] 2001				✓			✓				
9	Akerblad et al.,[28] 2003			✓	✓			✓				
10	Kwon et al.,[29] 2003		✓					✓				
11	Sleath et al.,[41] 2003										✓	
12	Capoccia et al.,[44] 2004							✓				
13	Aikens et al.,[30] 2005	✓							✓		✓	
14	Brook et al.,[31] 2005	✓					✓					
15	Brown et al.,[32] 2005								✓	✓		
16	Rickles et al.,[33] 2005	✓	✓								✓	
17	Russell and Kazantzis,[34] 2008									✓		✓
18	Yeh et al.,[39] 2008							✓				
19	Ten Doesschate et al.,[12] 2009								✓			
20	Ten Doesschate et al.,[15] 2009								✓			
21	Gabriel and Violato,[47] 2010											
22	Interian,[35] 2010						✓		✓			
23	Lee et al.,[36] 2010					✓	✓	✓				
24	Prukkanone et al.,[42] 2010	✓										
25	Interian et al.,[37] 2013						✓		✓			
26	Gabriel,[48] 2015											
	Summary (26)	6	2	1	3	2	7	10	7	2	4	1
	Initiation	5	1	0	1	1	3	5	1	0	2	0
	Implementation	6	2	1	3	2	7	10	7	2	4	1
	Discontinuation	2	1	0	2	1	4	4	7	0	2	0

No	Subjective data		N[a]	Reliability			Validity			Agreement[b]	Adherence phase[c]		
	Self-report	Clinician rating scale											
	AAS			Provided reliability data	Referred to other	No data	Provided validity data	Referred to other	No data		Initiation	Implementation	Discontinuation
1			1	✓					✓		✓	✓	
2			2			✓			✓	✓	✓	✓	✓
3			2			✓			✓	✓	✓	✓	
4			2			✓	✓				✓	✓	✓
5			1			✓		✓			✓	✓	✓
6			1		✓				✓			✓	
7			4			✓	✓				✓	✓	✓
8			2			✓			✓	✓		✓	✓
9			3			✓	✓					✓	
10			2		✓				✓	✓		✓	✓

(*continued on next page*)

Table 2 (*continued*)

No	Subjective data		N[a]	Reliability			Validity			Agreement[b]	Adherence phase[c]		
	Self-report	Clinician rating scale											
	AAS			Provided reliability data	Referred to other	No data	Provided validity data	Referred to other	No data		Initiation	Implementation	Discontinuation
11			1		✓			✓				✓	
12			1			✓			✓	✓	✓	✓	✓
13			3			✓		✓		✓		✓	✓
14			2			✓	✓				✓	✓	
15			2	✓	✓		✓					✓	✓
16			3			✓		✓		✓	✓	✓	
17			2		✓			✓				✓	
18			1	✓			✓					✓	
19			1			✓		✓				✓	✓
20			1			✓		✓				✓	✓
21	✓		1	✓			✓					✓	✓
22			2	✓			✓					✓	✓
23		✓	4			✓			✓	✓		✓	
24			1		✓				✓		✓	✓	
25			2		✓			✓				✓	✓
26	✓		1	✓			✓					✓	✓
	2	1	–	6	7	14	9	8	9	8	10	26	15
	0	0	–	1	1	7	3	2	5		–	–	–
	2	1	–	6	7	14	9	8	9		–	–	–
	2	0	–	3	3	9	6	5	4		–	–	–

Abbreviations of medication adherence measures.
AAS: the Antidepressant Adherence Scale.[47]
BMQ by Horne: Beliefs about Medicines Questionnaire.[45]
BMQ by Svarstad: Brief Medication Questionnaire.[49]
MARS: Medication Adherence Report Scale,[63] MEMS: Medication Event Monitoring System.
MGLS: Four-item Morisky, Green, and Levine Self-Reported Medication Taking Scale,[14] also reported as Medication Adherence Questionnaire (MAQ)[12,15] and Self-reported Medication Taking Scale (SMTS).[35,37]

[a] N = number of adherence measures.
[b] Agreement between different adherence measures.
[c] Adherence phase categorized by the researchers under the ABC definition.

3) **Pill counts**

Pill counts were used to evaluate medication adherence in 2 studies.[26,36] George et al. reported a significant correlation between pill counts and percentage of days on which openings were detected by MEMS ($r = 0.616$; $P < 0.001$). However, when the authors compared data with the MGLS and serum concentration of antidepressant medicines, they concluded that some patients may open the container and discard the medicine, rather than take it, hence the poor correlation between MEMS and pill counts in this study.[26] Another study reported a significant but low correlation between pill counts and MEMS of 0.419 (95% confidence interval: 0.254, 0.561).[36] The kappa value between the two measures was 0.38, which reflected a fair to poor agreement.

3.4. Subjective adherence measures

Self-report was the most commonly used subjective measure of adherence. Prior to 2004, researcher developed self-report measures were commonly used. Kwon et al. reported high agreement between claims data and the researchers' developed self-report scale, especially at 4-months.[29] However, the self-report measure used was imprecise as all values were dichotomized. Katon reported an agreement between prescription refills with a self-report scale for long-term treatment (4-months) but did not specify the questions asked.[23] Saunders reported high agreement (91% agreement with kappa = 0.80) between prescription refill and self-report data on both the premature discontinuation of antidepressants and adequate dose consumption. Agreement regarding dosage adequacy was also higher later in treatment, but the kappa values were quite low: 0.52 at 1 month and 0.65 at 4 months.[24]

After 2004, established self-report measures such as MGLS became more widely used.

1) **Four-item Morisky, Green, and Levine Self-Reported Medication Taking Scale (MGLS)**

The MGLS is a well-established adherence measure with a Cronbach's alpha value of 0.61 as reported from the original research in patients with hypertension.[14] The MGLS consists of 4 items to assess the forgetfulness, carelessness, and stopping due to feeling worse or feeling better interferes with medication adherence. It is noteworthy that one of the ways in which the MGLS differs conceptually from the Morisky Medication Adherence Scale-4 (MMAS-4)[46] is in the second item; with the former assessing carelessness, and the latter assessing problems remembering to take medicines. In this review, the MGLS was used in 7 studies, mostly for the implementation and discontinuation phase.[12,15,26,30,32,35,37] It has been shown to have adequate reliability when assessing adherence to antidepressant medicines, specifically for the implementation phase of adherence, with a Cronbach's alpha of 0.62[32] and 0.70.[35] The MGLS scale also has a good correlation with MEMS for detecting poor adherence, with sensitivity 72.2%, specificity 74.1% for ≥80% adherence.[26] Interian also reported a correlation between MGLS and MEMS, however, the correlation was only moderate ($r = -0.43$).[35] The scale was also shown to have high agreement with a 3-month medication possession ratio (72% agreement), which was computed from pharmacy refill data.[30]

2) **Antidepressant Adherence Scale (AAS)**

The AAS was developed based on the MGLS scale. The AAS consists of four items to assess the degree to which forgetting, carelessness, and stopping due to feeling worse or feeling better interferes with medication adherence in the last 4 weeks. Responses are converted to a continuous numerical score as opposed to a categorical response (yes or no). In this review, the AAS was used in 2 studies for the implementation phase of treatment.[47,48] Both studies reported acceptable levels of internal consistency reliability (Cronbach's alpha 0.52–0.86), content, convergent and construct validity (see Table 3).

3) **Beliefs about Medicines Questionnaire (BMQ by Horne, 1999)**

The BMQ by Horne comprises two parts, namely the BMQ-specific and the BMQ-general.[45] It assesses both necessity beliefs and concern beliefs about medicines. The psychometric properties have been evaluated using confirmatory factor analysis. The BMQ has been tested in patients with psychiatric conditions, asthma and diabetes. For psychiatric conditions, the internal consistency reliability (Cronbach's alpha) of the BMQ has been reported at 0.74 for specific-necessity beliefs, 0.63 for specific-concern beliefs, 0.73 for general-overuse beliefs, and 0.70 for general-harm beliefs.[45]

In this review, the BMQ by Horne was used in 2 studies for both implementation and discontinuation phase of treatment.[32,34] However, only one of these studies reported statistical evidence of reliability and validity of the measure.[32] Brown et al. reported adequate internal consistency and good construct validity of the BMQ (Cronbach's alpha of 0.80 for BMQ specific-necessity beliefs, 0.75 for BMQ specific-concern beliefs, 0.71 for BMQ general-overuse beliefs and 0.67 for BMQ general-harm beliefs). Brown et al. found that beliefs about medications for depression were significantly related to self-report adherence.[32] Using confirmatory factor analysis, the BMQ was shown to have construct validity in consumers with depression. The hypothesized 4-factor model provided a fair to good fit (RMSEA = 0.056, 90% confidence interval for RMSEA = 0.041–0.070, CFI = 0.95, GFI = 0.89).[32]

4) **Brief Medication Questionnaire (BMQ by Svarstad, 1999)**

The BMQ by Svarstad consists of two parts. The first part contains 3 main items that ask patients how they took each medicine in the past week and assesses beliefs about drug efficacy and bothersome effects. It detects repeat non-adherence (patients who take ≥20% more or less than the prescribed number of doses), sporadic non-adherence (patients who take 1–19% under or over prescribed number of doses) and no non-adherence (patients who take 100% of doses). The second part contains 11-items that ask patients about the difficulties in remembering medication-taking behaviour. It assesses physical and cognitive barriers to adherence and self-efficacy. Validity of the BMQ by Svarstad has been demonstrated with the regimen and belief screens having 80–100% sensitivity for "repeat" non-adherence and the recall screen having 90% sensitivity for "sporadic" non-adherence.[49]

The findings of this review showed that the BMQ by Svarstad has been evaluated in 4 studies.[30,33,41,43] One study reported significant correlation when it evaluated one question which was similar to the question in BMQ by Svarstad, with the true rate of dose omission by MEMS over a 7-day or 30-day period.[33]

4. Discussion and conclusion

4.1. Discussion

This is the first systematic review to comprehensively evaluate the psychometric properties of all measures of medication adherence used to assess medication taking behaviour in consumers with unipolar depression. For this review, the measures of adherence were mapped to the three phases of adherence in accordance with the ABC framework, that is, the initiation, implementation and discontinuation of pharmacotherapy.[1] According to the continuous process of adherence, the

Table 3
The psychometric evaluation of antidepressant adherence measures captured between implementation and discontinuation phase.

Type of adherence measures		Reliability	Validity	Other evaluation
Objective measures	Pharmacy records/Prescription refill	No data reported	*Concurrent validity*: Pharmacy records was reported underestimation adherence during implementation by 5% when compared with MEMS.[a,31]	A significant correlation between 7-day self-report missed doses and missed doses according to pharmacy records ($r = 0.760$; $P \leq 0.001$).[33]
	Pill counts	No data reported	*Concurrent validity*: ● A significant correlation between pill counts and MEMS[a] ➢ $r = 0.616$; $P < 0.001$.[26] ➢ concordance correlation coefficient rc = 0.419, 95%CI 0.254–0.561[36] ● A significant correlation between (dichotomized) pill count and MEMS (kappa = 0.380)[36]	No data reported
Subjective measures	Four-item Morisky, Green, and Levine Self-Reported Medication Taking Scale (MGLS)[14]	*Internal consistency:* ● Cronbach's alpha = 0.62[32] and 0.70[35]	*Concurrent validity*: ● A negative correlation between MGLS and MEMS[1] ($r = -0.43$) ● The sensitivity of MGLS was reported between 72% and 84% for detecting poor adherence when compared to MEMS[1] and a specificity between 55% and 74%[26]	● A significant agreement of 72% between (dichotomized) MGLS and the 3-month medication possession ratio was reported.[30]
	Antidepressant Adherence Scale (AAS)[47,48]	*Internal consistency:* ● Cronbach's alpha = 0.66[47] ● Cronbach's alpha = 0.52–0.86 over time (at baseline, 4, 8, and 12 weeks) was reported.[48]	*Content validity:* Ninety percent agreement among experts was reported to ensure that the items were highly relevant to medication adherence.[47] *Convergent validity:* A positive significant correlation ($p < 0.05$) between the scores of the four-item (knowledge and attitude subscales and adherence items) was reported.[47] *Construct validity:* A construct validity of AAS over time (item loadings following principal component analysis with varimax rotation) was reported; at baseline: 0.43–0.89, 4 weeks: 0.70–0.90, 8 weeks: 0.40–0.91, and 12 weeks: −0.31-0.90. The percent variance explained was reported as 47–57% in the intervention group and 45–72% in control group.[48]	● A significant correlation between depressive symptomatology scores and adherence scores was reported at 12 weeks ($P < 0.001$).[48] ● A significant positive correlation between non-adherence scores of the AAS, and the perceived stigma subscale of the attitudes scale was reported, especially among patients who indicated that they had stopped the antidepressants once they felt better.[47]
	Beliefs about Medicine Questionnaire (BMQ by Horne)[45]	*Internal consistency:* Cronbach's alpha = 0.80 for BMQ specific-necessity, Cronbach's alpha = 0.75 for BMQ specific-concerns, Cronbach's alpha = 0.71 for BMQ general-overuse, and Cronbach's alpha = 0.67 for BMQ general-harm)[32]	*Construct validity:* Confirmatory factor analysis for the BMQ was reported. The hypothesized 4-factor model provided a fair to good fit to the observed data (RMSEA = 0.056, 90% Confidence interval for RMSEA = 0.041–0.070, CFI = 0.95, GFI = −0.89).[32]	No data reported
	Brief Medication Questionnaire (BMQ by Svarstad)[49]	No data reported	*Predictive validity:* Predictive validity was reported when compared BMQ with dose omissions as measured by MEMS over a 7-day or 30-day period.[49]	A significant correlation between the 7-day BMQ self-report missed doses and missed doses according to pharmacy records was reported over the first 3-month period ($r = 0.760$; $P \leq 0.001$).[33]
Self-report by Katon et al., 1994[38]	*Test-retest reliability:* Self-report quit date for antidepressant medicine during an interview conducted was reported at 1 and 4-month.[38]	No data reported	No data reported	
	Self-report by Katon et al., 1996[23]	No data reported	No data reported	A significant agreement between self-report and refill records was reported during the implementation phase of therapy, at 1 and 4 months. At 1 month; K statistics = 0.83, SE = 0.12, $P = 0.001$. At 4 months; K statistic = 0.90, SE = 0.13, $P = < .001$[23]

(*continued on next page*)

Table 3 (*continued*)

Type of adherence measures		Reliability	Validity	Other evaluation
	Self-report by Saunders K., 1998[24]	No data reported	No data reported	The agreement between two measures of adherence (self-report and prescription refill data) was reported at 1-month and 4-months using kappa. At 1-month they reported a kappa of 0.33 and at 4-month a kappa of 0.72. The agreement was lower at 1-month because prescription refill data provided a higher estimate of antidepressant medicine use than self-report.[24]
Self-report by Peveler et al., 1999[25]	No data reported	*Concurrent validity*: Adherence was monitored by MEMS[1] in a subgroup of patients to check the validity of self-report adherence. Self-report and MEMS was significantly related with mean duration of monitored treatment 41.7 (SD 5.8) days in patients reporting continuation compared with 26.1 (SD 15.9) days in those reporting cessation ($t = 6.6$, df = 82, $P < 0.001$)[25]	No data reported	
	Self-report by Sirey, 2001[27]	No data reported	No data reported	The concordance between chart records of steady-state plasma drug concentrations and patients' reports of adherence was reported in a subsample of 14 patients (10%) whose charts had data on plasma drug concentrations. Eighty percent of them had plasma drug concentrations within the target range, suggesting that self-reports of patients in the sample were in most cases a good approximation of patients' medication taking behaviour.[27]
	Self-report by Kwon et al., 2003[29]	No data reported	No data reported	A kappa of 0.69 was reported, indicating overall agreement between direct self-report antidepressant medication adherence and claims records. The "List" of self-report medicines and claims measures were in agreement in 91% of case with a kappa value of 0.82 (0.73–0.90).[29]
	Self-report by Lee et al., 2010[36]	No data reported	*Concurrent validity*: A significant correlation between (dichotomized) self-report adherence and MEMS (kappa = 0.495).[36]	No data reported
	Clinician rating scale	No data reported	*Concurrent validity*: A significant correlation between (dichotomized) clinician rating scale score and MEMS (kappa = 0.320)[36]	No data reported

[a] MEMS was chosen as a criterion measure of adherence.

capability of some adherence measures to capture more than one adherence phase (i.e. MGLS, AAS, and BMQ by Svarstad can capture both implementation and discontinuation of treatment), and incomplete data reported from recruited studies, led to difficulty in differentiating the different adherence phases. Although some studies assessed medication adherence from initiation of treatment, the psychometric properties of adherence measures were mainly evaluated at the implementation phase. Therefore a large proportion of results reported in this study were categorized at the implementation phase. None of the studies assessed medication adherence nor reported the psychometric properties of adherence measures at the initiation phase.

At implementation, MEMS was the most commonly used objective measure followed by pharmacy records. MEMS is generally recognized as a "gold standard" of adherence. Although observing actual medication ingestion (Directly Observed Treatment or DOT) is recognized as the true gold standard of adherence measurement,[50] it has not been used in patients with depression. This is probably because DOT is an impractical measure in the clinical setting, where chronic therapy for unipolar depression is indicated. Therefore, MEMS was selected as the criterion measure in this review, to which other measures of adherence could be validated. Similar to previous studies in other conditions, pharmacy records and prescription claims data have been used at each phase of adherence and have been reported to be somewhat "accurate" as long-term adherence measures.[23,24] Longitudinal assessment of prescription refill data can capture (indirectly) the changes in medication taking behaviours over time from initiation to discontinuation.[51] The review findings showed a strong positive relationship between pharmacy records and MEMS ($r = 0.760$; $P \leq 0.001$),[33] in line with another study in patients with hypertension or heart failure.[52] Pill counts have been used almost exclusively for the implementation of adherence, but their "accuracy" has been questioned by some especially when the time of the pill count is known by the patient.[26] Unannounced and random home-based pill counts present a possible solution to improve the validity of the measure.[50]

Self-report measures were the most commonly used subjective measure of adherence and were used at each phase of adherence. They are regarded as the most practical and least costly method for assessing medication adherence in clinical settings but the reliability and validity of these measures have not always been considered. However, since 2004 there has been an emphasis on reporting the psychometric properties of self-report measures, particularly the MGLS and BMQ by Horne.

A commonly used self-report measure, the MGLS scale, demonstrated acceptable reliability (Cronbach alpha range 0.62 and 0.70)[32,35] sensitivity and specificity when compared to MEMS.[26] It has also been shown to have significant agreement with 3-month medication possession ratio data,[30] suggesting that the MGLS scale may be considered as an acceptable measure for assessing medication adherence for the implementation phase of treatment. This scale has been useful in detecting non-adherence during the implementation and discontinuation phases of adherence in both unipolar depression[12,34] and other chronic conditions.[53] However one study in hypertensive patients commented that the MGLS scale does not fully assess the different dimensions of the ABC taxonomy.[51] Whilst Nguyen et al. reported that the MGLS evaluated the implementation and discontinuation phases of adherence, by identifying barriers to adherence such as forgetfulness, poor medication taking behaviours and adverse effects.[53] Similarly, Tan et al. reported that it was a useful measure for screening and monitoring medication taking behaviour.[54] In addition, the MGLS can identify intentional and unintentional medication nonadherence. However, the limitations of the MGLS scale should be considered, as it only assesses barriers to adherence (medication underuse or omission) and not self-efficacy, which has been found to be an important predictor of medication adherence.[55] Another limitation of the MGLS scale is that it does not assess adherence over a specific time frame.[50] To counter this, a modified Morisky (eight-item Morisky Medication Adherence Scale or MMAS-8)[56] has been developed, which shows better reliability and validity albeit in hypertensive patients (Cronbach's alpha value is 0.83, sensitivity and specificity are 93% and 53% respectively) when considering a specific time frame of 2 weeks.[54]

The Antidepressant Adherence Scale (AAS) represents another modification of the MGLS scale. The psychometric properties of the AAS in unipolar depression are comparable to the MGLS scale,[47,48] hence it may be used as an alternative measure to the MGLS scale. The AAS is considered as a useful measure to detect medication non-adherence at the discontinuation phase.[47] A positive correlation between non-adherence scores of the AAS and the perceived stigma subscale has been reported. This positive correlation was also related to the discontinuation of antidepressant treatment when the patients felt better.[47]

The Beliefs about Medicines Questionnaire (BMQ by Horne, 1999) is another commonly used self-report measure of medication adherence. The sub-scales have "acceptable" to "good" internal consistency reliability and "fair to good" construct validity when used as a measure of medication adherence in depression.[32] A systematic review of validated self-report adherence scales in many health conditions (such as asthma, diabetes, and other psychiatric conditions) also reported significant correlations with the Reported Adherence to Medication Scale, the Medication Adherence Report Scale (MARS-5), and MGLS.[53] Although the BMQ by Horne is not a stand-alone comprehensive adherence scale, it may be used to reveal the drivers behind patients' non-adherence by identifying barriers and beliefs that influence medication adherence rather than measuring medication-taking behaviour itself.[53]

The Brief Medication Questionnaire (BMQ by Svarstad, 1999), another self-report measure, has been recommended for use in individuals taking antidepressant medicines for depression as well as for other medicines/conditions.[55] It has been used during the implementation and discontinuation phases of adherence. It is noteworthy that the psychometric properties of BMQ by Svarstad have also been tested and reported in other chronic conditions (e.g. hypertension, diabetes, and hypercholesterolemia), however, only weak correlations with pharmacy refill records have been demonstrated.[17]

The majority of included studies evaluated concurrent validity of adherence measures via correlating the measures with a standard measure such as MEMS.[25,26,31,35,36] Among self-report measures, the AAS demonstrated higher levels of validity (convergent and construct validity), while BMQ by Horne demonstrated acceptable construct validity.[32,47] and MGLS and AAS showed acceptable reliability.[35,48]

It is notable that whilst older studies of medication adherence used single measures, most contemporary studies now apply multiple measures of adherence,[16,50,57] recognizing that individual measures evaluate different aspects of adherence. This is the case for both depression as well as other chronic conditions such as heart failure and hypertension.[52] Specifically a combination of both subjective (self-report) and objective adherence measures is recommended.

The majority of studies included in this review evaluated medication adherence during the implementation and discontinuation phases of therapy. It is noteworthy that no study has specifically assessed medication adherence at the initiation phase of therapy. This indicates a significant gap in the literature because data on the proportion of consumers, who have been prescribed an antidepressant medicine, for the first time, but not had it dispensed or had it dispensed but not commenced taking the medicine (primary non-adherence), is not known.[58] That is, studies have focused on the period after an antidepressant medicine has been dispensed and the first dose taken.[58]

Some studies have evaluated the initiation of antidepressant medicines (i.e. starting therapy) as an inclusion criterion,[23–26,31,33,38,42–44]

using pharmacy records or self-report or MEMS as a measure. However, determining whether consumers actually commenced management with antidepressant medicines is not known.

There are several strengths and limitations of this systematic review. Firstly, this systematic review is the first to evaluate the psychometric properties of medication adherence measures used in consumers taking antidepressant medicines for depression without comorbidity. Knowledge of whether the adherence measures are reliable and valid is critical to informing and determining the effectiveness of antidepressant medicines. It is likely that in some cases, the assumption of "good" adherence, in consumers who are non-adherent, may contribute to the conclusion that a particular antidepressant medicine is not effective for the individual. Hence the importance of knowing the psychometric properties of measures of adherence. Secondly, this review is based on an established framework for medication adherence which conceptualizes medication taking behaviour as the initiation, implementation, and discontinuation of therapy. This is important because depending on the phase of adherence, different evaluation measures (for adherence) and strategies to address non-adherence may be required.

There are also some potential limitations. Firstly, this systematic review required the assessment of the adherence phase being evaluated, and the evaluation of adherence measures used at these different phases. Most studies did not conceptualize adherence in the same way nor did they include comprehensive details about the statistical procedures used to determine the psychometric properties of the measures. Although any assumptions were kept to a minimum when extracting data, the researchers did not attempt to contact authors for clarification, in cases of incomplete or missing data. This is because the researchers acknowledge that the focus of this review was different to the focus of most of the included studies. Secondly, although a standardized framework was used for adherence, lack of standardized definition for adherence in the included articles and the use of different terms (e.g. compliance, concordance), sometimes used interchangeably, meant that it was challenging to extract data from some papers. Similarly, some papers used the terms - reliability and validity – without further explanation or details about the type of reliability or validity measured (Table 1) or the statistical procedures. Hence the data extracted from some of the articles were based on the researchers' interpretation of the articles. Lastly, although the initial search for the relevant articles and results extraction was conducted by one researcher, twenty percent of included articles were cross-checked by a second researcher.

This study focuses on people with unipolar depression without comorbidity, in order to enhance the internal validity of findings. The external validity of the findings may be limited, for example, consumers with unipolar depression and co-morbidity.

4.2. Conclusion

A range of objective and subjective measures have been used to assess antidepressant adherence in consumers with unipolar depression, mainly during the implementation and discontinuation phases of adherence. No measure exclusively assessed medication adherence at the initiation phase, which is especially critical for consumers with depression. Self-report measures were the most commonly used and were also practical measures of medication adherence for consumers with depression in the clinical setting. Although the psychometric properties of various measures of medication adherence have been evaluated, a standout measure with strong reliability and validity was not apparent.

Practice implication

In the absence of a gold standard measure which captures adherence across the three phases of adherence or instruments with strong psychometric properties across the different phases of adherence, a range of different subjective and objective measures of adherence should be combined, as a practical approach to assessing adherence in consumers with depression. This systematic review provides a practical comprehensive evaluation of measures of medication adherence which can be used to assess antidepressant medication taking in consumers with depression. These data may be used to guide patient care with the view to improving outcomes in depression. It is also recommended that future studies clearly indicate the phase of adherence being assessed, in order to better understand the complexities associated with the use of antidepressant medicines for the management of unipolar depression.

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Conflicts of interest

The Authors declare that there is no conflict of interest.

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Appendix

Table 1A
Characteristics of included articles

Author, Year (Country)	Setting (n)	Study design	Duration	Study sample (n)	The specific measure of adherence used	Procedures/details for measure adherence	Adherence/Non-adherence definition	Phase of adherence*
Katon et al., 1994[38]	Primary care clinic (2)	Two - group prospective study	4 months	2 groups (164) 1. Minor depression (78) 2. Major depression (86)	Patient self-report: by telephone interview	There were 3 main questions about adherence: 1) Whether the patients were taking the medicine at the time of the interview 2) When they quit their medicine 3) How many days they took antidepressant medicine in the last 2 weeks	No data available	Initiation and implementation
Katon et al., 1996[23]	Primary care clinic (1)	Randomized controlled trial	7 months	4 groups (153) 1. Major depression: intervention (31) 2. Major depression: control (34) 3. Minor depression: intervention (46) 4. Minor depression: control (42)	1. Patient self-report: by telephone interview 2. Automated prescription refills	The authors did not provide details of the interview questions.	Patients were considered adherent if they reported having taken their medicine on at least 25 of the last 30 days and 116 or more days at 4 months. Refill records were processed to determine whether patients continued treatment with antidepressant medicines for at least 30 days and used medicines at or above the lowest dosage level in the range of therapeutic doses recommended by the Agency for Health Care Policy and Research (AHCPR) guidelines.	Initiation, implementation, and discontinuation
Saunders, 1998[24]	Primary care clinic (1)	Single - group prospective study	4 months	1 group (164)	1. Patient self-report: by telephone interview 2. Automated prescription refills	For self-report: two main questions were asked: 1) How recently they took an antidepressant? 2) How many days they took the medicine in the last month?	They defined patients as a current user when s/he reported that s/he had taken antidepressants at least 25 out of the last 30 days and when s/he received enough pills in the fill.	Initiation and implementation
Peveler et al., 1999 (UK)[25]	Primary care clinic (no data)	Single-blind randomized controlled trial	3 months	4 groups (213) 1. No intervention (55)	1. Confidential self-reporting by participants 2. MEMS	The authors did not provide details of the self-report questions.	No data available: They reported continuous and discontinuous antidepressant treatment.	Initiation, implementation, and discontinuation

				2. Leaflet only (53) 3. Drug counseling only (52) 4. Leaflet and counseling (53)				
Bultman and Svarstad, 2000[43]	Community pharmacy (23)	Single - group prospective study	2 months	1 group (100)	Patient self-report: by telephone interviews	Self-report adapted from Brief Medication Questionnaire 1) "Are you currently taking antidepressant?" 2) Missing doses in the past week and over the study period 3) Clients reporting that they were no longer using antidepressant were asked about the circumstances leading to discontinuation.	Participants currently taking antidepressant were considered to have continued treatment. They defined medication omissions as: 1) Missing at least one dose over the study period 2) Definitely missed one or more doses in the past week 3) Completely stopped their medicine	Initiation, implementation, and discontinuation
Claxton et al., 2000 (UK)[40]	Primary care center (18)	2 phase: 1. Single – group prospective study 2. Multi-center, open-label, randomized controlled trial	Phase1:1. month Phase2: 3 months	Phase 1: 1 group (117) Phase 2: 2 groups 1. Control (53) 2. Treatment (56)	MEMS	Percentage of adherence was calculated for each patient as the number of adherent doses divided by the number of prescribed doses multiplied by 100. The percentages of adherence doses were averaged to yield the overall adherence for each randomly assigned group.	Adherence with the prescribed dosing regimen was calculated by coding each dose as adherent or non-adherent (0/1) on the basis of whether the dose was taken within the prescribed interdose interval ± 25%.	Implementation
George et al., 2000 (UK)[26]	General practice (no data)	Randomized controlled trial	3 months	4 groups (88): 1. Control (23) 2. Intervention 1 3. Intervention 2 (23) 4. Intervention 3 (22)	1. Patient self-report 2. MEMS 3. Blood test 4. Pill counts	1. The four-item Morisky, Green, and Levine Self-Reported Medication Taking Scale (MGLS) 2. MEMS: percentage of monitored days on which the container was opened (assumed as the correct number of doses were taken) 3. Blood test: the ratio of metabolite to parent drug	Adherence was defined as: 1. MGLS scores (0 = high adherence, 3–4 = low adherence) 2. MEMS: 80–100%, 3. Blood test: ratio of nordothiepin: dothiepin < 1.1 4. Pill counts: the number actually removed was expressed as a percentage of the	Initiation, implementation, and discontinuation

						4. Pill counts: the number of tablets/capsules issued and the number remaining in the bottle were recorded and the difference compared with the number that should have been taken according to general practitioner's instructions.	number which should have been taken.	
	Sirey J.A., 2001[27]	Outpatient clinic[64]	Single – group prospective, naturalistic study	3 months	1 group (134)	1. Patient self-report and adherence scale: by brief interview 2. Chart records of plasma drug concentration	1. Self-report and adherence scale: Adherence was assessed through a brief interview designed to identify the pattern of medication use. The patients were asked in a nonjudgmental manner the frequency and pattern of missed doses and whether they had stopped taking their medication completely. 2. The chart record of plasma drug concentrations	1. Adherence scale on a Likert scale ranging from 1 to 6, where 1–5 was interpreted as non-adherent and 6 as adherent 2. Therapeutic plasma concentrations of nortriptyline between 50 and 150 ng/mL was classified as adherent. (Systematic non-adherence, defined as missing > 15% of scheduled doses)	Implementation and discontinuation
	Akerblad et al., 2003 (Sweden)[28]	Outpatient clinic (no data)	Randomized controlled trial	6 months	3 groups (1,031) 1. Adherence enhancing program (366) 2. Therapeutic drug monitoring (326) 3. Control (339)	1. Questioning by the general practitioners 2. Serum level 3. Appointments kept 4. Composite index	1. Adherence based on questioning, “Has the patient taken antidepressant as prescribed?” 2. Adherence based on measurable serum levels. Serum level determined by means of high-performance liquid chromatography with ultraviolet-detection. 3. Adherence based on appointments kept to pre-set visits at week 4, 12 and 24. 4. Adherence based on a composite index: of (1–4) above	Patients had to fulfill the adherence criteria for all three assessments (1–3) to be classified as adherent. Patients not fulfilling the adherence criteria were classified as non-adherent.	Implementation
	Kwon et al., 2003[29]	Primary care setting: (9): general medical practices, and a community health center	Cross-sectional, longitudinal study	18 months	1 group (422)	1. Claims data 2. Patient self-report: a mailed questionnaire	Three dichotomous measures of current antidepressant use (see below), two from self-report and one from claims data, were recorded. These variables produced a yes/no indicator of whether the patient was	1. Claims data: the appearance of antidepressants on claims database using the same set of antidepressant generated earlier from	Implementation and discontinuation

						currently taking an antidepressant. 1. Claims data: the appearance of antidepressant medicines on claims database within 90 days prior to the study 2. Self-report medication adherence: 2.1) Direct self-report measure using 2 questions "Do you now take any prescription medicines for depression?" and "Are you now taking a prescription medicine for depression?" 2.2) Patients were asked to write down the names of all their medicines ("List" self-report).	the "list" of self-report medicines. 2. Self-report: 2.1) A Yes answer to the question "Do you now take any prescription medicines for depression?" was classified as adherent. 2.2) A list of antidepressant medicines on their medication self-report list.	
	Sleath et al., 2003[41]	Community pharmacy (8)	Cross-sectional study	No data available	1 group (81)	Face-to-face interview	Face-to-face interview: using Brief Medication Questionnaire (BMQ) with additional 4 questions, which were 1) What antidepressant the patient was taking? 2) How long the patient had been taking the antidepressant (months)? 3) How many times per day the patient took the antidepressant? and 4) Demographics data, side effects experienced	Based on interview data and BMQ questionnaire: patients who were 80 percent or more adherent to their antidepressant during the past week were classified as adherent. (Total doses taken divided by total doses should have taken multiplied by 100)	Implementation
	Capoccia et al., 2004[44]	Primary care clinic (1)	Randomized controlled trial	1 year	2 groups (74) 1. Enhanced care (41) 2. Usual care (33)	Patient self-report by telephone interview	They asked patients about the number of days they took their antidepressant medicine in the past month.	The use of antidepressants for at least 25 of the past 30 days was classified as adherent.	Initiation, implementation, and discontinuation
	Aikens et al., 2005[30]	Primary care setting: Physician family medicine clinic (12)	Cross-sectional study	No data available	1 group (81)	1. Two types of patient self-report 2. Pharmacy refill data	1. Self-report: 2 separate aspects of adherence were assessed 1.1) Recent percentage of adherence was measured using - The first 3 items from Brief Medication Questionnaire	No data available	Implementation, and discontinuation

							- Participants indicated the number of days in the past 2 weeks that they took their antidepressant, the dosage they took, and the number of the doses they took per day. Self-report number of days of treatment adherence was divided by 14 and multiplied by 100 to reflect the recent percentage of adherence (adherence rate). 1.2) Overall (general) adherence was assessed by MGLS 2. Pharmacy refill data: 3-month medication possession ratio was computed	1. Adherence calculation on MEMS: The number of recorded openings on MEMs divided by the number of monitored days in the prescription period. 2. Pharmacy medication records: The pharmacists recorded class of medication per patient, the number of pills, the date that the prescription was actually filled, and the date on which the patient had to come to the pharmacy to refill the container.	No data available	Initiation and implementation
Brook et al., 2005 (The Netherlands)[31]	Community pharmacy (19)	Randomized controlled trial	6 months	2 groups (147) 1. Intervention (64) 2. Control (71)	1. MEMS 2. Pharmacy medication records				
Brown et al., 2005[32]	Primary care section (no data)	Cross-sectional study	No data available	1 group (192)	2 types of patient self-report			1. Beliefs about Medicines Questionnaire: 18-item self-report (BMQ-specific and BMQ-general) to assess patients' views about antidepressant medication and medicines in general. 2. MGLS to assess medication taking behaviour.	No data available	Implementation and discontinuation

Rickles et al., 2005[33]	Community pharmacy (8)	Randomized controlled trial	6 months	2 groups (63) 1. Intervention (31) 2. Usual care (32)	1. Pharmacy records 2. Insurance claims data 3. One question self-report via telephone (similar to the Brief Medication Questionnaire)	1. Pharmacy records: the number of missed doses was calculated by multiplying the number of prescribed doses per day times the number of days late between refills for the first 3-month period and second 3-month period. Results were multiplied by 100 to yield the percentage of missed doses for each period. 2. Insurance claims data: the consistency between insurance claims data and pharmacy records was compared 3. Self-report: patients were asked, “in the past 7 days ending yesterday, how many times did you miss taking a pill?” This item is similar to the item used in the Brief Medication Questionnaire (BMQ by Svarstad). Which has been proved previously[49] to have excellent predictive validity.	No data available	Initiation and implementation
Russell and Kazantzis, 2008 (New Zealand)[34]	Primary care section (no data)	Cross-sectional study	No data available	1 group (85)	2 types of patient self-report	1. MARS: Medication Adherence Report Scale 2. Beliefs about Medication Questionnaire	No data available	Implementation
Yeh et al., 2008 (Taiwan)[39]	Outpatient clinic (no data)	Cross-sectional study	No data available	1 group (181)	Patient self-report questionnaire	A structured self-report questionnaire with 5 point Likert scales adapted from the adherence questionnaire for elderly hypertensive patients in Taiwan by Hu et al. (1996). The present study added 5 questions to address patient-specific issues.	Summative scores were computed with higher values indicating better medication adherence.	Implementation
ten Doesschate et al., 2009a (The Netherlands)[15]	Psychiatric centers (no data)	Cohort study	2 years	1 group (91)	Patient self-report	Adherence scores from the Medication Adherence Questionnaire (MGLS).	1. Patients taking > 80% of their antidepressants medicines were classified as adherent. 2. Patients missing 20% or more of the doses of	Implementation, and discontinuation

							their antidepressant medicines were classified as non-adherent. 3. Based upon 7 assessment points, patients classified as always adherent (adherent at all assessments) or as non-adherent (not adherent at all assessments) over 2 years.	
ten Doesschateet a-l., 2009b (The Netherlands)[12]	Not reported	Single – group prospective study	2 years	1 group (131)	Patient self-report	Adherence scores from MGLS reported as the Medication Adherence Questionnaire	1. Patients taking > 80% of their antidepressants medication were classified as adherent. 2. Patients were classified as always non-adherent (all assessments non-adherent), intermittently adherent (not all assessments adherent) and always adherent (all assessment adherent).	Implementation, and discontinuation
Gabriel and Violato, 2010[47]	Outpatient (no data)	Cross-sectional	No data available	Patients (63)	Patient self-report	The Antidepressant Adherence Scale (AAS) developed by modifying MGLS. Responses about medication adherence were limited to the four weeks prior the current adherence assessment and were converted to a numerical response, instead of a categorical response.	Patients who missed taking their antidepressant for any reason five times or more during the four weeks following psychiatric consultation were considered as non-adherent.	Implementation and discontinuation
Interian, 2010[35]	Outpatient at a community mental health center (1)	Randomized controlled trial	5 weeks	2 groups (47) 1. Intervention (no data) 2. Usual care (no data)	1. Patient self-report 2. MEMS	1. MGLS 2. MEMS: adherence percent was calculated as the number of days the medication was taken, divided by the total number of days (% of days medication taken).	1. MGLS scores = 0–4 (higher scores indicate poorer adherence) 2. MEMS ≥80% was classified as adherent.	Implementation and discontinuation
Lee et al., 2010 (Korea)[36]	Outpatient clinic (1)	Two – group prospective study	1 month	2 groups (76) 1. Adherence (40)	1. Patient self-report 2. Pill counts 3. MEMS	1. Self-report: Patients were asked to estimate their adherence between 0 and 100%.	The following criteria were classified as adherent: 1. Self-report: Adherence threshold > 80%	Implementation

				2. Non-adherence (36)	4. Clinician rating scale	2. Pill counts: A pill count adherence index was derived from the ratio of the actual pill counts as recorded by the investigator at the follow-up visit. 3. MEMS: They measured adherence as the proportion of the times vial caps were opened in a given month relative to the prescribed doses for that month. 4. Clinician rating scale: An ordinal scale of 1–7, with the higher numbers meaning better adherence. Adherence was evaluated in two ways- a continuous variable (self-report, pill counts and MEMS) and dichotomous variable (adherent and non-adherent). All continuous variables were then converted to dichotomous variables.	2. Pill counts: Pill count index > 80% 3. MEMS: > 80% 4. Clinician rating scale: A score of 5 or more.	
Prukkanone et al., 2010 (Thailand)[42]	Outpatient Hospital (1)	Single – group retrospective study	6 months	1 group (1,058)	Pharmacy records	Medication possession ratio (MPR): the number of days for which the drugs have been supplied during the follow-up period divided by the number of days elapsed during the period.	MPR > 80% or 0.8 were classified as adherent.	Initiation and implementation
Interian et al., 2013[37]	Community mental health center (1)	Randomized controlled trial	5 months	2 groups (50) 1. Usual care (24) 2. Enhanced treatment (26)	1. Patient self-report 2. MEMS	1. MGLS 2. MEMS: Adherence was calculated by dividing the number of days that the container was opened by the number of days in the time period.	No data available	Implementation and discontinuation
Gabriel, 2015 (no data)[48]	Outpatient (no data)	A randomized single-blinded, perspective study	12 weeks	2 groups (70) 1. Intervention (40) 2. Standard care (30)	Patient self-report	The Antidepressant Adherence Scale (AAS)	No data available	Implementation and discontinuation

*Research evaluation based on adherence definition from the European consensus on medication adherence (The Ascertaining Barriers to Compliance project: ABC project[1]).

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PART C - FACTORS INFLUENCING TO MEDICATION ADHERENCE TO ANTIDEPRESSANT MEDICINES IN UNIPOLAR DEPRESSION

CHAPTER FOUR – Consumer related factors influencing antidepressant adherence in unipolar depression: A qualitative study

Chapter introduction

It is important to realise that adherence to antidepressant medicine is crucial to the treatment of unipolar depression; this is because depression requires long-term treatment from acute to maintenance phases. In general, regular consumption of antidepressant medicine is recommended for at least of 6–9 months after the alleviation of depressive symptoms for the first episode of depression, and even longer in people with recurrent episodes. Nevertheless, a low rate of adherence is often reported after six months of treatment initiation, in particular during the maintenance phase in which the person is symptom-free. As discussed in Chapter Three, it is not only the right measure that is required to yield a reliable adherence rate, but a better understanding of the potential causes of non-adherence from the consumer perspective in order to improve medication adherence in unipolar depression. Despite many studies that have explored factors pertaining to medication adherence in unipolar depression, none have employed the ABC taxonomy. In addition, the existent information of the facilitators of and barriers to medication adherence throughout the adherence process is fragmented. Therefore, this part of the thesis (Chapters Four and Five) aimed to collect and explore the facilitators of and barriers to medication adherence at each adherence phase (initiation, implementation, and discontinuation) from the consumer's perspective.

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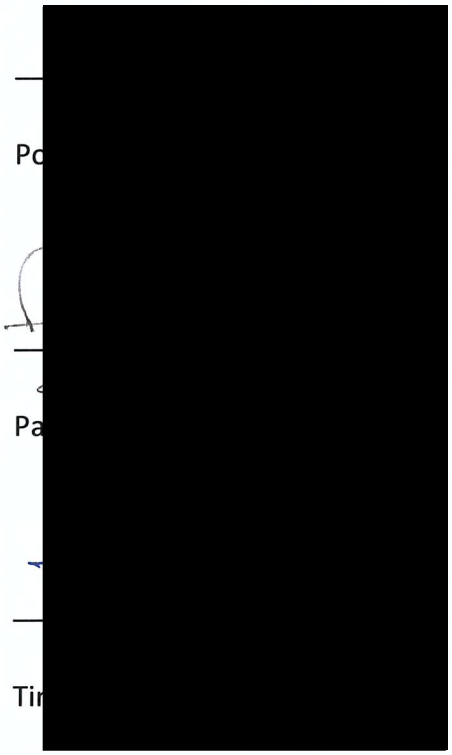
Authors' Contributions

Timothy F Chen conceptualised the study. Timothy F Chen and Pornchanok Srimongkon conducted data collection (face-to-face interviews). Pornchanok Srimongkon wrote the first draft of manuscript. Timothy F Chen and Parisa Aslani assisted in conducting the study and critically revised the manuscript.



Patient Preference and Adherence

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ORIGINAL RESEARCH

Consumer-related factors influencing antidepressant adherence in unipolar depression: a qualitative study

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Patient Preference and Adherence

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Purpose: To explore factors which facilitate and negatively impact adherence, at initiation, implementation and discontinuation phases of adherence to antidepressant medicines.

Patients and methods: Semi-structured, face-to-face interviews were conducted with patients suffering from unipolar depression. The digitally audio-recorded and transcribed verbatim were used. Transcripts were thematically content analyzed and data managed using N-Vivo software.

Results: Twenty-three interviews were conducted. The predominant factors facilitating initiation of therapy included self-motivation and severity of depression. Factors aiding persistence with therapy included belief in, and effectiveness of, antidepressants. Stigma and fear of adverse events inhibited initiation of therapy, whilst adverse events and ineffectiveness of antidepressants contributed to discontinuation. Patients with strong perceptions of the necessity and few concerns about antidepressants were more likely to adhere to treatment at all phases of adherence.

Conclusion: Different factors influence medication adherence at the different phases of adherence. These factors were based on individual perceptions about depression and its treatment, and actual experiences of antidepressant treatment. This information should be considered by health care professionals in delivering targeted and tailored interventions to foster adherence. Strategies to address medication non-adherence in unipolar depression patients should consider the phase of adherence and individual perceptions about depression and its treatment, along with previous experiences with treatment for depression.

Keywords: depression, adherence, influencing factors, facilitators, barriers

Introduction

The most frequently cited definition of medication adherence, developed by the World Health Organization, is "the extent to which a person's behavior-taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider".[1] More recently, medication adherence has been defined by a European consortium of researchers (ABC project: the Ascertaining Barriers for Compliance of medicines) as a continuous process, comprising three phases: initiation, implementation and discontinuation of therapy.[2] Initiation occurs when the patient takes the first dose whilst discontinuation occurs when the patient stops taking the prescribed medication. Implementation of therapy refers to the actual dosing of medication consumption from initiation until the last dose.[2]

Globally, the total number of people living with depression was estimated to exceed 300 million in 2015, equivalent to 4.4% of the world's population.[3] This estimation increased by 18.4% between 2005 and 2015.[3] Depression is ranked by the WHO as

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the single largest contributor to global disability and suicide deaths.[3] However, medication adherence rates in depression are low. Approximately 30% of patients with depression do not complete their treatment.[4] The average length of treatment in unipolar depression has been reported as <6 months, with 50%–60% discontinuation rates within the first 10–16 weeks of treatment.[4–7] In one study, only 20% of patients reported good adherence (adherence rate above 80%) at 4 months after treatment initiation,[5] while most treatment guidelines recommended continuation of antidepressant treatment for 6–9 months after recovery.[8,9]

Depression itself is a risk factor for non-adherence.[10,11] A meta-analysis showed that medication non-adherence was three times higher in patients with depression compared to other conditions.[11] Antidepressant non-adherence may lead to unnecessary switches in antidepressant medications, superfluous instructions to increase the dose, initiation of unwarranted adjuvant treatments, and misclassification of patients as treatment resistant.[12] One study in the USA reported that 4.8% of patients did not initiate antidepressant treatment at 6 months after an antidepressant was prescribed, and 12.2% reported ceasing therapy within the first 6 months.[13] The most important reason for those who did not commence antidepressants was concern about potential adverse drug reactions (ADRs), while the most important reason for ceasing antidepressant treatment was that the antidepressant was not helping.[13] Other factors contributing to early discontinuation of antidepressant medicines include adverse effects, severity of illness, comorbidity, personality traits, and lack of support from health providers.[14,15] Previous studies have shown that the symptoms of depression improving or becoming worse, the uncertainty about the usefulness of antidepressants, experience of side effects or adverse events, perceived stigma, peer pressure, adverse media stories, preexisting beliefs, difficulties with cost and the availability of care, and preference for other interventions, particularly counseling, are common reasons for individuals to stop taking antidepressant medicines.[16–19] While some studies have shown that personal experiences with antidepressant medicines have a major impact on treatment continuation, such as belief in and acceptance of antidepressant medicines as a treatment option, acceptance of their condition, no side effects, fear of recurrence of symptoms of depression if antidepressant medicines are ceased, positive attitudes and interaction with doctors directly influence whether consumers take antidepressant medicines.[19,20]

Medication adherence is a continuous and dynamic process that can change over time and is an individual patient behavior which is complex and is simultaneously influenced by several factors.[21,22] Moreover, non-adherence may occur more frequently during a particular phase of treatment.[23] To maximize treatment outcomes, it is crucial to consider the potential factors influencing adherence at each phase of adherence. Although existing studies have discussed a range of factors influencing medication adherence, most of them have focused on the implementation and discontinuation phases[16–20] or have not specified the phase(s) of adherence assessed. For this reason, a qualitative approach which focuses on the way people interpret their lived experiences[24] was employed in this study. The aim of this study was therefore to explore the facilitators or positive influencing factors which promote medication adherence at three phases of adherence (ie, initiation, implementation, and discontinuation) in unipolar depression from patients' perspectives; and to explore the barriers or negative influencing factors which reduce medication adherence at all phases of adherence.

Patients and methods

This was a qualitative study which used a phenomenological approach, to explore individual lived experiences of antidepressant medicine taking (the phenomenon of interest) in consumers with unipolar depression who lived in the Sydney metropolitan area. This approach allowed for the collection of detailed self-reported information relating to individual attitudes and perceptions while also providing a basis for disclosure and comparison between responses. This study was approved by the Human Research Ethics Committee of the University of Sydney and has been reported in accordance with the consolidated criteria for reporting qualitative studies (COREQ32).[25] The inform consent and relevant information had been given to the participants, therefore the consent form was signed prior to the commencement of an interview process.

Study participants

A purposive sample of consumers with unipolar depression was recruited to ensure mix of gender, age, duration of current and previous use of antidepressants. The inclusion criteria for this study were: 1) age ≥18 years, 2) able to speak English fluently, without needing a translator, and 3) antidepressant medicine prescribed for unipolar depression currently or consumers who had ceased antidepressants in the 6 months prior to recruitment.

Recruitment

A three-pronged recruitment strategy was employed which included recruitment of participants from community

pharmacies located within 15 km of the University of Sydney, through advertising on Internet websites and via a market research company. For the first strategy, 27 pharmacies were approached and 19 agreed to participate. Of those who did not participate, five did not respond and three refused to participate (one pharmacy did not have a policy to participate in research, one did not agree with the recruitment process and another did not give a reason). Participating community pharmacies displayed study advertisements and provided flyers to potential participants who were collecting a repeat prescription for an antidepressant for unipolar depression. Potential participants who were interested in taking part in the study were then directly contacted by the researchers via e-mail, text message, or phone.

Interview guide

A semi-structured interview guide was developed to address the specific study objectives. The interview guide was based on the ABC conceptual framework for adherence, published literature and the experience of research team members. Key topics included personal experiences of depression, previous experiences of taking antidepressants and side effects, effectiveness of antidepressants, support network, relationship with doctors and other health care professionals, stigma experienced, alcohol consumption, smoking behavior and lifestyle.

Data collection

Individual, face-to-face interviews were conducted. The interviews were digitally audio-recorded and transcribed verbatim. Participants fulfilling the inclusion criteria were interviewed by one of the researchers, P.S. (n=16) or T.C. (n=7). Participants gave written consent for interview recording and for publication of de-identified data. The study participants' names were replaced by a code number once the interviews were transcribed. The transcripts were also checked for accuracy against the original recordings by P.S. The interviews lasted between 20 and 69 minutes and were carried out between February and August 2015. Data analysis was performed during July 2015 to February 2016. Interviews were conducted until data saturation,[26] which was reached at the 21st participant. An additional two participants were interviewed to ensure that there were no further emergent themes.

Data analysis

Coding of the transcripts was carried out using iterative thematic analysis, with NVivo10 program for data management. The codes were extracted and grouped according to the themes and subthemes.[24] Themes were derived from data extraction and grouped under the ABC framework for positive and negative factors at the three phases. Initial coding was performed by the first author (P.S.). Findings were cross checked by the other two investigators, experienced in qualitative data analyses.

Results

Twenty-three participants were recruited. Of these participants, eight were recruited from community pharmacies, and 15 were recruited via a market research company. No participants were recruited via online advertising. No data on the response rate for participants recruited by the market research company or through community pharmacies were available. Participant characteristics and the current use of antidepressant medicines are presented in Table 1.

This research focused on patient-related factors, derived from their actual experiences, which were reported to influence medication adherence, from initiation to discontinuation. The results obtained related to the first antidepressant

Table 1 Characteristics of the participants (n=23)

Characteristics	N
Demographic data	
Age range (years): 19–63, median: 37, mean: 40	
Gender: females/males	15/8
Self-report ethnic group	
– Oceania (Australia or New Zealand)	16
– Others (Americas, South-East Asia, North-West Europe, South African, Southern and Eastern Europe)	7
Living circumstances	
– Living with partner or family	10
– Living with roommate/housemate	5
– Living alone	8
Highest level of education completed	
– Secondary	6
– Diploma	3
– Bachelor	9
– Postgraduate	3
– Other*	2
Prescription of antidepressant: $<5/\geq 5$ years	13/10
Current antidepressant medicines prescribed	
SSRIs: citalopram, escitalopram, fluoxetine, paroxetine, sertraline	9
SNRIs: desvenlafaxine, duloxetine, venlafaxine	7
TCA: amitriptyline	1
Others: mirtazapine, phenelzine, reboxetine	3
Most recently ceased antidepressant medicines prescribed	
SSRIs: escitalopram, sertraline	3

Note: *Primary school, certificate.
Abbreviations: SSRI, selective serotonin reuptake inhibitors; SNRI, serotonin-norepinephrine reuptake inhibitors; TCA, tricyclic antidepressants.

ever prescribed through to the most recent one for the participant. Most participants had tried a range of different antidepressant medicines over a period of time in order to find the "right one". A few participants had recently ceased taking their antidepressant medicine or reported intermittent consumption. Some of those who had ceased their antidepressant medicine were looking for an affordable and effective medicine with less or no ADRs. The majority of participants had chronic depression, and so had experience of restarting new treatment cycles with different antidepressant medicines. Some participants tried to cease their antidepressant medicines to see if they could cope without them. Most participants realized the need for antidepressant medicines in order to boost their mood and day-to-day function.

At initiation, participants were more likely to commence antidepressants once they accepted that their depression was real and if they valued antidepressant treatment. Belief in and awareness about the need for antidepressants, as well as positive treatment effects, encouraged participants to adhere to antidepressant medicines. Although, fear of possible ADRs was not common, it was a strong barrier at initiation. Unpleasant ADRs, unsatisfactory treatment outcomes and depressive symptoms were common barriers which led to discontinuation of treatment. The index of the terms used in this study, in relation to influencing factors is shown in Table S1.

Positive factors

A broad range of positive influencing factors at the three phases of adherence were identified. Self-motivation; self-management; and belief in and awareness about the need for, the importance of, and the effectiveness of antidepressant medicines were main facilitators reported at all phases. At initiation, the predominant factors were self-motivation, patient perception that depressive symptoms were real and manageable, and willingness to follow doctor's order. During the implementation phase, positive effect of antidepressant treatment with minimal ADRs experienced, and the ability to self-manage were reported as the main facilitators. To prevent discontinuation of therapy, positive influencing factors included self-motivation and belief in antidepressant therapy. Figure 1 shows a schematic representation of positive factors reported to influence medication adherence at all phases.

Positive factors at initiation of therapy

Multiple factors were reported to encourage medication adherence at initiation: self-motivation, the acceptance of depression diagnosis, willingness to follow doctor's orders, the severity of depressive symptoms, and recognition of antidepressant medicines. The majority of participants revealed that they wanted to feel better. Some participants wanted to be "cured" or "feel like normal" and that was the main factor that motivated them to commence antidepressant therapy

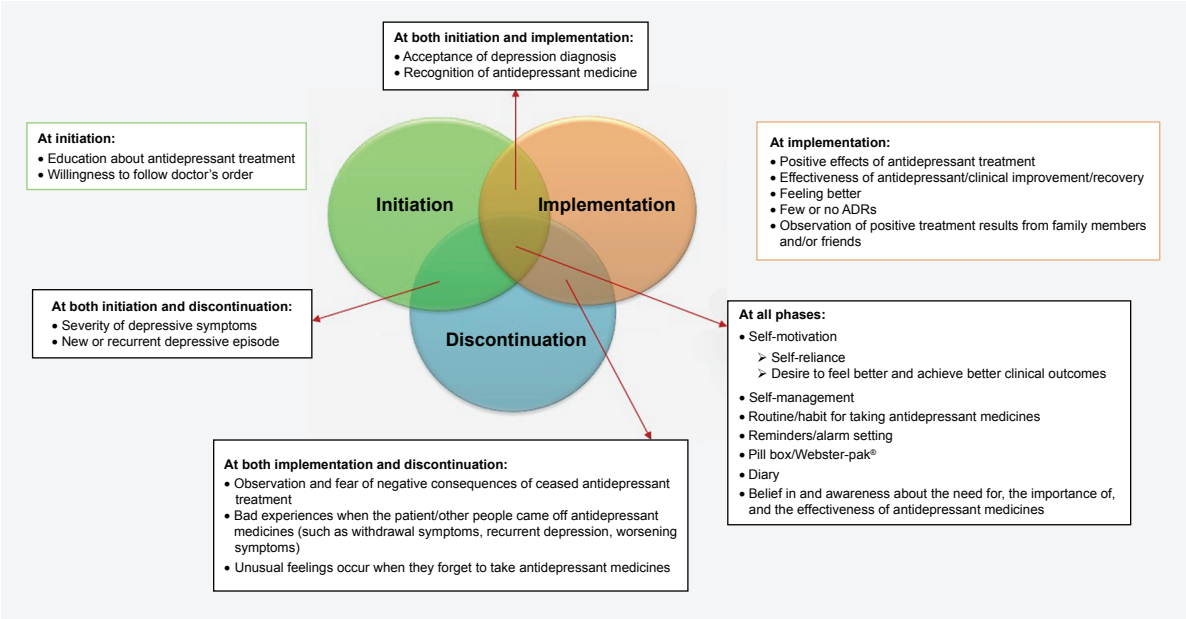

Figure 1 Factors which positively influenced medication adherence at the three phases of adherence: initiation, implementation, and discontinuation of therapy.
Abbreviation: ADRs, adverse drug reactions.

(quote no 1, Table 2). Once participants realized that they were experiencing depressive symptoms, they were more likely to start an antidepressant. When patients believed in and valued antidepressant medicines, they were more likely to take them regularly. Some participants mentioned that the severity of depressive symptoms compelled them to commence antidepressants. More severe depressive symptoms provided a greater motivation to commence the treatment. However, in a few cases when patients were too ill to make a critical decision about their treatment, they relied more on their doctor rather than their own decision. Some participants indicated that they believed in their doctor's judgment, and therefore followed their doctor's advice.

Most participants suggested a variety of strategies which might encourage adherence to antidepressants such as early detection of depression and providing more education about the value of antidepressant medicines to target population.

Positive factors at implementation of therapy

A range of predominant factors were identified as positively influencing adherence at the implementation phase: positive effect of antidepressant therapy, belief in and realizing the need for antidepressant medicines, self-management, and fear of the effects if antidepressant therapy is ceased. The majority of participants reported that positive effects of antidepressant treatment, particularly the effectiveness of antidepressant medicines was the main reason to adhere to antidepressants. Participants were likely to continue their antidepressant medicine if depressive symptoms were lessened with few or no undesirable ADRs.

Self-management was a predominant positive factor for the majority of participants for persisting with therapy. A number of participants revealed that once they realized the importance of antidepressant therapy and believed in them, they organized a routine for taking their medicine regularly. The majority of participants reported a variety of techniques that they used to remind themselves to take their antidepressant regularly, for example, using a pill box, or setting an alarm (on their phone), putting their antidepressant medicine in a noticeable spot (such as next to the coffee maker or on a bedside table), choosing a regular time to take their antidepressant (such as the first thing to do in the morning, after breakfast, or before going to bed). In one case, a participant used a diary to remind herself to take her antidepressant routinely. Self-management was also important at this phase. Some participants indicated that they believed

Table 2 Indicative quotes of positive and negative factors influencing the three phases of adherence

Factors	Themes	Quotes
Positive	Self-motivation	1. [I wanted] to lessen some of the symptoms that I had […] I was down, really down and upset [No 9/M/30 Y; Adherence phase: I/P/D]
		2. I'll just keep going down and down and down until I feel I've got to get back up again. I'll start that [antidepressant] again. [No 5/F/57 Y; Adherence phase: I/P/D]
	Fear of negative consequences of ceased antidepressant medicines	3. It took nearly a week [for them] to work and since then I've had a fear of stopping them so I've never really done it because I am too scared to stop and get those feelings back. [No 20/F/53 Y; Adherence phase: P/D]
	Belief in and the effectiveness of antidepressant medicines	4. I'm a little bit doubtful, but, […] I've seen medication [used] in family and friends, and I've seen it work. [No 15/M/44 Y; Adherence phase: I/P/D]
Negative	Fear of anticipated ADRs	5. I was really worried about weight gain and I didn't want to take medication that would make me gain weight. [No 22/F/28 Y; Adherence phase: I]
	Self-stigma	6. I really didn't want to [take them] in the beginning. I think it's just […] embarrassing […] I felt like there's something wrong with me […] [but] I could just talk myself into being happy instead of having to take it. [No 22/F/28 Y; Adherence phase: I/P/D]
	Experiencing unpleasant ADRs	7. The Avanza® [mirtazapine], it was prescribed to me, I was in a pretty difficult position and with Avanza it helps you sleep but I didn't like it because I stacked on the weight [No 21/M/45 Y; Adherence phase: I/P/D]
	Economic issue	8. The newest one that I tried which I went off was Valdoxan® [agomelatine] because it was so expensive [No 5/F/57 Y; Adherence phase: P]
	Forgetfulness	9. First thing I'll do is just put that [antidepressant] in my hand and take it. I made the mistake of putting my tablet two days ago into my dressing gown pocket, and that's where it stayed. I found it the next day. Forgetfulness is also a symptom of depression and I find that I do suffer [No 19/F/60 Y; Adherence phase: P]
	Previous negative experiences of antidepressant medicines	10. When I read the symptoms or side effects of it, I thought, yeah, I've had this before. I'm not going on it. [No 18/M/28 Y; Adherence phase: D]

Abbreviations: M, male; F, female; Y, years old; I, initiation; P, implementation; D, discontinuation.

in antidepressant medicines, and trusted and were willing to follow doctor's order.

Some participants stated that they feared the effect if they ceased their antidepressant medicine, as they had previously had experienced or heard about negative outcomes in other people (quote no 3, Table 2). Some participants observed positive results of antidepressant treatment from other people, which effectively motivated them to continue therapy.

A few participants mentioned that they wanted better health outcomes and so this motivated them to continue their antidepressant medicine. Two participants revealed unusual feelings when they missed a dose (one explained an electric shock-like feeling, another one reported a "zapping" sensation), and this reminded them to continue to take their medicine.

Comorbidity can affect medication adherence in different ways. One participant had depression along with chronic pain, and was willing to take antidepressant medicines regularly, because they relieved both conditions. While another participant reported some difficulties in adherence to antidepressant medicines because of attention deficit hyperactivity disorder.

Most participants realized the benefits of commencing and maintaining some activities or lifestyles that improved depressive symptoms such as meditation, gentle exercise, hobbies and social activities. In a few cases, although participants stated that they believed more in alternative treatments such as acupuncture or herbal medicines, they decided to stay on antidepressant treatment.

Positive factors at discontinuation of therapy

The discontinuation phase of adherence occurred when an individual stopped taking their antidepressant medicine of their own accord. Unlike initiation and implementation, which are "positive" behaviors, discontinuation is a "negative" behavior. Therefore, in contrast to initiation and implementation, positive factors contribute to discontinuation, whilst negative factors stop discontinuation. Hence, positive factors at this phase were similar to negative factors at the implementation phase.

Negative factors

Participants reported a wide range of factors that could adversely influence adherence to antidepressant medicines, at all phases of adherence. This included stigma associated with the use of antidepressant medicines, experiencing or anticipating ADRs, and personal issues such as not believing in the effectiveness of antidepressant treatment and unwilling to rely on medicine. At initiation, negative factors were mainly related to fear of or anticipating ADRs and self-stigma. At implementation, experiencing ADRs and ineffective treatment played a significant part in negatively influencing adherence. Other negative factors included forgetfulness, feeling better, and the existence of depressive symptoms. At the discontinuation phase, previous negative experiences with taking antidepressant medicines led to discontinuation of therapy and failure to start a new cycle of antidepressant therapy. Figure 2 shows a schematic representation of negative factors reported to influence medication adherence.

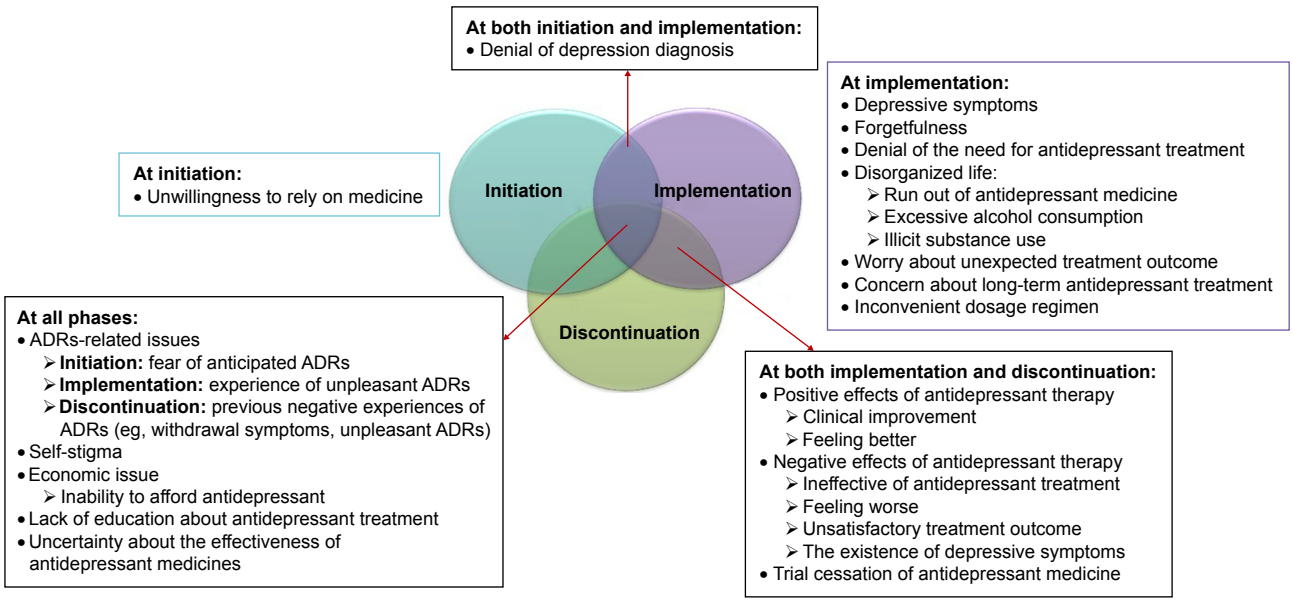

Figure 2 Factors which negatively influence medication adherence at the three phases of adherence: initiation, implementation, and discontinuation of therapy.
Abbreviation: ADRs, adverse drug reactions.

Negative factors at initiation of therapy

A number of factors were identified: unwillingness to rely on medicine, denial of depression diagnosis, fear of anticipated ADRs (eg, concern about weight gain) and self-stigma (eg, the feeling of being embarrassed when getting their prescription dispensed). Two participants reported that they did not want to rely on medicines, another one identified herself as an "anti-medication" type person, and one participant indicated lack of support from family, which resulted in delayed initiating antidepressant therapy. Two participants who revealed the hesitation to commence an antidepressant at the initial diagnosis, hence the initiation phase was delayed, and later, they reported experiencing recurrent episodes of depression. However, most of them were on their antidepressant at the time of interview.

Negative factors at implementation of therapy

A range of negative factors were identified: experiencing unpleasant ADRs, ineffectiveness of antidepressant medicines, uncertainty about the effectiveness of antidepressant medicines, forgetfulness, clinical improvement in depressive symptoms, and having depressive symptoms. These factors meant that participants did not persist with antidepressant therapy and this sometimes led to discontinuation of antidepressant medicines. In most cases, unpleasant ADRs and the ineffectiveness of antidepressant treatment were mentioned as reasons for not persisting with antidepressant medicines. Some participants mentioned that after they started to feel better, they were more likely to discontinue their antidepressant medicine. Depressive symptoms such as forgetfulness, lethargy and laziness were reported in some cases as negative influencing factors, which interfered with medication taking behavior. A few participants doubted the effectiveness of antidepressant treatment and conducted their own trials to cease their medicine to see how they would be without it. In some cases, excessive alcohol consumption and illicit drug use interfered with adherence to antidepressant therapy. A few participants revealed that they denied both their diagnosis of depression and the necessity of antidepressant treatment. In other cases, self-stigma, inability to afford antidepressant medicines, concern about long-term effects of taking antidepressant medicines, an inconvenient dosage regimen, and lack of education about antidepressant medicines were noted as negative factors which adversely influenced medication adherence.

Negative factors at discontinuation of therapy

As described above, discontinuation is a "negative" behavior. Therefore, negative factors at discontinuation stop discontinuation of antidepressant therapy.

Discussion

The results of this study are based on participants' self-reported actual experiences of antidepressant treatment as well as their perceptions and beliefs towards the use of antidepressant medicines for unipolar depression. This study comprehensively discussed factors influencing antidepressant adherence, and was able to capture information about facilitators of, and barriers to, antidepressant adherence at the three phases of medication taking (initiation, implementation, and discontinuation). Although there have been previous qualitative studies investigating medication adherence, this study is different because it uses the conceptual framework provided by the ABC consortium to allow for a more comprehensive analysis. This study therefore has the potential to inform tailored-interventions, based on the phase of adherence, for people prescribed antidepressant medicines.

The findings emphasized that consumers traded off the pros and cons of taking antidepressant medicines from initiation to discontinuation of therapy, based on the integration of their own experiences, beliefs about their health conditions and perceptions of antidepressant treatment effectiveness, observing the experiences of other consumers taking antidepressants, specifically close family and friends, and concerns about the ability to afford antidepressant treatment, before making their own decision.[20] Similarly, Schofield et al have reported that patients learn to trade off the risks and benefits of antidepressant treatment based on trial and error.[16] The majority of participants who continued antidepressant treatment in this study acknowledged the advantages of the treatment over the disadvantages, although some were burdened by their experiences with ADRs.[27] In line with the Necessity-Concerns Framework,[20,28–34] higher adherence rates were also reported by participants when they held stronger beliefs of the necessity of treatment than they did for concerns about treatment.[28,35]

Although participants identified a range of strategies that helped their medication adherence, it is noteworthy that the factors which may influence medication adherence in people with depression are likely to be both condition and medicine-related. For some, depressive symptoms drove participants to seek help and commence antidepressant medicines. Thompson et al also found that increasing depressive symptoms prompted participants with depressive symptoms to seek help.[36] Once participants had decided to seek help, they could participate in the decision-making process by weighing up the necessity to take the antidepressant medicines against their concerns of taking them.[17,37]

At initiation, personal attitude and acknowledgement of their depressive condition and belief in antidepressant medicines were key factors facilitating medication

adherence.[38] Conversely, a negative attitude toward their depressive condition and lack of belief in antidepressant medicines inhibited medication adherence.[39] Previous studies have also indicated that knowledge about disease and treatment combined with faith in the doctor motivates patients to start using medicines.[39,40] Hence, strategies which may aid medication adherence in people recently diagnosed with depression and prescribed antidepressant medicines should include and emphasize, at the outset, education about depression and antidepressant treatment at the early stage.[36] This process should also include accurate and consistent information from health care professionals, including the pros and cons of antidepressant treatment. Specifically, education should include discussion about the condition itself (depression) as well as the use of antidepressant medications. Participants indicated that the symptoms of depression such as constantly feeling sad, forgetfulness, loss of motivation, or a sense of hopelessness, may themselves inhibit adherence, such as delaying the initiation of treatment, or reducing motivation to persist with antidepressant medicines once prescribed.[12,23] Hence education about depressive symptoms and their impact on daily activities was important. In terms of specific education about the use of medicines, participants reported the need for specific counseling on the delayed onset of antidepressant medicine effects and anticipated short and long-term ADRs especially at initiation of therapy.[12,23] It is noteworthy that fear of anticipated ADRs, unwillingness to rely on medicines, and uncertainty about the effectiveness of antidepressant medicines could delay the initiation of therapy. Although only some had a fear of anticipated ADRs, this fear played a strong role in delaying the commencement of antidepressant medications.

Once the treatment was initiated, participants reported constantly balancing the positive and the negative impact of taking antidepressant medicines. If the benefit outweighed the harm, most participants were motivated to remain adherent. For example, when they felt better (clinical improvement) and/or believed in and perceived the need for antidepressant treatment over unpleasant ADRs and stigma. In contrast, when harm exceeded the perceived or actual benefit, they became non-adherent. If negative factors significantly outweighed the positive factors, such as the unbearable ADRs and unsatisfactory treatment outcome, they would consider ceasing or having a break in therapy.

Treatment efficacy, belief, and perceptions about the antidepressant were major influencing factors during the implementation phase of adherence. Belief in and perceived need for medications have been previously linked to medication adherence.[31,41] Similarly, Ho et al have also found that clinical improvement was the major reason for patients to adhere to antidepressant treatment.[42] Although positive effects of antidepressant therapy was one of the most powerful facilitators, paradoxically it also led to discontinuation, in some cases, as individuals felt they no longer needed treatment, as they were "better".[17,43] From a different perspective, fear of the effect when ceasing an antidepressant medicine was a major facilitator for persisting with treatment. In contrast, ineffectiveness of antidepressant treatment and experiencing unpleasant ADRs, specifically sexual dysfunction, have been previously identified as the major barriers leading to discontinuation.[13,20,44–48] Our study findings were therefore in line with previous findings which have also reported that perceived potential harmfulness (concerns) were significantly related to prior experience of ADRs.[31,41]

At discontinuation, new or recurrent depressive episodes prompted the majority of participants to seek out and commence the new treatment cycle of antidepressant medicines. In some cases, unsatisfactory treatment outcome and experiencing ADRs meant that consumers preferred alternative treatments (to antidepressants) such as acupuncture, herbal remedies, and counseling.

Many factors facilitated adherence at more than one phase. These included self-motivation, medication self-management for antidepressants, and trust in the doctor, whilst troublesome ADRs, self-stigma, and economic issues were significant barriers from initiation to discontinuation of therapy. Most of them were considered as modifiable factors (eg, attitudes, perceptions, beliefs about effectiveness of depression treatment, patient/provider communication, including stigma).[49] Although, stigma was reported as a well-known barrier,[23,38,50,51] we found that it was manageable once the consumer realized the need of antidepressant treatment.[13]

Strengths

Our research design specifically focused on the different phases of adherence to medicines (ie, initiation, implementation, and discontinuation) using the ABC framework. It comprehensively covered both facilitators of and barriers to medication adherence at these different phases. In taking this approach, we gained important insights into consumer perspectives, which are often overlooked by health care professionals. The recruitment process resulted in a wide range of experiences of depression and antidepressant treatment, duration of antidepressant treatment, age and background which likely reflects many consumers prescribed antidepressant treatment for depression management.

Limitations

A relatively small number of participants was included in this study, as is the case with all qualitative studies. However, the sample size allowed us to reach theme saturation. Also, the participants in this study may not be representative of all people with unipolar depression. Specifically, all participants in this study acknowledged, recognized and had lived experience of depression. However, our study did not or could not include individuals (or groups) who do not acknowledge depression as a condition, and consequently the place of antidepressant medicines for the management of depression. Additionally, our initial recruitment approach of identifying consumers with depression through community pharmacy was low. Recruitment of participants for in-depth interviews about a potentially sensitive topic is challenging. Specifically for this study, the stigma associated with depression,[52] in both consumers and society, may have contributed to the recruitment process. Hence, we added an alternative method of recruitment via a market research company to identify consumers.

Directions for future research

Since medication adherence is a multidimensional and complicated process, numerous factors typically affect the use of antidepressant medicines among people with unipolar depression. More specific aspects should be further explored such as antidepressant class-specific factors, and cultural-related factors in future studies.

Conclusion

Different factors influence medication adherence at the different phases of adherence. These factors were based on individual perceptions about depression and its treatment, and actual experiences of antidepressant treatment. This information should be considered by health care professionals when advising patients about adherence to antidepressant medicines, at the different phases of adherence, to ensure that targeted and tailored interventions are delivered to facilitate medication-taking behavior.

In order to optimize the use of antidepressant medicines, health care professionals should consider both positive and negative influencing factors at the different phases of adherence. To facilitate medication adherence, health care professionals should facilitate and encourage tailored use of positive influencing factors, and similarly address the negative influencing factors, at each of the phases of adherence. This approach is (more) likely to enhance treatment outcomes in people living with unipolar depression.

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Disclosure

The authors report no conflicts of interest in this work.

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Supplementary material

Table S1 Index of the terms used in this study, in relation to influencing factors

Influencing factors	Definition in the study
Positive factors	
Education about antidepressant treatment	Patient's knowledge about the use of antidepressant medicines in depression treatment, including health literacy.
Willingness to follow doctor's order	Willingness and ability to follow doctor's order pertaining to the use of antidepressant medicines in treatment of depression.
Acceptance of depression diagnosis	Acceptance that one has a diagnosis of depression.
Recognition of antidepressant medicine	The recognition of the importance of antidepressant medicines in the treatment of unipolar depression.
Positive effects of antidepressant treatment	Experiencing or beliefs about experiencing positive effects form the use of antidepressant medicines, such as, the effectiveness of antidepressant, clinical improvement, recovery, feeling better, few or no ADRs, and the observation of positive treatment outcomes from family members and/or friends.
Self-motivation	The reliance on one's own powers and resources rather than those of others. This includes a desire to feel better and achieve better clinical outcomes as well as self-reliance.
Self-management	The management of oneself pertaining to the consumption of antidepressant medicines; the taking of responsibility for regular consumption. This includes routines for taking antidepressant medicines, use of reminders or alarms, pill box, Webster-pak®, diary etc.
Negative factors	
Unwillingness to rely on medicine	The reluctance to use antidepressant medicines.
Denial of depression diagnosis	Belief that one does not have depression.
Denial of the need for antidepressant treatment	Belief that one does not need an antidepressant medicine for treatment of depression.
Disorganized life	Relevant factors pertaining to everyday living that negatively influence medication adherence such as running out of antidepressant medicine, excessive alcohol consumption, illicit substance use, etc.
Concern about long-term antidepressant treatment	Negative thoughts and concerns about long-term use of antidepressant medicines including fear of addiction, interference with natural functions of the brain or body, etc.
Self-stigma	The process of an individual accepting society's negative evaluation and incorporating it into his or her own personal value system and sense of self.[1]
Negative effects of antidepressant therapy	Experience or beliefs about experiencing negative effects from the use of antidepressant medicines; including ineffective antidepressant treatment, feeling worse, unsatisfactory treatment outcome, the existence of depressive symptoms, etc.
Trial cessation of antidepressant	Personal experiment to cease antidepressant medicine without the guidance of health practitioners.

Abbreviation: ADR, adverse drug reaction.

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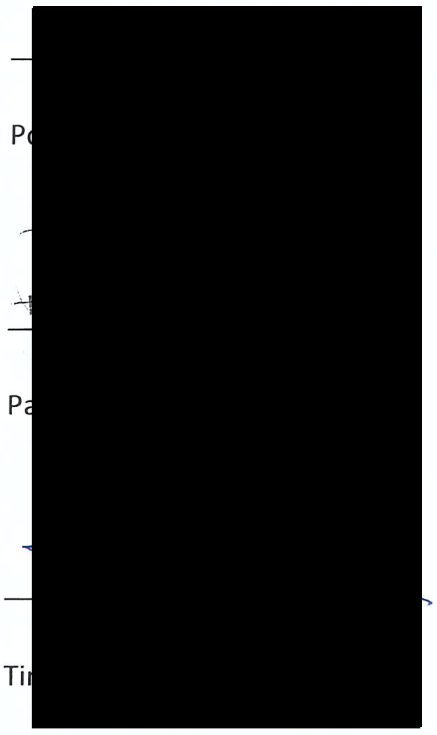
CHAPTER FIVE – The influence of the health care system and society on adherence to antidepressant medicines: consumer perspective

Srimongkon P, Aslani P, Chen TF. The influence of the healthcare system and society on adherence to antidepressant medicines: consumer perspective. ***Research in Social and Administrative Pharmacy.*** **(Manuscript in preparation)**

Authors' Contributions

Timothy F Chen conceptualised the study. Timothy F Chen and Pornchanok Srimongkon conducted data collection (face-to-face interviews). Pornchanok Srimongkon wrote the first draft of manuscript. Timothy F Chen and Parisa Aslani assisted in conducting the study and critically revised the manuscript.



Title: The influence of the healthcare system and society on adherence to antidepressant medicines: consumer perspectives

Abstract

Background: Non-adherence to antidepressant medicine is a major barrier to successful treatment in consumers living with unipolar depression. Understanding potential factors influencing medication adherence from the consumer perspective is a crucial step to improve adherence. The taxonomy proposed by the ABC project team, which conceptualises adherence into three phases: initiation, implementation, and discontinuation, was adopted in this study to elaborate potential factors influencing medication adherence.

Objective: To explore influencing factors related to healthcare system and society which facilitate and negatively impact adherence, at initiation, implementation and discontinuation phases of adherence to antidepressant medicines in consumer with unipolar depression.

Methods: Semi-structured, face-to-face interviews were conducted in consumers with unipolar depression. Interviews were digitally audio-recorded and transcribed verbatim. Transcripts were thematically content analysed and data managed using N-Vivo software.

Results: Twenty-three interviews were conducted. At initiation, family and friends played an important role in encouraging consumers to seek help for depression and commence antidepressant medicines. At implementation, health care professional manner and support from government (Medicare) were central to good adherence. Lack of good bedside manner by health care professionals and an inability to support antidepressant medicine were major causes contributing to the discontinuation phase. Some factors such as stigma (e.g. societal stigma, stigma among health care

professionals) inadequate information about depression treatment from health care professionals, and difficult access to mental health specialist, negatively influenced adherence, but are modifiable.

Conclusions: A number of factors influence medication adherence across the three phases. Health care professionals should consider distinct factors at each of the phases in order to deliver targeted and tailored interventions to foster adherence. Strategies to address medication non-adherence in consumers with unipolar depression should consider the phase of adherence, along with greater support from health care professionals and understanding of the healthcare system.

Keywords: Depression, Adherence, Influencing factors, Facilitators, Barriers

The influence of the healthcare system and society on adherence to antidepressant medicines: consumer perspectives.

INTRODUCTION

Medication adherence is considered as a key to successful treatment in chronic conditions, including unipolar depression. In 2012, a new concept of medication adherence was proposed by a European consortium of researchers, known as the ABC project, which defined medication adherence as a continuous process, comprising 3 elements: initiation, implementation, and discontinuation of medicines. *"Initiation occurs when the patient takes the first dose of a prescribed medication. Implementation of the dosing regimen [is] defined as the extent to which a patient's actual dosing corresponds to a prescribed dosing regimen, from initiation until the last dose is taken. Discontinuation marks the end of therapy, when the next dose to be taken is omitted and no more doses are taken thereafter"*.[1]

Unipolar depression is a highly prevalent mental health disorder globally. In 2015, more than 300 million people around the world were reported to be living with unipolar depression.[2] The consequences of depression are huge. The World Health Organization has reported it as the major contributor to suicide deaths for approximately 800,000 persons per year, and unipolar depression was the single largest contributor to global disability.[2, 3] Depression is a unique mental health condition that lowers medication adherence in itself [4-6], due to demotivating symptoms such as lack of motivation and constantly feeling sad with a sense of hopelessness. Those with depression both delay commencement and have reduced adherence during treatment.[7, 8] Non-adherence to antidepressant medicines has a significant impact on both clinical and economic outcomes. This includes the increased risks of relapse and/or recurrence, emergency department visits, and hospitalisation rates.[9] Also, non-adherence in depression has led

to unnecessary switches in antidepressant treatment, unneeded instructions to increase doses, initiation of unwarranted adjuvant treatments, and misclassification of treatment resistant.[7]

Antidepressant medicines are considered a major modality of treatment for depression.[10-12] Most clinical practice guidelines recommend antidepressant medicines for a minimum course of 6-9 months after symptom recovery.[11, 13] However, the adherence rate to antidepressant medicines has been reported to be relatively low. Generally, good medication adherence has been defined as an adherence rate greater than or equal to 80% as measured by dispensing records.[14] However an estimated 50-60% of people living with depression have ceased antidepressant medicines within the first 10-24 weeks of treatment [15-19] with the most common reasons given as 'feeling better' followed by 'adverse events' and 'fear of drug dependence'.[19] Nearly 25% of people have reported to have stopped antidepressant treatment without informing their doctor.[15, 19, 20] In one study, 5% of patients reported to have never commenced antidepressant medicines.[21]

Adherence is simultaneously influenced by several factors. WHO has categorized these factors into 5 dimensions; social and economic, healthcare team/system, characteristics of the disease, therapies and patient-related factors.[3] Patient-related factors have been well studied, however, there has been little research conducted on the impact of the healthcare system (HCS) and healthcare professionals (HCPs) on adherence to medicines from the consumer's perspectives. This study therefore focused on HCPs, HCS and social-related factors that impact adherence from the consumer perspective. Many studies have indicated that HCPs, specifically general practitioners (GPs) play an important role in patient management including medication adherence in unipolar depression, within the first 3 months of starting antidepressants.[22-24] Patients who experienced unsatisfactory interactions with HCPs were more likely to stop taking their antidepressant and vice versa.[24] Family and peer support were recognised as supportive

factors for consumers with a mental illness.[25] While stigma among HCPs and stigma in the society were reported as significant barriers to depressive treatment.[26, 27]

Although a range of reasons related to HCPs and HCS have been reported as factors influencing medication adherence in unipolar depression, most studies appear to have focused on medication adherence at the implementation phase, while some were unclear about the phase(s) of adherence studied.[24, 26, 28-34] Some studies focused on one aspect, either the facilitators of or the barriers to adherence.[27, 32, 35, 36] The ABC framework emphasises that medication adherence is a dynamic, sophisticated, continuous and modifiable process.[1] Hence, it changes over time. It is therefore crucial to better understand how HCPs and society influence medication adherence at each phase, from initiation to discontinuation, through the views of consumers with depression. This would likely provide a useful guide for HCPs in order to create tailored interventions to encourage medication adherence at each specific phase. The aim of this study was to explore the strategies or positive influencing factors related to the family and society, HCPs, and HCS which promote medication adherence at the three phases of adherence (i.e. initiation, implementation, and discontinuation) in unipolar depression from the consumers' perspectives; and to explore the barriers or negative influencing factors related to the family and society, HCPs, and HCS which reduce medication adherence at all phases of adherence.

METHODS

Individual semi-structured, face-to-face interviews were conducted to collect detailed information relating to individuals' attitudes, perceptions, and actual experiences about antidepressant treatment while also providing a basis for comparison between responses. This study is the second part of a research project exploring consumer-related factors influencing adherence to antidepressant medicines in unipolar depression from the consumers' perspective. Approval for the conduct of this study was obtained from

the human research ethics committee of the University of Sydney, protocol number 2014/967. The study has been reported in accordance with the consolidated criteria for Reporting Qualitative studies (COREQ32).[37]

Recruitment

A purposive sample of consumers with unipolar depression was recruited from community pharmacies located in the Sydney Metropolitan area, via on-line advertising (such as gumtree and locanto.com.au), and via a market research company, until data saturation was reached, i.e. when no new information or themes were observed.[38-41] For purposive sampling, the basic elements for metathemes tend to be generally present at six interviews, and saturation can occur within the first twelve interviews.[38]

Overall, 27 pharmacies were approached and 19 agreed to participate. Twenty-three participants took part in the study. Of these participants, 8 were recruited from community pharmacies, 15 were recruited via a market research company, and none via the Internet.

Participants

Participants were consumers who had been diagnosed with unipolar depression, were either on a recently prescribed antidepressant medicine or had ceased an antidepressant medicine in the 6 months prior to recruitment, were aged 18 or above, and spoke English fluently. The interviews were conducted at the School of Pharmacy, Faculty of Medicine and Health, The University of Sydney and audio-recorded with the participant's permission. Participants gave written consent for audio-recording and to publish the data without any identifiable information, prior to the interview starting.

Interviews

Semi-structured qualitative interviews were selected for data collection as they are well suited for the exploration of perceptions and opinions of respondents regarding complex and sensitive issues and to enable probing for more information and clarification of answers.[42] Open-ended questions were used to explore consumers' views about facilitators and barriers which influenced medication adherence at all phases. The interview guide was developed to address the study objectives and was based on the ABC conceptual framework for adherence, published literature and the experience of the research team.

Participants fulfilling the criteria were interviewed by one of the researchers, P.S. or T.C., who have been trained in qualitative research. Seven participants were interviewed by T.C. and sixteen participants by P.S. Interviews were conducted until data saturation,[38, 43] which was reached at the 21st interview. Two additional participants were interviewed to ensure that there were no further emergent themes.

Data presentation and analysis

Thematic analysis was used to describe, identify, and analyse the key issues, and categorise data in ways that can be summarised, and reported as themes or patterns within data.[44, 45] Verbatim transcripts of the interviews were iteratively analysed, using Nvivo10 program to assist with the data management for coding and thematic analysis. The codes were extracted and grouped according to the themes and grouped under ABC framework for positive and negative factors at all phases. Initial coding was performed by the first author (P.S.). Findings were cross checked by the two other investigators, experienced in qualitative data analysis. An Ishikawa model was created to visually display data. These models depict a "cause-and-effect diagram" which is useful way to illustrate multiple influencing factors across different constructs (family, society, and economy; health care professionals; and healthcare system) and the three phases of

adherence (Figure 1).[46] The model was colour coordinated to represent different phases of medication adherence (e.g. factors influencing initiation in green).

The operational definitions and theme descriptors used in this study is presented in Table 1.

Table 1 Operational definitions and theme descriptors used in this study

	Operational definition
Family and social-related factors	Factors which indicated how family, friends, and society (e.g. neighbourhood, workplace, work colleagues) influenced medication taking behaviour from the consumer perspective.
Health care professionals-related factors	Factors which related to GPs, psychiatrists, pharmacists, and nurses, generated from the consumer perspective.
Healthcare system-related factors	Factors which related to health care system, generated from the consumer perspective.
Positive factors at initiation	Any thoughts or events which encourage consumers to commence the first dose of an antidepressant medicine.
Positive factors at implementation	Any thoughts or events which encourage consumers to adhere to antidepressant medicines on a daily basis.
Positive factors at discontinuation	Any thoughts or events which encourage consumers to cease their antidepressant medicine.
Negative factors at initiation	Any thoughts or events which discourage or prevent consumers from commencing the first dose of an antidepressant medicine.

	Operational definition
Negative factors at implementation	Any thoughts or events which discourage or prevent consumers from continuing with their antidepressant medicine and leads to discontinuation.
Negative factors at discontinuation	Any thoughts or events which discourage or prevent consumers from discontinuing their antidepressant medicine.

RESULTS

This research focused on how family, society, HCPs, and HCS impact medication taking behaviour from the perspectives of consumers with depression. The participants spoke about their experiences and opinions pertaining to the first antidepressant medicine they had ever been prescribed to the most recent one. Twenty-three participants were involved in the study with an age range from 19 to 63; fifteen were female; and sixteen were Australian born. The majority of participants were prescribed selective serotonin reuptake inhibitors (SSRIs) followed by serotonin and noradrenaline reuptake inhibitors (SNRIs). The time since depression diagnosis ranged from 3 months to 42 years, while the duration of antidepressants treatment ranged from 6 weeks to 40 years. A number of participants had tried a range of antidepressants over several years in order to find the "right" one for them. Although, few participants had successfully ceased antidepressant medicines due to socioeconomic issues (e.g. unable to afford the medicines, unstable life conditions), one participant wanted to recommence antidepressant medicines when he could afford it.

Family and society, HCPs, and HCS all influenced medication adherence from the initiation to discontinuation phases and were both facilitators of and barriers to adherence. However, their influence varied for different individuals. At initiation, once

the participants were able to access health services, the bedside manner of HCPs played a major role either to support or discourage participants to commence an antidepressant medicine and adhere to it in the long-run. Support from the HCS was another key factor especially at the implementation phase, to facilitate consumers throughout their treatment journey. An Ishikawa model was created to present potential factors influencing medication adherence at the three phases (Figure 1). Example quotes have been provided indicated in Table 2.

Three broad themes relating to the influencing factors were identified: the role of family and society in depression treatment, health professional's manner towards the consumer, and the role of the HCS in depression treatment. Findings have been described below, together with illustrative quotations for the themes and sub-themes identified.

Figure 1: Positive and negative influencing factors at the three phases of adherence

1

Role of family and society in depression treatment

Family and society influenced medication adherence differently for different individuals. Approximately half of the participants perceived the need for support from family members, friends, teachers, and counsellors. At the initiation phase, the detection of depressive symptoms by family and community was important and assisted the participants in receiving the initial consultation from HCPs. At implementation, support was more related to monitoring depressive symptoms and encouraging regular medicine taking (Quote No.4, Table 2). At the discontinuation phase, where no further doses of antidepressant medicine were taken, the main facilitator was convincing the participant to recommence antidepressant medicines under the supervision of their physician.

Family support played an important role for participants who were diagnosed with depression at a young age. In this respect, parents' support was crucial to arrange the treatment plan, organise a medication taking schedule, and administer medicines (e.g. crush up the pill and give them every morning) (Quote No.18, Table 2). In turn, lack of family support was also reported. One participant noted that his parents believed that his depression was made up, and this led to delayed medication initiation (Quote No. 5, Table 2). Although lack of family support was a barrier to medication adherence, in most cases, it was not strong enough to hinder the participants to commence and adhere to antidepressant medicines once they realised the necessity of the treatment. A few disclosed that their family members had become very supportive right after a serious circumstance such as a suicidal attempt. Since then, their family seemed to realise the impact of depression and the importance of taking an antidepressant medicine. It was notable that family members living with depression played a strong role across the three phases for both direct and indirect support. First-hand experiences from family and friends with depression apparently facilitated a number of participants to adhere to their antidepressant. Family members learnt from the actual experiences of participants about the importance of medication adherence. For example some observed the

consequences of early discontinuation of antidepressant medicines (such as withdrawal symptoms and worsening depression) which emphasised the importance of adherence to antidepressant medicines. Participants reported that family members also observed a significant improvement in health outcomes when participants consistently consumed antidepressant medicine. This reassured participants and family members about the benefits of the medicine (Quote No.19, Table 2). Direct support from family members and/or friends who lived with depression such as advice about the use of antidepressant medicines was also mentioned as a strong facilitator of adherence at the implementation phase. Support from family and people around them was essential to encourage and maintain good adherence in particular cases in which the participants needed extra support, for example people with immobility, and disability. In some cases, unstable family situations (e.g. moving out of home, frequent moving) was a major reason to discontinue antidepressant medicines, for both intentional and unintentional discontinuation.

Because of stigma, a number of participants were ashamed of their diagnosis and related depression to personal weakness, hence they did not want to disclose their depression to others especially to their employer. Most participants hid their medicines and only took their medicines at home, in private

Mental health support groups were acknowledged as a helpful resource in some cases such as in an emergency situation, however, most were did not directly influence medication adherence. Some argued that support groups could be both useful and stressful at the same time. A few participants refused to join support groups as they had enough support, they did not want to listen to others' stories of their depression, and they did not believe that support groups could help them. In one case, a meditation group at a Buddhist temple was reported as a beneficial choice in terms of effectiveness and cost savings.

Health care professional's manner to the consumer

All participants mentioned that HCPs' manner directly influenced medication adherence, whether or not to take antidepressant medicines throughout the adherence process, particularly during implementation. HCPs with good bedside manner encouraged participants to commence, adhere to antidepressant and detect when they needed to resume treatment. Practitioners with good bedside manners displayed altruism and accountability (e.g. an open supportive understanding relationship, good communication and listening skills and trust, provided enough time to discuss information about antidepressant medicines) facilitated participants to commence and adhere to their antidepressant (Quote No.3, Table 2). At initiation, most participants were too ill to make a rational decision about their treatment. Hence, they relied more on their HCPs, especially GPs to make a decision on their behalf. At the implementation phase, experienced HCPs in mental health and good bedside manner (e.g. good relationship, open discussion, understanding) were critical and closely linked to the continuation of antidepressant medicines (Quote No. 10, Table 2). Having a regular HCPs also encouraged them to commence and adhere to their antidepressant medicine. A few revealed that they had more confidence to persist with their antidepressant medicine when they were treated by an experienced doctor rather than a young one. Close monitoring, having a good healthcare team with access to needed services, adequate information about the treatment plan and antidepressant medicines provided to consumers also encouraged participants to adhere to antidepressant medicines (Quote No.13, Table 2). Supportive services form pharmacy were additional key factors at the implementation phase (Quote No.15 and 16, Table 2). Some participants admired pharmacy support in terms of ease of access, as well as the pharmacist providing enough consultation time and information, and their willingness to answer questions. In one case, the pharmacist provided spare antidepressants to cover a gap while the participant was waiting for a new prescription from their doctor. Another participant reported the

helpfulness of a short message reminder to refill their prescription from the local pharmacist.

On the other hand, potential barriers were strongly related to lack of good bedside manner (e.g. one-way/passive communication, rushed doctor, lack of understanding, insufficient information provided to the participant) especially at the implementation phase (Quote No.11 and 14, Table 2). A few participants revealed that they did not receive enough information about antidepressant medicines at the initial dose. Consequently, they ceased it right after side effects occurred. A paternalistic approach to healthcare, limited experience, and limited competency in mental illness were also mentioned as main barriers which contributed to discontinuation of treatment in some cases. A few participants indicated that the pharmacist did not influence their treatment because the pharmacist could not access their full treatment history (Quote No.17, Table 2). This reflected the fragmentation of the HCS and health services. Furthermore, some participants did not have a regular pharmacy, and therefore could not establish good rapport with a pharmacist. A few participants reported experiencing stigma when they refilled their prescription at a pharmacy, and in some situations when they needed to disclose their current use of medicines, therefore their antidepressant, when visiting a pharmacy. As they felt uncomfortable and embarrassed, they felt that they were treated differently by pharmacists (Quote No.12, Table 2) which negatively influenced their adherence.

Healthcare system role towards depression treatment

Easy access to health services was the most important facilitator at the initiation phase, while the government subsidy for antidepressant medicines was a major factor supporting the implementation phase of adherence. In many cases, financial issues were considered paramount. Most participants acknowledged the benefits from the Australian government subsidy provided through Medicare Benefits Schedule (MBS).

The prescribed medications were supported through the Pharmaceutical Benefits Scheme (PBS) and Repatriation Pharmaceutical Benefits Schedule (RPBS). Medicare offers free treatment as a public patient in a public hospital, refunds for professional health services under the MBS, and subsidies for prescription medicines under the PBS. These factors were key facilitators supporting participants' access to the HCS and promoting adherence to long-term treatment. All participants highlighted that they appreciated less out-of-pocket costs for antidepressant medicines as well as partial support to see mental health specialists (Quote No.7, Table 2). The subsidy made the price of their antidepressant reasonable and therefore the treatment was judged to be affordable. While a few participants gratefully received financial support in the form of a pension for other conditions (Quote No.6, Table 2). Collectively these factors were considered to be important positive influencing factors for facilitating medication adherence Likewise, private health insurance was mentioned as a facilitator in one case due to a significant reduction in out-of-pocket costs along with better services provided. A few participants disclosed a preference for receiving generic brand antidepressants as they were cheaper.

Difficult access to mental health specialists and HCS were mentioned as a major barrier at the initiation phase in one case. As the participant was not an Australian citizen, there were unable to obtain Medicare support, and struggled to commence the treatment (Quote No.2, Table 2). Despite Medicare support, at the implementation phase, a few participants reported that they could not afford the out-of-pocket costs to consult with mental health specialists regularly. Additionally, some antidepressant medicines were not fully covered by the PBS, hence patients had to pay the full price. As a consequence, this led to premature cessation of the antidepressant medicine due to being unaffordable (Quote No.8, Table 2). Another issue was related to the need of pension to support people with depression when they were unable to work during severe depressive episode (Quote No.9, Table 2). In a few cases, lack of continuity of care in the public system due to high doctor rotation (every couple of months), long waiting times

at primary health centres, and long waiting period for an appointment with mental health specialists were also reported as barriers. At the implementation phase, clearly, affordable treatment was a key for good adherence. Although high cost unaffordable antidepressant medicines were not common, this was a powerful factor contributing to early discontinuation.

Table 2 Example quotes throughout medication adherence process

Themes	Positive influencing quotes	Negative influencing quotes
At the Initiation		
Health care System: Medicare services	• "I think once I get my health insurance or Medicare, I might also try other antidepressants, see if it works out for me, like the more expensive brands I couldn't afford back in my country." *Quote No.1, Participant No.7 (Male, age 19)*	• "At the moment, I can't afford the price (of depressive treatment) here. It's too expensive. If I get the Medicare (card) I'd love to try other antidepressants." ***Quote No.2**, Participant No.7 (Male, age 19)*
Health care professionals: Medical professionalism and expertise in mental health	• "The first time I didn't know I had to take them until the doctor explained why he'd like to send me to the psychiatrist and why do I need to take antidepressant. I was so desperate, so desperate that I wanted anything that was going to help me at that moment." ***Quote No.3**, Participant No.20 (Female, age 53)*	-

Themes	Positive influencing quotes	Negative influencing quotes
Family and society: Initiate organise health care professional consult by family members	• "What started me in the beginning? I was depressed. I was struggling to get up in the mornings. I'd been taking a lot of cocaine before I went in. It probably was chemical depression as well as the other behavioural depression or whatever it is. My Mum and the woman who ran the rehab knew each other very well. My Mum works in health. They decided that I should be on antidepressants." ***Quote No.4,*** *Participant No.8 (Female, age 30)*	• "With the antidepressants, they (my parents) actually didn't believe in my depression because I was kind of hiding it for the most part… they didn't really believe me about how depressed I was. They thought I was just acting up." ***Quote No.5,*** *Participant No.7 (Male, age 17)*
At the Implementation		
Healthcare System: Affordability of health care system under Medicare and PBS	• "Well, I'm very lucky. I am a pensioner. That means that I don't have to pay very much for my pills, $5.60 per packet….. With my pharmacy, if you get blister packs and you get the generics, they don't charge you for your medication. I am blessed. I get about $80 worth of meds for nothing a month." ***Quote***	• "That last one, probably the newest one that I tried which I went off was the …(the name of antidepressant)… because it was so expensive…and it was not covered by the PBS" ***Quote No.8*** *, Participant No.8 (Female, age 57)* • "..I'm lucky that I'm legally blind because it's a lot

Themes	Positive influencing quotes	Negative influencing quotes
	***No.6**, Participant No.17 (Female, age 63)* • "Cost would have been a big one. If it was really expensive and I wasn't sure if I need to be on it, I might have tried to take myself off early, but it is so cheap. Makes a big difference." ***Quote No.7**, Participant No.1 (Female, age 31)*	harder to get a pension for a mental health issue condition…. You go to Centrelink and say I need a pension because I'm depressed. They tell you to just get on with it. Everyone gets sad - deal with it and it's not that easy. I think what makes it worse is people that have depression, it's not all the time that you are depressed." ***Quote No.9**, Participant No.22 (Female, age 28)*
Health care professionals: Bedside manner	• "My new psychiatrist likes to have a conversation first and figure out recommendations to do. …The appointment that I usually have has 20 minutes (as) a kind of update on my thoughts and feelings about how things are going and then if I want (to) change anything. The next 20 minutes is kind of his ideas of what to do on it. And 25-30 minutes are like the final results of what is continue" ***Quote No.10**,*	• "I feel like my doctor was not listening to me when I tried to explain what's going on but she just seemed to [47] say 'we've got the best which is working with me anyway' so I switch over to another doctor" ***Quote No.11**, Participant No.6 (Female, age 24)* • "I felt that I was treated differently at the clinic when they (health care professionals) knew that I'm

Themes	Positive influencing quotes	Negative influencing quotes
	Participant No.6 (Female, age 24)	on …(the name of antidepressant). They stared at me and I felt really uncomfortable." ***Quote No.12*** *, Participant No.22 (Female, age 28)*
- *GPs:* Accountability, altruism, bedside manner, professionalism and expertise	• "We've got the support 24/7 of the nurses and doctor and also the fact that if you go through the washout period of changing from one medication to another, you've got that support. If you do it in the community, that might be very hard for you… He's (GP) doing such a really good job he will call me in the middle of the night for results, if it was urgent. He's really wonderful… I feel that I could pretty much contact him any time if I had any difficulties. And his staff are really wonderful too." ***Quote No.13****, Participant No.4 (Female, age 38)*	• "I had a doctor before then. As soon as I mentioned stuff like this (depressive symptoms), his hands were already on the script. I'm like come on. What's going on here? I can't talk to him in detail. I think that's more the busyness of him. He's just rushing all the time. Now, I changed to another doctor. I think he's got more time to talk, about anything. I think that's good." ***Quote No.14****, Participant No.9 (Male, age 30)*
- *Pharmacy:* Service	• "Occasionally Mum would forget to order a new script for me from my psychiatrist	• "No I don't really think talking to pharmacists is useful because they don't

Themes	Positive influencing quotes	Negative influencing quotes
	but our pharmacist was really nice and would give me a bit of medication to tide me over while we got the script ... Which was really good because if I stopped this medication, I had really bad experience with that before." ***Quote No.15**, Participant No.11 (Female, age 26)* • "They (the pharmacy) keep your scripts for 4 or 5 of my repeat (medicines) and they'll send you a message to come and pick up your medicines. It's not that beneficial for me but for other people I thing that would help." ***Quote No.16**, Participant No.3 (Female, age 30)*	know your full background and history and everything. So they are kind of just guessing." *Quote No.17, Participant No.22 (Female, age 37)*
Family and society: Support and understanding	• "I used to not be able to swallow tablets so every morning my mother would crush up the pill and put it in honey on a teaspoon and give it to me with my breakfast. Yeah, certainly until I was about 17, 18 my Mum was the one who gave it to me every	• "I still do think I don't really want anyone at my work knowing particularly, because of the negative stigma that is associated. Because I know people that probably should be on medication that criticize people that are on

Themes	Positive influencing quotes	Negative influencing quotes
	day." ***Quote No.18**, Participant No.11 (Female, age 26)* • "She's (his partner) been quite encouraging and educated as well, to sharing the importance of staying on something (antidepressant), and committing to it until the end. Because she was on antidepressants as well" ***Quote No.19**, Participant No.15 (Male, age 44)* • "At the moment I've got my Mum, and she has an alarm on her phone. She sends me a text message twice a day to say, take your meds. And I've got an alarm on my phone, but I still forget to take the meds." ***Quote No.20**, Participant No.3 (Female, age 30)*	medication. It's, yeah. It does have a little bit of, I like to keep it secret." *Quote No.21, Participant No.15 (Male, age 44)* • "Not many of my friends know the full story (of depression). They might not understand. And because I don't want them to look at me like this, something sad and wrong with me. Also because depression is … someone who wakes up, sometimes feel like crying every day." *Quote No.22, Participant No.8 (Female, age 30)*
At the Discontinuation		
Health care professionals: *GPs:* bedside manner	• "I trust him more than I trusted the other doctor and he's known me already. I saw him immediately, as soon as I got to the area and I've been there	• "I think I got scared because of how I spiralled (down) when he took me off it quickly. I think I got a fear of the tablets themselves. He

Themes	Positive influencing quotes	Negative influencing quotes
	now since 2007. When I felt the depression I knew I could tell him. He said, "I want to talk to you about it too. Because I know how you've been prior and I've noticed this slowly but surely change within you, so I'm glad you brought it up." *Quote No.23, Participant No.16 (Female, age 56)*	apologized at the end when he finally finished, he said, "I'm really sorry." I said to him, "You're a doctor, you should've known that you shouldn't take people off them immediately like that." *Quote No.24, Participant No.16 (Female, age 56)*

DISCUSSION

Medication adherence is an inherently dynamic and complicated behaviour influenced by multidimensional factors. This study explored consumers' view of the external factors (HCPs, HCS, and family and society) influencing medication adherence at specific phases of medication taking. These factors build on our previously published research which has reported on the influence of consumer-related factors on medication adherence to antidepressant medicines.

Participants reported that the people around them such as family members and friends played an important role for the initial detection of depressive symptoms and encouragement to seek help from HCPs. Hence accessibility to HCS and HCPs were main factors which facilitated or hindered participants in accessing and initiating treatment for their depressive symptoms. Specifically, once consumers had consulted with their doctor, the health care professional's manner was a key to encourage them to commence and adhere to the treatment. Health care professionals with good bedside manner and who built trust and rapport with their patients using good communication skills facilitated the initiation of antidepressant medicines and ongoing implementation. Specifically for pharmacists, good service which included Webster paks® provided by the pharmacy which also supported consumers to consistently use antidepressant medicines. During the implementation phase, Medicare services also played a major in role in supporting adherence in terms of the subsidy for medicines and specialised treatment. Affordable medicines was emphasised by the majority of participants and was mentioned as a crucial factor for good adherence in the long run. Private health insurance also positively influenced adherence in some cases as it facilitated access to quality care with lower out-of-pocket expenses. On the other hand, consumers who could not detect depressive symptoms and/or were unable to access the HCS reported poorer medication adherence.

The findings highlighted that distinct factors played a strong role at specific phases. At the initiation phase, early detection and the ability to access HCS are crucial

especially in severe cases. Among the consumers who had commenced antidepressant medicines, many reasons prompted them to cease treatment early, especially when they did not share a good relationship with HCPs or their HCPs lacked a good bedside manner.[22, 24, 33, 48-50] For some this poor bedside manner was manifest as a paternalistic approach which lacked accountability and a sense of altruism. This negatively influenced adherence to antidepressant medicines. In other cases when consumers realised the advantages of antidepressant medicine over those negative factors, they traded-off these negative factors and consistently took antidepressant medicines. For example, stigma-related issue regarding the employment is a well-accepted factor that was negatively influencing medication adherence.[22, 26] It was manageable once the consumers perceived need of antidepressant medicines over concern of the stigmatisation. In the same way, some factors (e.g. the fragmentation of HCS, stigma among HCPs, stigma in family and society, the retirement of HCPs, HCPs with less expertise in mental health, lack of public awareness about depression, and lack of education about depression in society) negatively influenced adherence but these factors did not necessarily stop individuals from taking their antidepressant medicines. In part this may be explained by the Necessity-Concerns framework (NCF framework).[51] The NCF states that higher adherence was associated with stronger perceptions of necessity of treatment and fewer concerns about treatment.[51]

However in some cases, these potential barriers also has the potential to lead to early discontinuation of antidepressant medicines. One of the stronger negative influencing factors was the ongoing cost of antidepressant medicines as higher cost-sharing is a significant barrier to medication adherence.[31] Some factors often influence adherence/non-adherence at all phases of medication taking such as stigma (societal stigma and stigma among HCPs), access to HCS, health services, Medicare support, and constant support from HCPs and family members. Not surprisingly, mental health stigma about depression also presented challenges for the recruitment of participants to this study.

For participants, the support of their family was linked to monitoring the progress of depressive symptoms and to encouraging regular consumption of antidepressant medicines. Building on previous studies, support from family members with depression was highlighted as an important facilitator from the initiation to the discontinuation phases, for both direct and indirect support (e.g. second-hand experience). This is may be due to full understanding about the condition and its treatment. In contrast, lack of family support was associated with low health literacy about depression (non-acceptance as a medical condition) and the consequent stigma attached to the person and the family as a result. Mental health advocacy organizations were helpful in some cases, specifically in emergency situation.

The findings from this study about the views of HCPs aligned with those of previous research which pointed to the need for more collaboration (shared decision making with a patient-centred approach) between patients and HCPs, in order to improve adherence and treatment outcomes.[49] At the discontinuation phase, once consumers ceased their medicines, early detection of recurrent symptoms had to be prompted by HCPs and/or family members, highlighting the importance of family support and access to HCPs. Notably, the majority of negative factors that contributed to the early discontinuation of antidepressant medicines were modifiable, such as lack of public awareness about depression, HCPs manners in practice, and better health services.

Participants commented that some modifications to health care systems were required in order to improve medication adherence and health outcomes. This has previously been reported.[31] Practical changes from the consumer perspective included increasing the number of subsidised mental health specialist visits per year, increasing the number of mental health specialists actively working in the HCS, and government social support for those with depression. Specifically for medicines, and in line with previous studies, an even greater range of subsidised antidepressant medicines and continued and increased use of more affordable generic medicines were reported by participants as aiding medication adherence.[52, 53] Interestingly, participants also reported on fragmentation within the health care system caused by

lack of a shared patient medical record amongst HCPs which inhibited a multidisciplinary health care team approach.

Strengths and limitations of the study

This study focused on both facilitators for and barriers to medication adherence at specific phases of medication taking from initiation to discontinuation of therapy. Detailed first-hand experiences of people with unipolar depression provided meaningful insights into the impact of HCPs, HCS and family on adherence to medicines .

One notable limitation was that it was not possible to recruit consumers with primary non-adherence, that is those who had been provided treatment with an antidepressant medicine but who did not initiate therapy or those who did not acknowledge that they had a depressive disorder. Individuals who did not have access to the health care system were also not able to be recruited to this study. It should be noted that the participants in this study were those who were willing to share their treatment experiences and maybe more likely to adhere to antidepressant medicines. Additionally, the majority of recruited participants were unemployed or pensioners receiving government support who lived in the Sydney metropolitan area. Comparisons with those residing in in rural or remote areas was not possible and might present other factors which may positively or negatively influence medication adherence.

CONCLUSION

This study examined the influence of HCS, HCPs, and society on adherence to antidepressant medicines, across the different phases of medication taking, in people with unipolar depression. This study demonstrated that there are substantial factors which go beyond the more commonly reported consumer-related factors which influence medication adherence. Strategies to address medication adherence should consider the broader impact of the HCS, HCPs and society if medication adherence and health outcomes for people with depression are to improve. This study identified

that specific factors influence medication adherence at particular phases of medication taking. At initiation, easy access to HCS and HCPs, HCPs with good bedside manner, and early detection of depressive symptoms were the greatest influencing factors. At the implementation, constant support from HCPs and financial support via Medicare played a major role in maintaining adherence to antidepressant medicines in the long run. However, increased support from HCS and HCPs was also identified, predominantly through a stronger patient-centred focus and better integration of the health system. Participants identified a number of factors which are potentially modifiable such as the bedside manner of HCPs, pharmacy services, and communication between HCPs and consumer with unipolar depression.

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The findings of Chapters Four and Five highlighted the complexity of medication adherence in consumers with unipolar depression. Many factors can influence consumer behaviour across adherence phases, in terms of either positive or negative impact, particularly as these may be linked to personal beliefs about and perceptions of depression and antidepressant medicines. For example, clinical improvement contributes to good adherence in many cases once the consumers realises that the effectiveness of antidepressant medicines over the disadvantages. However, it may also lead to the discontinuation of treatment due to recovery in certain cases. The implication here is that consumer beliefs should be a key element of medication adherence. Therefore, it is important to engage in a patient-centred shared-decision making approach in order to improve adherence to medicines in people with unipolar depression. In addition, patient engagement is necessary for successfully encouraging behaviour change and maintain adherence in long-term treatment.

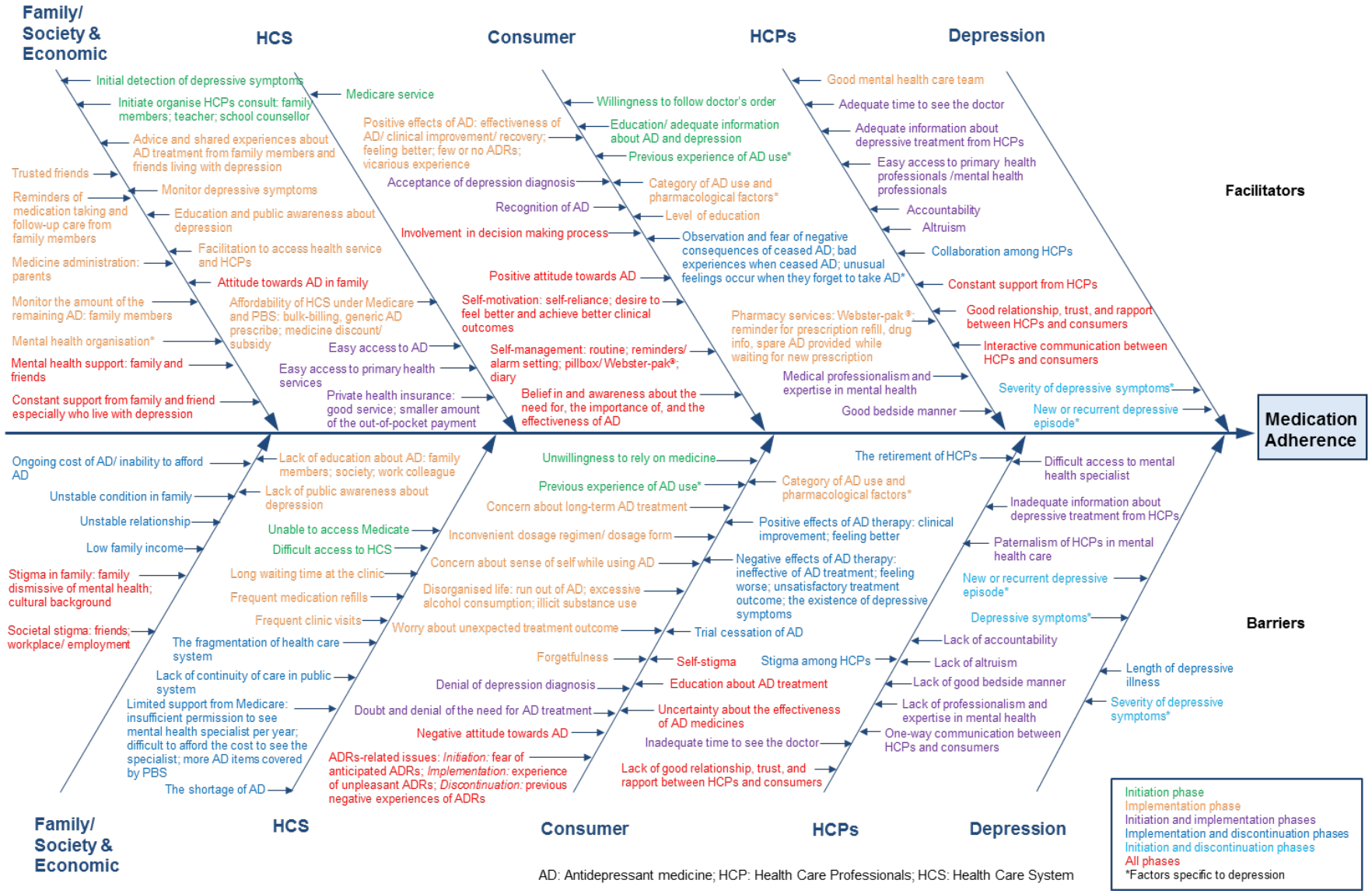
This part of the thesis has highlighted factors specific to the condition of depression and antidepressant medicines. Because the inherent symptoms of depression (e.g. trouble concentrating, remembering details, and making decisions) generally decrease adherence to antidepressant medicines as well as the pharmacological properties of antidepressants negatively impacted medication adherence (e.g. unbearable ADRs, particularly sexual dysfunction and delayed onset of the actions of antidepressant medicines). In general, depressive symptoms may commonly influence adherence at the initiation and discontinuation phases, whereas the consequences of using antidepressant medicines largely influence medication adherence across the three phases, particularly at the implementation phase. Furthermore, these factors may be interlinked and therefore influence other factors. For example, in most cases, although the effectiveness of antidepressant medicines played a major role in medication adherence at the implementation phase, other factors such as its ADRs and belief about the need of antidepressant medicines should also be considered concurrently.

Although many factors influence medication adherence across the three phases, the impact of each factor at each phase of adherence may be different. For example, despite the education on antidepressant medicines playing a role towards medication adherence from the initiation to the discontinuation phases, it had the strongest impact at the initiation of the treatment, as the decision of whether or not to commence taking antidepressant medicines was directly related to the initial decision-making process. A lower impact was discovered at the implementation and discontinuation phases. These findings emphasise the need for health professionals to clearly understand potential factors influencing medication adherence at specific phases, as it is a crucial step to effectively solve non-adherence problems.

Because medication adherence is a multidimensional process, this thesis classified the influencing factors into five categories: consumer-related factors [126]; factors related to health care professionals; factors related to health care systems; depression-related factors; and family-, society-, and economy-related factors. The operational definitions and theme descriptors used in this thesis are presented in Chapter Five, Table 1.

The Ishikawa model is a commonly used method for visually depicting complex processes or behaviours such as medication adherence. Here this method has been used to combine the data presented in Chapters Four and Five. Specifically, different colours in the model represent the factors influencing medication adherence at each phase of medication taking behaviour (e.g. green for the initiation phase) (Figure 3). In the Ishikawa model, factors specific to unipolar depression have been marked with an asterisk (e.g. severity of depressive symptoms, new or recurrent depressive episode, whilst it is acknowledged that other factors may apply to other health conditions. Factors which positively influence adherence are depicted in the top half of the Ishikawa model and those which negatively influence medication adherence are depicted in the lower half of the model.

Figure 3: Factors which positively and negatively influencing medication adherence at the three phases of adherence: an Ishikawa model



AD: Antidepressant medicine; HCP: Health Care Professionals; HCS: Health Care System

PART D - DEVELOPMENT AND VALIDATION OF MEDICATION ADHERENCE FRAMEWORK IN CONSUMERS WITH UNIPOLAR DEPRESSION

CHAPTER SIX – The development and validation of medication adherence conceptual framework in consumers with unipolar depression

Chapter introduction

Medication adherence is a multidimensional process which involves not only consumers, but also health professionals, family, society, and the health care system. For this reason, the above-mentioned aspects must be integrated when dealing with the non-adherence problem. Therefore, it is crucial for health care professionals to clearly understand what would happen to their patients once antidepressant medicines have been prescribed, including potential factors influencing medication-taking behaviour across the adherence process from the patient's viewpoint. Consequently, there must be appropriate interventions to enhance medication adherence, while all possible barriers should be restricted.

The proposed framework has been developed in order to illustrate the adherence process and factors influencing medication-taking behaviours in consumers with unipolar depression at specific phases of adherence, based on the consumer's perspective. The framework aimed to guide the physician to better understand their patients when antidepressant medicines were prescribed, from the first dose to the last dose of treatment. This proposed framework has been based on the research presented earlier in this thesis, specifically the review of the literature (Chapter Three), distillation of the qualitative studies (Chapters Four and Five), and the experience of the research team.

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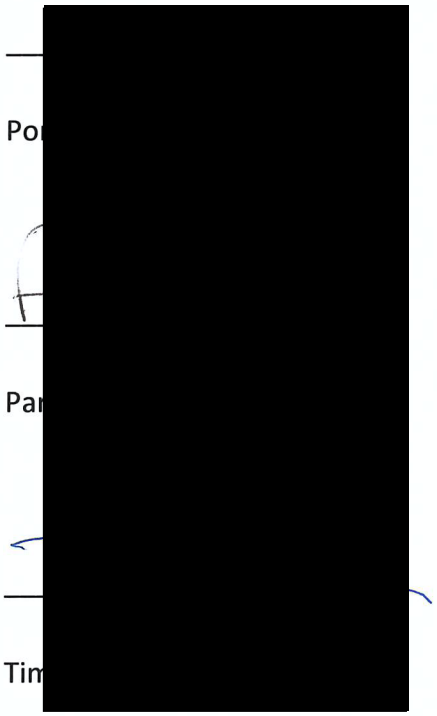
Authors' Contributions

Timothy F Chen conceptualised the study. Pornchanok Srimongkon conducted data collection (development and validation the conceptual framework). Pornchanok Srimongkon wrote the first draft of manuscript. Timothy F Chen and Parisa Aslani assisted in conducting the study and critically revised the manuscript.



The development and validation of medication adherence conceptual framework in consumers with unipolar depression

Introduction

Depression is a common mental illness that affects approximately 300 million people around the world, equating to 4% of world population in 2015. It contributes to a significant in global health loss including suicide death.[1] Depression may then require long-term treatment. Most treatment guidelines recommended continuous use of antidepressant medicines for 6-9 months after recovery from depressive symptoms, for the first episode.[2-7] The duration of treatment is longer for recurrent depression. However, adherence to antidepressant medicines was reported to be relatively low at approximately 50-80% after 4-6 months of treatment.[8-10] Reasons for non-adherence in people with depression are numerous and multifactorial.[11-13] Notable influencing factors are related to clinical characteristics of depression and pharmacological properties of antidepressant medicines. Depression itself is a well-known risk factor for non-adherence as depressive symptoms negatively influence medication adherence.[14-16] Common causes of non- adherence are adverse drug reactions (ADRs), unsatisfactory interactions with health care professionals (HCPs), and ineffective clinical response to antidepressant medicines.[11, 17-19] Non- adherence to antidepressant medicines increases the risk of relapse and/or recurrence of depression, emergency department visits and hospitalization rates, and can increase the severity of depression.[20, 21]

In 2012, a taxonomy for medication adherence was established by a European Consortium who conceptualised the ABC framework for medication adherence.[22] This taxonomy divides medication adherence into 3 components: initiation, implementation, and discontinuation.[22] Initiation starts when the consumer commences the first dose of medication. The process continues with the implementation of the dosing regimen, until the last dose is taken and no further doses are taken. The latter marks the discontinuation phase.[22] Adherence is a

complex and dynamic process that can change over time.[12, 22] The factors which influence adherence at the different phases of adherence differ.[11] For example, more intensive contact with and support from HCPs are particularly helpful to consumers who have just commenced antidepressant medicines.[11] Furthermore, multidisciplinary and multilevel approaches are necessary to optimise adherence.[12, 23-25] A recent systematic review and meta-analysis of medication adherence outcomes of over 700 intervention trials suggested that HCPs should focus intervention content on behavioural strategies, especially habit-based interventions, more than cognitive strategies designed to change knowledge and beliefs.[26] In order to do so, a solid understanding of the entire process of medication adherence, a crucial fundamental for tailored-interventions, is necessary.

A conceptual frameworks is *'a network of interlinked concepts that together provide a comprehensive understanding of a phenomenon or phenomena'*.[27] They outline[28] the relationships between the concepts presumed to account for the phenomenon, by fitting the explanations into a set of categories.[28] Conceptual frameworks have been applied to a variety of health conditions (e.g. HIV, heart failure, hypertension) to elucidate relationships between concepts of interest, including medication adherence. [29-33] Most of the existent frameworks in unipolar depression are mainly created to improve quality of treatment in people with depression.[34-36] Nevertheless, no existing frameworks has been created specifically to solve non-adherence problem in people with depression.

Much of the focus of existing frameworks aimed at improving medication adherence has been the perspective of HCPs.[24] Existing frameworks have not necessarily focused on the characteristics of depression or antidepressant medicines which may impact adherence. Nor have they considered the consumer perspective or health care system related factors. A detailed understanding of the factors influencing medication adherence at the specific phases of medication taking behaviour (initiation, implementation, and discontinuation) may be important for HCPs to aid better management of their patients. This may facilitate the implementation of

tailored interventions designed to improve medication adherence.[37-44]

This study aimed to develop and validate a conceptual framework that illustrates potential factors influencing medication taking behaviour in consumers with unipolar depression. This conceptual framework was intended to describe the adherence process and identify factors influencing medication adherence at specific phases (i.e. initiation, implementation, and discontinuation) in people with unipolar depression, from the perspective of consumers.

Methods

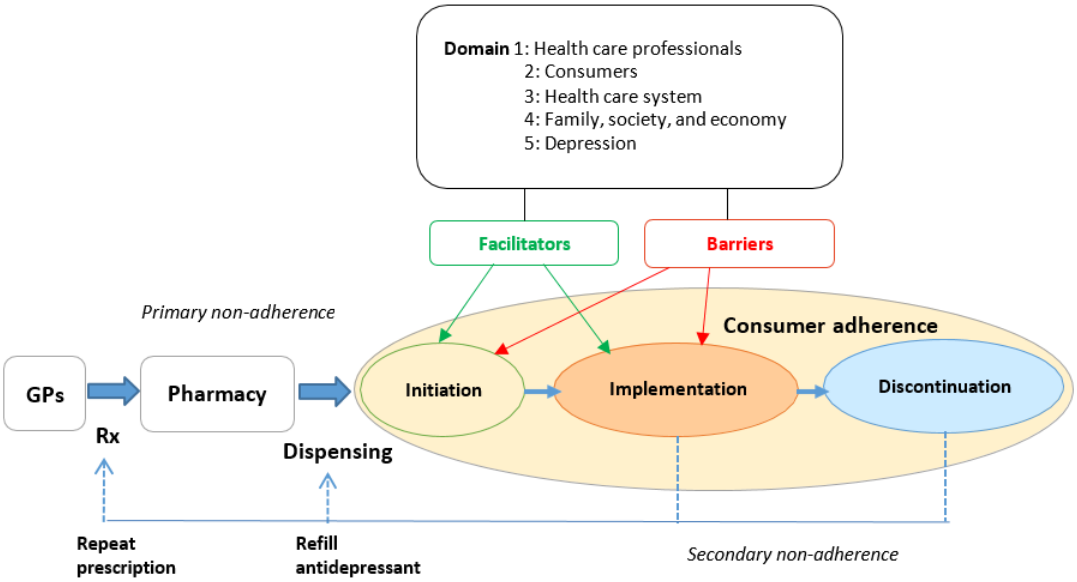
This study consisted of 2 main parts: the development of a medication adherence conceptual framework for people with unipolar depression and the content validation of this framework. The development phase was created in accordance with Lynn (1986) method, and was undertaken by the research team.[45] The face and content validation involved an internet-based survey using an expert panel. This study was approved by the Human Research Ethics Committee of The University of Sydney.

1. The development of a medication adherence conceptual framework for people with unipolar depression

The ABC taxonomy was used to guide the development of the framework.[22] The framework aimed to document potential factors which influence adherence to antidepressant medicines at the three phases of medication taking, from the consumer perspective**.** Item generation (i.e. factors influencing medication adherence/ non-adherence) at the three phases of the adherence process was informed by multiple sources. The specific content of the framework was generated from qualitative studies conducted by the research team (Part C, Chapters Four and Five), published literature on factors known to influence medication taking behaviour and the experience of the research team. This content was used to build an item bank of statements pertaining to factors which may influence medication adherence (Appendix Four, Table A). The items were then grouped into 5 domains and mapped

onto the ABC taxonomy. Figure 1 presents the conceptual framework of medication adherence in people with unipolar depression. The operational definitions and theme descriptors used in the framework are presented in Table 1. T.C. conceptualised the framework and constructs and P.S conducted the item generation process. Following internal review by the authors, items were transferred to Survey Monkey□, for face and content validation via an expert panel.

Figure 1: conceptual framework of medication adherence in consumers with unipolar depression



GPs: General practices
Rx: medical prescriptions

Table 1: The operational definitions and theme descriptors used in the framework

Domain	
Health care professionnals	Factors pertaining to health care professionals, such as GPs, psychiatrists, pharmacists, and nurses, which may impact medication adherence, generated from the consumer perspective.
Consumers	Factors pertaining to the consumer experience of taking antidepressant medicines, both physical and emotional aspects, which may impact medication adherence.
Health care system	Factors pertaining to the health care system which may impact medication adherence, generated from the consumer perspective.
Family, society, and personal finance considerations	Factors pertaining to family, friends, and society (e.g. neighbours, workplace, community) which may impact medication adherence.
Depression	Factors pertaining to unipolar depression which may impact medication adherence, generated from the consumer perspective.
Facilitators at the initiation phase	Any factors which encourage consumers to commence (initiate) the first dose of an antidepressant medicine.
Facilitators at the implementation phase	Any factors which encourage consumers to adhere to antidepressant medicines.
Factors leading to early discontinuation	Any factors which lead to the early discontinuation of an antidepressant medicine.
Barriers at the initiation phase	Any factors which discourage or prevent consumers from commencing the first dose of an antidepressant medicine.
Barriers at the implementation phase	Any factors which discourage or prevent consumers from continuing with their antidepressant medicine and lead to early discontinuation.
Factors preventing early discontinuation	Any factors which discourage or prevent the early discontinuation of an antidepressant medicines.

The framework starts when a consumer first consults with their health care professional and receives a prescription for an antidepressant medicine. Following the receipt of a prescription for an antidepressant medicine, consumers may or may not choose to have their antidepressant medicine dispensed. When the first dose of the antidepressant medicine is taken, medication adherence commences. This point is recognised as the initiation phase of medication adherence. In contrast primary non-adherence occurs when a consumer does not have their antidepressant medicine dispensed or does not initiate therapy with the medicine. The ongoing process of consistently taking and having their antidepressant medicine dispensed refers to the implementation phase. Discontinuation occurs when the last dose of the antidepressant medicine is taken without any further doses consumed. Secondary non-adherence occurs if the implementation phase of antidepressant medicine taking is sub-optimal or with the early discontinuation of the medicine. The adherence cycle resumes when a consumer decides to recommence their antidepressant medicine for a different episode of management. The main focus for this framework is the reporting of factors which may impact medication adherence (facilitators of and barriers to) at the specific phase of adherence.

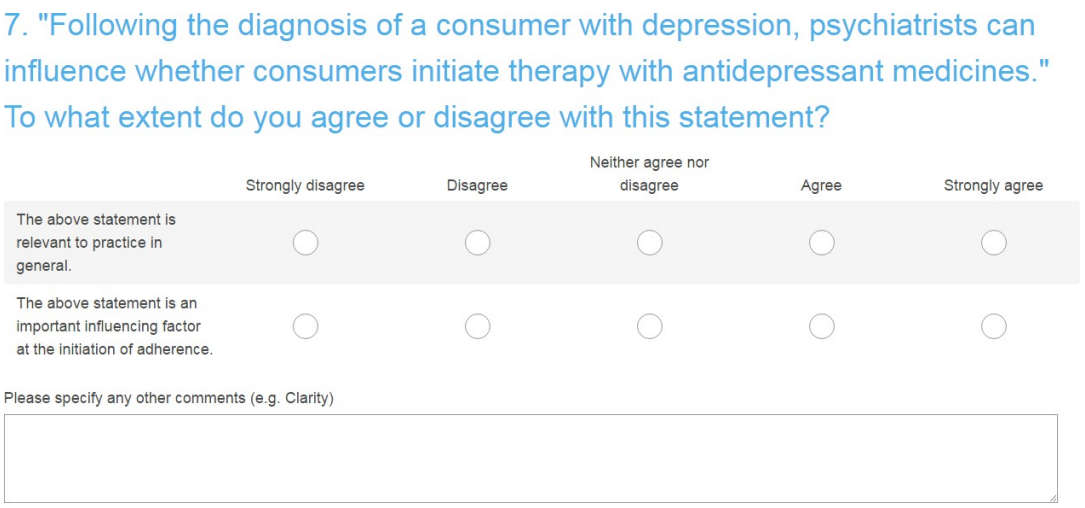
2. Validation of conceptual framework

Face and content validity are primary assessments when a new tool or framework is developed.[46] Face validity has been defined as validity conferred by a layperson's acceptance that the tool or framework appears to be sound or relevant.[45] Content validity is a crucial process for the development of any form of tool or framework to assess the representativeness of its content and appropriateness of the development process.[45, 47] Hence, it is considered a fundamental part of the validation assessment process.[47] Content validations follows a two-step process with the first step pertaining to the development process followed by second step which is the judgement-quantification process

using a panel of experts to evaluate the instrument elements.[45, 47, 48] In this study, an internet-based survey using an expert panel was employed to assess both of face and content validity of the framework due to the convenience for both researchers and expert panel, as it provides rapid feedback, ease of data management, and the possibility of recruiting international panel members.[49-51]

The expert panel was asked to rate their opinion towards the items bank generated for the framework. Specifically, the relevance and importance of the influencing factors (items) at each phase of adherence were evaluated.[52, 53] In this study, relevance refers to the extent to which the statement is relevant to practice at the specified phase of medication adherence. Importance refers to the extent to which the statement is important for the specified phase of medication adherence. Blank space was also provided for each item to allow expert panel members to provide further comments such as the clarity of items (Figure 2). Five-point Likert scales, which included the following options: 'strongly agree', 'agree', 'neither agree nor disagree', 'disagree', and 'strongly disagree', were employed in this study.[47, 52, 54] When compared to four-point scales, they reduce the risk of losing critical information and chance agreement.[47]

Figure 2: The example of item provided on internet platform



The Content Validity Index (CVI) is the most widely used method used to quantify experts' degree of agreement regarding the content relevance and importance of an instrument.[47, 55, 56] The CVI is a basic index of interrater agreement that expresses the proportion of agreement among the expert panel.[55] Two main types CVI adopted for this study were for individual items (I-CVIs) and content validity of the overall scale (S-CVI/Ave). I-CVIs is a proportion of agreement about relevance for each item, it is computed as the number of experts giving a rating of either 'agree' or 'strongly agree', divided by the number of experts.[56] S-CVI/Ave refers to the proportion of items given rating 'agree' or 'strongly agree' by the raters involved for the whole scale. In general, both I-CVIs and S- CVI/Ave of 0.80 or higher are acceptable.[55, 56] Items are categorised as having moderate level of consensus when the I-CVIs score are between 0.70- 0.79, and low when <0.70.

The expert panel members were chosen based on their extensive experience in medication adherence and/or depression and/or health services research. A purposive sample[57] was used to recruit the panel under the following criteria: 1) belonging to one of the following professions: general practitioners (GPs), pharmacists, or academic researchers 2) currently involved in or working in mental health, medication adherence, or medication taking behaviour. A set of specific instructions were provided to expert panel members to facilitate the content validation process. Initially, an email invitation including all relevant information and link to survey host was sent to 19 potential experts. Twelve responded, 2 declined to participate due to their bust scheduled, while 5 did not respond to the invitation. In this respect, it is difficult to state the reason for those who did not respond. Nevertheless, 2 experts who agreed to participate did not complete the survey. Therefore, overall, 10 experts fully participated in this study.

Results

- Expert panel members

Ten multidisciplinary expert panel participated in the validation process and were recruited from (Australia, Canada, Nepal, United Kingdom, and Switzerland) as showed in Table 2.

Table 2: Overview of panel member characteristics

Disciplines	General practitioners	Pharmacists	Academic Researchers*
Number	2	4	4
Years in practice	27 (15-39)	24 (20-30)	22.5 (10-35)
Countries			
• Australia	2	2	1
• Switzerland	-	1	1
• Nepal	-	-	1
• Canada	-	1	-
• United Kingdom	-	-	1

*University lecturer and researcher in pharmacy practice

- Face and content validity

Seventy-two items were evaluated (Table 3) with forty-six items (63.9%) reaching 80% agreement or more for both relevance and importance. The S-CVI/Ave for relevance and importance were 0.7 and 0.76 respectively, indicating moderate consensus for the overall conceptual framework. The I-CVI and clarity data for all items under the framework were presented in Table 3.

Table 3: I-CVIs of all items under the conceptual framework

Domain	Item	I-CVIs		Clarity	Level of agreement
		R	I		
At the initiation phase					
1. Health care professionals	1. Following the diagnosis of a consumer with depression, GPs can influence whether consumers commence therapy with antidepressant medicines.	1	1	Y	High
	2. Following the diagnosis of a consumer with depression, psychiatrists can influence whether consumers commence therapy with antidepressant medicines.	1	1	Y	High
	3. Following the diagnosis of a consumer with depression, community pharmacists can influence whether consumers commence therapy with antidepressant medicines.	0.8	0.8	Y	High
	4. Good relationships between GPs and consumers can influence whether consumers commence therapy with antidepressant medicines.	0.9	1	Y	High
	5. Good relationships between psychiatrists and consumers can influence whether consumers commence therapy with antidepressant medicines.	0.8	0.9	Y	High
	6. Good relationships between community pharmacists and consumers can influence whether consumers commence therapy with antidepressant medicines.	0.9	0.9	Y	High
	7. Good support from the GP is critical to whether a consumer with depression commences therapy with an antidepressant medicine.	0.8	0.8	Y	High
	8. Good support from a psychiatrist is critical to whether a consumer with depression commences therapy with an antidepressant medicine.	0.7	0.8	Y	Moderate

Domain	Item	I-CVIs		Clarity	Level of agreement
		R	I		
	9. Good support from the community pharmacist is critical to whether a consumer with depression commences therapy with an antidepressant medicine.	0.9	0.9	Y	High
	10. Any perceived stigma displayed by healthcare professionals toward depression can inhibit a consumer from commencing an antidepressant medicine.	1	1	Y	High
	11. GPs beliefs about the efficacy of antidepressant medicines influences whether a consumer commences therapy with an antidepressant medicine.	0.8	0.8	Y	High
	12. Psychiatrist beliefs about the efficacy of antidepressant medicines influences whether a consumer commences therapy with an antidepressant medicine.	0.8	0.8	Y	High
	13. Community pharmacist beliefs about the efficacy of antidepressant medicines influences whether a consumer commences therapy with an antidepressant medicine.	0.7	0.5	Y	Low
2. Consumers	1. Self-motivation of a consumer is a factor in whether they commence therapy with an antidepressant medicine.	0.9	0.9	Y	High
	2. Consumers who acknowledge their depressive condition, tend to commence therapy when prescribed an antidepressant medicine.	0.5	0.5	Y	Low
	3. Consumers who are involved in the treatment decision-making process are more likely to commence therapy with an antidepressant medicine.	0.9	0.9	Y	High
	4. Consumers who have previous unfavourable experiences with	0.9	0.9	Y	High

Domain	Item	I-CVIs		Clarity	Level of agreement
		R	I		
	antidepressant treatment are less likely to commence therapy with antidepressant medicines.				
	5. Consumers who have previous unfavourable experiences with antidepressant treatment are less likely to commence therapy with antidepressant medicines.	0.6	0.6	Y	Low
	6. Stigma about depression can be a barrier to a consumer to commence antidepressant therapy.	1	1	Y	High
	7. Consumer beliefs about the efficacy of antidepressant medicines influences whether they commence therapy with an antidepressant medicine.	1	1	Y	High
	8. Concern about possible adverse drug reactions can influence whether a consumer commences therapy with an antidepressant medicine.	1	1	Y	High
	9. Consumers with higher levels of education are more willing to commence antidepressant therapy.	0.2	0.2	Y	Low
3. Health care system	1. The accessibility of the health care providers affects when a consumer commences therapy with an antidepressant medicine.	0.8	0.8	Y	Accept
	2. Private health insurance influences whether a consumer commences therapy with an antidepressant medicine.	0.4	0.4	Y	Low
4. Family, society, and economy	1. Consumers who live with a partner are more likely to commence antidepressant therapy.	0.3	0.3	Y	Low
	2. The cost of antidepressant medicines influences whether a consumer commences taking antidepressant therapy.	0.8	0.7	Y	Moderate
	3. The cost of health care influences when a consumer	0.5	0.6	Y	Low

Domain	Item	I-CVIs		Clarity	Level of agreement
		R	I		
	commences therapy with an antidepressant medicine.				
	4. Consumers who have family support are more likely to commence antidepressant.	0.5	0.5	Y	Low
	5. Consumer who have peer support are more likely to commence antidepressant therapy.	0.7	0.5	Y	Low
	6. Any perceived stigma displayed by a family member or carer toward mental health can be a barrier to a consumer commencing antidepressant therapy.	0.9	0.9	Y	High
	7. Stigma in society can be a barrier to a consumer commencing antidepressant therapy.	0.9	0.8	Y	High
	8. Mental health advocacy organizations such as BeyondBlue influence whether a consumer commences therapy with an antidepressant medicine.	0.6	0.5	Y	Low
5. Depression	1. Consumers who have more severe depressive symptoms are more willing to commence antidepressant medicines.	0.4	0.5	Y	Low
At the implementation phase					
1. Health care professionals	1. Following the diagnosis of a consumer with depression, GPs can influence whether consumers continue to take antidepressant medicines.	0.9	0.9	Y	High
	2. Following the diagnosis of a consumer with depression, psychiatrists can influence whether consumers continue to take antidepressant medicines.	0.9	0.9	Y	High
	3. Following the diagnosis of a consumer with depression, community pharmacists can influence whether consumers continue to take antidepressant medicines.	0.9	0.9	Y	High

Domain	Item	I-CVIs		Clarity	Level of agreement
		R	I		
	4. Experienced GPs can influence whether consumers continue to take antidepressant medicines.	0.8	0.6	Y	Low
	5. Experienced psychiatrists can influence whether consumers continue to take antidepressant medicines.	0.8	0.6	Y	Low
	6. Experienced community pharmacists can influence whether consumers continue to take antidepressant medicines.	0.9	0.7	Y	Moderate
	7. Good relationships between GPs and consumers can influence whether consumers continue to take antidepressant medicines.	1	1	Y	High
	8. Good relationships between psychiatrists and consumers can influence whether consumers continue to take antidepressant medicines.	1	1	Y	High
	9. Good relationships between community pharmacists and consumers can influence whether consumers continue to take antidepressant medicines.	1	1	Y	High
	10. Collaboration between GPs, psychiatrists, and pharmacists in a mental healthcare team can influence whether consumers continue to take antidepressant medicines.	1	0.9	Y	High
	11. Interactive communication and open dialogue between healthcare professionals and consumers can influence whether consumers continue to take antidepressant medicines.	1	1	Y	High
	12. Lack of adequate information about depressive treatment from healthcare professional can inhibit a consumer from continuing to take antidepressant medicines.	1	0.9	Y	High
	13. Stigma about depression from healthcare providers	0.9	0.8	Y	High

Domain	Item	I-CVIs		Clarity	Level of agreement
		R	I		
	can inhibit a consumer from continuing to take antidepressant medicines.				
2. Consumers	1. Consumers who believe in antidepressants are more likely to continue to take antidepressant medicines.	0.9	0.9	Y	High
	2. Consumers who are more able to self-manage are more likely to continue to take antidepressant medicines.	0.7	0.6	Y	Moderate
	3. Consumers who are involved in the treatment decision-making process are more likely to continue to take antidepressant medicines.	0.9	0.8	Y	High
	4. Consumers who have previous unfavourable experiences with antidepressant treatment are more unlikely to continue to take antidepressant medicines.	0.9	0.9	Y	High
	5. Consumers who are concerned about the effect of stopping antidepressant therapy are more likely continue to take antidepressant medicines.	0.9	0.9	Y	High
	6. Consumers who feel better after taking antidepressants tend to continue to take antidepressant medicines.	0.6	0.5	Y	Low
	7. Consumers who have trust in their healthcare professional are more likely to continue to take antidepressant medicines.	1	0.9	Y	High
	8. Consumers who have knowledge about depression and antidepressant therapy are more likely to continue to take antidepressant medicines.	0.7	0.7	Y	Moderate
	9. Forgetfulness can inhibit a consumer from continuing therapy with an antidepressant medicine.	0.9	0.9	Y	High

Domain	Item	I-CVIs		Clarity	Level of agreement
		R	I		
	10. Consumers with higher levels of education are more willing to continue to take antidepressant medicine.	0.9	0.9	Y	High
	11. Consumers who have positive experiences from antidepressant therapy are more likely to continue to take antidepressant medicine.	1	1	Y	High
	12. Consumers who have few adverse drug reactions from antidepressant medicines are more likely to continue to take them.	0.9	0.9	Y	High
	13. Ineffectiveness of antidepressant treatment can inhibit a consumer from continuing therapy with an antidepressant medicine.	1	1	Y	High
3. Health care system	1. Consumers who have private health insurance are more likely to continue to take antidepressant medicines.	0.3	0.2	Y	Low
	2. The accessibility of the health care services effects whether a consumer continues to take antidepressant medicines.	0.8	0.9	Y	High
	3. The accessibility of antidepressant medicines effects whether a consumer continues to take antidepressant medicines.	0.9	0.9	Y	High
	4. Lack of continuity of care in the public system can inhibit a consumer from continuing therapy with antidepressant medicines.	0.9	0.8	Y	High
4. Family, society, and economy	1. Consumers who live with a partner are more likely to continue to take antidepressant medicines.	0.4	0.3	Y	Low
	2. Consumers who can afford antidepressants are more likely to continue antidepressant medicines.	0.9	0.8	Y	High
	3. Societal stigma about depression can inhibit a	0.8	0.7	Y	Moderate

Domain	Item	I-CVIs		Clarity	Level of agreement
		R	I		
	consumer from continuing therapy with an antidepressant medicine.				
	4. Lack of support from family can inhibit a consumer from continuing therapy with an antidepressant medicine.	0.9	0.9	Y	High
	5. Stigma about depression by family members can inhibit a consumer from continuing therapy with an antidepressant medicine.	0.9	0.8	Y	High
	6. Mental health organizations such as BeyondBlue influence whether consumers continue to take antidepressant medicine.	0.6	0.5	Y	Low
5. Depression	1. Consumers who have more severe depressive symptoms are more likely to continue to take antidepressant medicines.	0.6	0.5	Y	Low
	2. Depressive symptoms can inhibit a consumer from continuing therapy with an antidepressant medicine.	0.8	0.9	Y	High
	3. Long term treatment of depression can inhibit a consumer from continuing therapy with an antidepressant medicine.	0.6	0.6	Y	Low

R= Relevance, I= Importance, Y = Yes, N = No

Framework sub-component at the initiation phase

At initiation, the majority of items related to HCPs were rated with high agreement such as items pertaining to 'good support from HCPs' and 'good relationship between HCPs and consumer with unipolar depression'. This means that the agreed that these factors serve as facilitators of adherence to antidepressant medicines. A few items related to the psychiatrist and pharmacist were rated as moderate and low agreement. This could be explained by the fact that many consumers do not receive specialist psychiatrist management for their depression; also, pharmacists do not always have access to the full health picture (e.g. diagnosis and treatment history).

In light of consumer-related factors, consumer self-motivation to receive treatment, being involved in the decision making process about treatment, and personal belief about the efficacy of antidepressant medicines were rated with high agreement as facilitators of adherence at the initiation phase. Stigma issues and unfavourable experience of antidepressant use were rated as relevant and import barriers. Whereas, having more severe symptoms, family and peer support, adequate information about depression and antidepressant medicine, higher level of education, and people who acknowledge their depressive condition received low agreement, as those factors are not routinely related to adherence to antidepressant medicines, although they could be for some people.

At this phase, the majority of factors relating to family, society, and personal financial consideration were rated low with a low level of agreement for both relevance and importance. Cost of antidepressant medicines was rated as relevant but not an important factor. Similarly, mental health organisation and private health insurance factors also received low agreement scores, although they could be for some people.

Framework sub-component at the implementation phase

When compared to the initiation phase, a similar pattern of ratings was obtained for both facilitators of and barriers to medication adherence. For HCPs-related factors, collaboration between HCPs in a mental health care team, and interactive communication between HCPs and consumers were rated with a high level of agreement for both relevance and importance. Consumer-related factors including belief in antidepressant medicine, concern about the effect of stopping antidepressant medicine, trust in their HCPs, ability to support antidepressant medicine, positive experiencing antidepressant medicine, and fewer ADRs were also rated as facilitators of adherence. Whereas, lack of adequate information about depressive treatment from HCPs, forgetfulness, lack of continuity of care in health system, ineffective antidepressant medicine, and depressive symptoms were rated as additional barriers of medication adherence at the implementation phase.

Experienced HCPs were rated relevant but not import for assisting medication adherence. In line with the initiation phase, the role of mental health organisations was also rated low with low agreement for the implementation phase. This is because the influence of advocacy organisations was predominantly aimed at the population or community level rather than a direct provider role Private health insurance was noted as relevant to National health plans.

The expert panel also provided additional written comments. These covered co-decision making between HCPs and patients as being dependent on personality; and some people not wanting to take responsibility of shared decision making with their HCPs.

The expert panel highlighted the need for trust and a good relationship between HCPs and people with unipolar depression. GPs were especially important for both initiation and implementation phases of medication taking. Consistent and on-going communication of messages was also noted as an important facilitator of medication adherence at all phases.

Other comments from expert panel members pertained to health beliefs regarding medicines (such as benefits and harms) and cultural beliefs (such as the experiences and perceptions of friends and family members toward antidepressant medicines).

Discussion

This framework developed and content validated in this research adopted the ABC taxonomy. It aimed to comprehensively evaluate potential factors influencing medication adherence at the specific phases of medication taking by consumers with unipolar depression. This framework may be used to guide HCPs to identify know facilitators of and barriers to medication adherence at the different stages of medication adherence. In turn this may inform the implementation of targeted individualised strategies to facilitate medication adherence.

For both phases, the results indicate that most of items related to HCPs and HCS were rated with high agreement (I-CVIs >0.8) except for an item which related to private health insurance. In contrast, the majority of factors related to family, society, and personal financial consideration were rated lower for both phases (I-CVIs range 0.3-0.7). This suggests that expert panel members valued professional/clinical issues more highly than other issues (e.g. family, society) which were beyond their own direct scope of influence. This results also points to the need to conduct a content validation process with non-health care professionals to further explore this issue. This point is important as the majority of items were generated directly from consumer perspectives. This misalignment between consumer perspectives and the assessment provided by the expert panel members points to a significant challenge in the delivery of a patient-centred, shared decision making approach to health care for people with unipolar depression.

With regard to the clarity of the items, the majority were assessed as clear, with >80% agreement. Notwithstanding this, some expert panel members commented on the ambiguity of adjectival descriptors such as ‘critical’, ‘tend to’, ‘experienced GPs’, and ‘accessibility’. However, most of these terms were not keywords for the individual

items concerned, thus the essence of the item would remain, even if these terms were removed. Additionally, some statements may not be mutually exclusive, for example, 'supportive', 'role' and 'relationship'. Nonetheless, those terms express different meanings as 'supportive' was used in a non-specific way whereas 'role' and 'relationship' were used to refer to interactions between HCPs and patients. Overall, the researchers therefore believe that the framework items yielded adequate clarity and validity.

It should be noted that some factors such as feeling better and severity of depression, have the ability to be either positive or negative influencer for individuals. Hence there was variability in the assessments made by expert panel members for these items as they can be both facilitators of and barriers to adherence. Furthermore, some factors were individualised such as 'support from peers, family members, and a partner' where the outcomes may either facilitate or hinder adherence. This explained why the Hence, the CVI scores for these items were relatively low, but points to a rationale for keeping them in the item bank, given the aim of producing a comprehensive framework for aiding medication adherence. In our study, a few items received low agreement among the panel which was in contrast to other studies e.g. more severe depression and cost of antidepressant medicines.[13, 58-63] This may be due to their own perspective which may need further clarity.[61]

Our framework has some similarities with other frameworks developed to aid adherence in other conditions such as diabetes Jaam (2017). However it is broader in the sense that it includes both facilitators of as well as barriers to adherence across the different phases of medication taking. [29]

Strength limitations and future directions

In light of the validation process, both of the size and scope of expertise of the panel members were important for the assessment of content validity. Lynn (1986) recommends a minimum of three panel members for content validation[45, 47] with ten participating in this study, increasing the credibility of the content validation

process.[54, 64] However, the inclusion of non-expert consumer panel is recommended to provide greater balance to framework validation.

The framework was created based on everyday practice in which the dispensing function is separated from physician function. Therefore, the implementation of the framework may be limited to other types of the health care system.

This framework did not provide influencing factors at the discontinuation phase. This is because medication adherence is a continuous process. The discontinuation phase is defined as the point when the last dose of medicine was taken; therefore, the barriers at this stage were similar to those factors that prevent the consumer to cease their medicine. In other words, the barriers at the discontinuation phase were similar to influencing factors at the implementation phase.

Conclusion

Factors identified under the ABC taxonomy indicated the complexity of adherence process in consumers with unipolar depression. This framework emphasised that greater attention should be provided at particular phases to increase adherence to antidepressant medicines along treatment process. This framework can be used as a guide to develop more efficient strategy to improve medication adherence based on consumer-specific intervention. Future study should consider to integrate other perspectives such as the payer and nonprofessional panels in order to complete the framework form multiple views.

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PART E - DISCUSSION AND CONCLUSION

CHAPTER SEVEN: Discussion

The research included in this thesis aimed to explore and examine issues pertaining to medication adherence in people living with unipolar depression with a particular focus on factors influencing adherence at specified phases from the consumer perspective: initiation, implementation, and discontinuation of therapy. Specifically, this thesis focused on obtaining a greater understanding of medication-taking behaviour in people with unipolar depression. This research developed a conceptual framework of medication adherence and identified facilitators of and barriers to adherence at each of the phases of medication-taking. The research included in this thesis involved a comprehensive identification and evaluation of these factors, with the proposed framework intended as a guide for health care professionals when individualising strategies to facilitate medication adherence in people with unipolar depression.

In this chapter, the research findings are discussed in five main sections: [1] implementation of the proposed framework, [2] framework development and framework components, [3] face and content validity of the framework, [4] selection of valid measurement(s) at specific phases of medication adherence, and [5] strength and limitation of the research presented in this thesis

7.1 Implementation of the proposed framework

Medication-taking is a complex behaviour and can change over time. Hence, an understanding of the factors that influence adherence to antidepressant medicines is likely to be multifaceted and different for individual patients and at different times. For these reasons, a framework which identifies different strategies to facilitate medication adherence to antidepressant medicines at different stages of medication-taking for individuals is important. It is unlikely that a single intervention will work for all consumers. Moreover, tailored interventions are likely to provide the best solution for individuals in whom medication adherence is a sub-optimal. Therefore, to develop a framework for medication adherence in consumers with depression, an in-depth

understanding of the adherence process and possible factors influencing medication-taking behaviour from the consumer's viewpoint is required. This framework was developed for the purpose of guiding health care professionals in facilitating adherence to antidepressant medicines in clinical practice, particularly in primary care where the majority of patients with depression are managed.

It is noteworthy that several conceptual frameworks have been created to improve medication adherence and help understand the barriers to medication adherence.[47, 94, 95, 108, 109, 117, 160] Related conceptual frameworks in the area of medication adherence have been specifically designed for other conditions which require long-term treatment, such as hypertension, AIDS, diabetes, and chronic heart failure; however, this has not been done for depression.[94, 95, 108, 109] Croghan et al. (2006)[98] developed a framework for the management of depression in primary care, but not with a specific focus on medication adherence. Building on this research, our conceptual framework was developed as an important part of depression treatment in primary care, with particular focus on medication adherence. Specifically, our framework identifies potential factors influencing medication adherence at specific phases of medication-taking, from the initiation to the implementation and discontinuation phases of adherence. In addition, the systematic review presented in Chapter Three identified specific measures of adherence for specific phases (initiation, implementation, and discontinuation) in order to evaluate the capability of the framework in optimising medication adherence. The selection of appropriate measures of medication adherence with good reliability and validity is critical if tailored strategies designed to facilitate adherence are implemented. Hence, the conceptual framework can be used as a guide to inform health care professionals to carefully monitor their patients and effectively tailor interventions for them. In addition, it is possible to integrate the framework with existing frameworks, such as the conceptual model developed by Croghan et al, in order to provide more individualized care for the management of depression.

The framework developed and presented in this thesis is the first conceptual framework that has been created specifically to understand the medication adherence process in people with unipolar depression, with a particular focus on consumer-related factors. As the major outcome of this doctoral research, the holistic framework of medication adherence was created to elucidate the entire process of adherence and potential factors influencing medication-taking behaviour at the different phases of adherence. The framework includes factors related to health care professionals; consumer-related factors; factors related to the health care system; family-, society-, and economy-related factors; and depression-related factors.

Our conceptual framework is similar to the one proposed by Jaam et al. (2017), which represented the complex network of factors associated with medication adherence in consumers with diabetes mellitus.[94] Specifically, both frameworks investigate a broad range of domains which might influence medication adherence. Although the barriers to and facilitators of medication adherence were stated in the same manner, a distinction between the frameworks is that we integrated the ABC taxonomy in our proposed framework. Hence, the factors influencing adherence were specifically mapped to particular phases of medication adherence. That is, comprehensive information pertaining to potential factors influencing medication adherence are included, from the first dose of antidepressant medicine to the last dose taken.

Various conceptual and theoretical behavioural models have also been used to support and facilitate medication adherence in consumers with unipolar depression. These include the Health Belief Model (HBM), theory of planned behaviour, the transtheoretical model of behaviour change, self-regulatory model, etc.[47, 109, 116-118] However, none of the existing conceptual frameworks or behavioural models are specifically focused on depression. There are many unique characteristics of depression and specific characteristics of antidepressant medicines which warrant the development of a specific framework for depression. These include the pharmacological properties of antidepressant medicines such as unbearable ADRs

and delayed onset of action. In addition, the inherent characteristics of unipolar depression, such as loss of interest in activities, cognitive dysfunction and forgetfulness, as well as the severity of depression are also closely connected to non-adherence to antidepressant medicine.[17, 23, 64, 173] Therefore, it is important to establish a clear and comprehensive conceptual framework that captures potential factors which may impact medication adherence to antidepressant medicines. This framework, based on a better understanding of consumer views on adherence to antidepressant medicines, may aid the implementation of strategies to optimise medication adherence and treatment outcomes.

The COM-B framework is a comprehensive framework which is intended to explain individual health-related behaviour based on three domains: capability, opportunity, and motivation.[116] This framework is generally applied in health science pertaining to behavioural issues including medication adherence.[116] However, it is difficult to map depression to the COM-B framework or the COM-B framework to depression because the effects of depression towards medication adherence can be explained by a number of different factors. Therefore, the COM-B framework may not be ideal for medication adherence in people with depression.[116] This issue emphasises the complexity of depression itself. This finding also indicates the need for a specific framework for medication adherence in unipolar depression.

Another well-known framework, the Necessity-Concerns Framework (NCF) postulates that adherence is influenced by implicit judgements of personal need for the treatment. This framework is closely related to personal belief (necessity beliefs) and concerns about the potential adverse consequences of taking it.[125] The NCF has been proven as a useful model for understanding patients' evaluation of prescribed medicines; therefore, it has been commonly used to explain non-adherence to prescribed medicines in patients with long-term conditions like depression.[110, 124, 125] However, the implementation of this framework is limited to the particular issue relevant to beliefs and concerns, as it does not intend to explain other aspects of adherence.

In terms of the implementation of the (our) conceptual framework to other chronic conditions, this framework can be used as a prototype for developing an adherence model in other chronic conditions. In practice, our framework is suitable for application in depression with comorbidities, as many factors also influence medication adherence in other chronic diseases. However, the application of the framework in this case should be done carefully.

7.2 Framework development and framework components

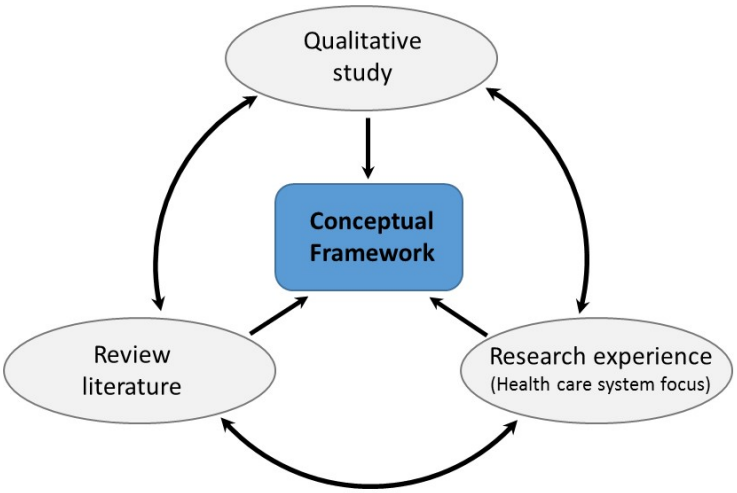
Mainstream approaches which support the role of patients to manage their health issues, such as patient-centred care, are being increasingly encouraged in practice.[174, 175] As is evident, the patient-centred approach (including shared-decision making, physician-patient communication, etc.) has contributed to significantly improved clinical outcomes in chronic conditions.[174-177] In addition, it also can enhance adherence to antidepressant medicines in people with unipolar depression.[178-182]

Our conceptual framework focuses on consumer behaviour with patient autonomy as the core principle.[98, 99, 101, 116] We acknowledge that the consumers have the choice to decide whether or not to take the medicines prescribed for them. Medication adherence may be influenced by a range of different patient-specific factors including the individual's perception of depression and towards antidepressant medicines themselves. It may also be influenced by the consumer relationship with their health care professionals, particularly when a co-decision is made about treatment options, and self-management practice with respect to medication-taking. This principle is in accordance with the global shift in the direction of health care from focusing on health care professionals (with the particular focus on disease) to patient and family or patient-centred care.[183] The concept of patient-centeredness refers to the care that is respectful of and responsive to individual patient preferences, needs, and values. Moreover, patient values should guide all clinical decisions. In essence, this concept highlights the importance of clinicians and patients working together to produce the best outcomes possible.[183] Similarly, this is evident from the shift of compliance terminology (focus on health care professionals, with patients somewhat

subservient to prescribers) to adherence terminology (the cooperation between prescriber and patient) which constructively aligns with the concept of patient-centred care and shared decision making.[2, 177, 179, 184-186] In essence, the active involvement by the patients in treatment decision-making is increasingly implemented in everyday practice and is an important strategy for enhancing treatment engagement and achieving successful treatment in long-term conditions.[179, 180] Further, the implementation of shared-decision making to improve medication adherence and depression outcomes in people with unipolar depression has been shown to be successful.[187, 188] However, we also acknowledge other important factors which may impact medication adherence, including the patients themselves, health care professionals, the health care system, family, and society.

With regard to framework development, the proposed conceptual framework was rigorously developed based on the integration of existing information from multiple sources. A process of triangulation was applied at this stage to ensure the comprehensiveness of the framework. Further, facilitators of and barriers to medication adherence at each phase were extensively generated from various sources, including a review of the literature, in-depth qualitative interviews, and the experience of our research team. A schema depicting the framework development is presented in Figure 4.

Figure 4 The triangulation of multiple sources to develop the framework of adherence to antidepressant medicine.



The framework has been developed as a pragmatic approach to medication-taking behaviour. It is known that many health care systems are fragmented and that this fragmentation can affect medication adherence. For example, the separation and lack of coordination between doctor and pharmacist may lead to specific and nuanced advice on treatment, which may appear to be conflicting from the consumer's perspective. That is, there may be inconsistency or conflict in the information conveyed to consumers. Furthermore, pharmacists do not always have timely access to relevant treatment history and diagnostic data, which may contribute to providing incomplete key information to consumers. Ideally, the adoption of an interprofessional approach to patient care combined with a patient-centred approach is preferred in order to improve patient outcomes, including adherence to medicines.[178, 187-189]

Another key aspect which directly impacts medication adherence is the relationship between consumers and health care professionals at each stage of the treatment

process.[178, 186, 190, 191] This includes the relationship between the GPs and consumers at the beginning of the process, which impacts primary non-adherence. Primary non-adherence refers to consumers who fail to have a new prescription dispensed within a defined number of days (commonly 30 or 60 days) after the medicine was ordered.[192]

The relationship between the pharmacist and consumer, commences when the prescription is dispensed for the first time or refilled, which impacts secondary non-adherence. Secondary non-adherence refers to consumers who do not begin taking their medicines as intended after they have had their prescriptions dispensed; this behaviour can range from not following the frequency or dose instructions of the prescription (e.g. skipping doses, taking medicines at incorrect times or in incorrect doses, taking more than prescribed), forgetfulness, errors of purpose, or use of inadvertent combinations.[3, 8, 46-49] The framework has the capability of elucidating the entire process of medication adherence in consumers with unipolar depression. In addition, facilitators of and barriers to adherence at specific phases were also illustrated. Because our framework focuses on the stage of adherence to medicines, all interactions between the consumers and health care professionals, health care system, and society were therefore delineated in the framework subcomponents. These considerations highlighted the endeavour to create a practical framework which elaborates on potential factors influencing medication adherence from the consumer's perspective. Consequently, a better understanding of the medication taking process can be achieved, which is an important step to establish effective strategies to promote medication adherence in consumers with depression.

Although there have been previous studies which have explored factors influencing medication adherence in unipolar depression, they have generally not focused on the ongoing nature of medication adherence, that is, the factors which may influence medication adherence may change over time for individuals.[80, 193-195] For example, during the early phase of treatment, early medication adherence may be enhanced by the provision of educational information concerning the nature of depression,

medicines used, and possible ADRs. Whereas, facilitators of adherence at six months of the treatment were more related to the previously used antidepressants and the consequence of using antidepressant medicines.[196] This point is crucial as it acknowledges the dynamic nature of medication adherence in unipolar depression. It is also noteworthy that none of the existing studies have conducted a detailed evaluation of factors mapped to the different phases of adherence identified by the ABC framework. Nor have most studies provided clear information pertaining to the adherence phase in their studies. Another point concerns the diverse results when one factor influences medication adherence in individuals in different ways due to their personal experiences and different perspectives. For example, stopping a medicine may be commonly interpreted as negative factor. On the other hand, the cessation of medicine due to unbearable ADRs should not be interpreted as negative factor. In this study, stopping a medicine was perceived as a negative factor because we were interested in the consumers' decision to cease antidepressant medicines without informing their doctor. For this reason, the interpretation and clarification of influencing factors should be undertaken carefully. Therefore, we conducted in-depth semi-structured interviews to identify factors influencing medication adherence at each phase of medication-taking.

When comparing the development process of our framework with other frameworks in medication adherence, most of the existent frameworks have been developed on the basis of review of the literature.[8, 94, 95, 98] Furthermore, a number of them did not provide detailed information about the development process;[8, 95, 98] therefore, it is difficult to evaluate the initial step between the frameworks.

7.3 Face and content validity of the framework

Validation of the framework is an important process which establishes scientific evidence that the proposed framework is capable of consistently delivering credible results. For the validation process, content validation using an expert panel was adopted because it is a well-accepted and widely used technique to evaluate content validity when new tool is established. In accordance with the purpose of the

framework, health care professionals were the target group which may directly apply the framework in practice. Therefore, they were selected as panellists to evaluate face and content validity of the framework.[172] An internet-based survey was selected to disseminate the survey link to ease storage and management of data, including data from international panel members.[197-199]

It was noted that expert panel members tended to prioritise their own professional views as health care professionals rather than focusing on patient-related factors. These findings point to the need to include a non-professional panel members (such as consumers and caregivers) in future studies to further support a patient-centred approach.[172] Inclusion of non-health care professional panel members may help refine the framework further resulting in improved CVI score (the overall instrument CVI or CVI/Ave). This is likely because the initial items (influencing factors at specific phases of adherence) were generated from multiple resources, but mainly extracted from consumer views. In addition, evaluations from non-health care professional panel members may enhance the reliability of the framework. Notwithstanding the composition of expert panel members in this study, the findings confirm that the proposed framework had acceptable content validity for the relevance and importance of the influencing factors (S-CVI/Ave for relevance and importance were 0.79 and 0.76, respectively).

With regard to framework subcomponents, some items were inconsistently rated by panel members when compared to the findings of our qualitative study and review of the literature. This may be because panel members based their responses on their expertise. Secondly, there may be differences due to the potential for interactions between influencing factors, which may impact consumers and health care professionals differently in different circumstances.

When comparing the validation process with existing frameworks in the area of medication adherence, the overall process of framework development and framework validation in the research included in this thesis is similar to the framework created by Jaam et al. (2006).[94] The validation process was a little

different in that Jaam et al applied the Delphi technique to finalise their model.[94] However most existent studies did not provide details pertaining to the validation of the framework, nor did they validate their framework.[94, 95, 108] Although one adherence model in hypertension verified feedback from patients as a part of model creation, the sample size was small and limited to the specific group of patients.[109] Therefore, it is difficult to present a detailed discussion about the validation process for existing adherence frameworks.

7.4 Selection of valid measurement at specific phases of medication adherence

The framework of adherence to antidepressant medicines was created with the particular focus of understanding adherence at each of the phases of medication taking behaviour. This was coupled with an understanding of the selection of a credible assessment of adherence to medicines for each of these phases, which is essential for both treatment evaluation and follow-up care. Critically this framework acknowledges that medication adherence is a dynamic process for individuals. Further, in clinical settings, there is a lack of a gold standard of an adherence measure. This indicates the need to identify valid and reliable measurement to evaluate medication adherence in chronic conditions.

The selection of valid tool(s) at a specific phase of adherence is important. This will aid clinicians to yield an accurate evaluation measure which is crucial for treatment evaluation and modification of the treatment plan. Hence we conducted a systematic review to identify appropriate measures of medication adherence for the different phases of adherence. The following two main aspects will be discussed in accordance with the identification and evaluation of the measures: 1) identification of the measure at a particular phase of adherence, and 2) the evaluation of the psychometric properties of each measure.

First, it was crucial to identify the measures that have been used to assess medication adherence at specific phases of adherence in accordance with the ABC taxonomy. At

this stage, no measure had been used to assess medication adherence at the initiation phase, as most studies focused on antidepressant consumption at the implementation and discontinuation phases. Similarly, all the psychometric tests have been done and reported at the implementation phase.

Because of the lack of a gold standard to assess medication adherence, multiple tools are suggested to assess medication adherence. In the initiation phase, it seems impractical to directly investigate the consumption of the first dose of the prescribed medicine. One possible solution, however, is that physicians and other health care professionals could ask their patients whether or not they have taken the first dose of medicine as well as explain to them any side-effects, if any, for the medicine prescribed. In the implementation phase, multiple tools are recommended. The most practical strategy is to use a standardised self-report tool, for example, the four-item Morisky, Green, and Levine Self-reported Medication-taking Scale (MGLS)[77] or the Antidepressant Adherence Scale in conjunction with pharmacy records (or prescription claims data),[34, 201] as they can capture both short and long-term adherence with acceptable reliability and validity (page xx, Table 3, Chapter 3). In addition, some of the standardised self-report measures such as the MGLS are able to capture both the implementation and discontinuation phases, where the patients intend to cease taking their medicines.[202] The Beliefs about Medicines Questionnaire (BMQ by Horne)[76] is another useful self-report measure at the implementation phase. It provides acceptable reliability and validity (page xx, Table 3, chapter 3) which considers an individual's beliefs, which in turn may prove useful in understanding the rationale underlying one's decision pertaining to medication adherence behaviour.

For the evaluation of the psychometric properties of each measure at the particular phases of adherence, we found that missing information and unclear data obtained from the existing studies contributed to difficulty in interpretation the psychometric properties of instruments. For example, unclear methods and ambiguous terms that have been used for the evaluation of measures (e.g. agreement, correlation, and

concordance between measures). In addition, the Kappa statistic, an important reliability test was commonly reported. However, specific types of Kappa statistics were often unspecified. Although a rigid procedure pertaining to the identification of the adherence phase has been determined by researchers, many studies did not detail information about the phase of adherence being evaluated. In other words, adherence processes were not conceptualized in the same manner, using the ABC framework.[2] That is, relevant information pertaining to the timeline when adherence was evaluated was limited. In this respect, we acknowledge that the original studies reviewed had a different purpose to our systematic review. This explains the limited and somewhat fragmented information presented in discussion part of Chapter 3 and table 1A (page xx, chapter 3).

With regard to the use of standardised patient self-report adherence measures, the interchangeable and inconsistent use of the terminology may also have contributed to challenges in extracting data about the medication adherence measures. In this respect, three main aspects will be discussed here: the similarity of abbreviated names of the tools, several names used for the same tool/s, and the inclusion of similar items among different tools.

First, two "BMQ" patient self-reports were identified. One was the BMQ, created by Horne et al (1999).[76] This tool comprises two sections: the BMQ-specific which assesses representations of medicine prescribed for personal use and the BMQ-general which assesses beliefs about medicines in general.[136] Further, another BMQ, the Brief Medication Questionnaire was created by Svastad et al. (1999).[203] This is a patient self-report tool for screening adherence and barriers to adherence. It includes a five-item regimen screen that asks patients how they took each medicine in the past week, a two-item belief screen that asks about drug effects and bothersome features, and a two-item recall screen about potential difficulties remembering. Therefore, it is important that the full name of the tool is clearly defined when it is employed.

Secondly, one tool can be called by different names. For example, the MGLS was also called the Medication Adherence Questionnaire (MAQ) and Self-reported Medication Taking Scale (SMTS).[19, 204-206] Although the most common terminology use was the MGLS, it could be the case that some researchers have used different names for the same instrument.

Lastly, some measures were created based on a previous version or were modified in some way, for example, the four-item Morisky Medication Adherence Scale (MMAS-4) was created via the modification of the MGLS.[207] The MMAS-4 comprises four items, similar to the MGLS. The only distinction is that the second question has been revised from the notion of *'the carelessness of taking medication'* to *'the problem of remembering to take your medication',* with the other three items being identical.[207] Furthermore, the study prior to 2011 often used the term 'Morisky' to represent the MGLS.[58, 208, 209] Therefore, the interpretation and implementation of the obtained information relevant to these slightly different measures should be performed carefully with precision.

In order to enhance the internal validity of the understanding of measurement of adherence in depression, only research which pertained to adults who lived with unipolar depression were included. We excluded comorbidities, as certain physical and mental conditions can alter medication-taking behaviour such as anxiety, attention deficit hyperactivity disorder (ADHD), and dementia.[6, 7] We also excluded specific age ranges as a particular population group may require specific measures pertaining to physical change; for example, the elderly may have greater difficulty when using patient self-report which is related to their memorising ability and other tools such as smartphone applications (Apps) may be more suitable for teenagers.[210] In addition, consumers below the age of 18 years were also excluded as the responsibility of medication-taking in this age group was undertaken by their parents or caregivers rather than the consumers themselves.

Smartphone apps are a relatively new strategy aimed at assisting consumers in better managing their chronic conditions.[211] Various utilities of the apps have been

proved for people with unipolar depression such as screening, use as the adjunctive treatment in lowering depressive symptoms in mild to moderate depression and in refractory depression, and assisting medication adherence.[210, 212-215] The apps have a potential to be effective in improving medication adherence as they are inexpensive, scalable, accessible to anyone with a smartphone, and do not require separate devices or packaging, which allows them to be easily implemented.[211] Therefore, smartphone apps and other technology-based solutions are becoming an important part in the future of mental health care.[216] However, the majority of the apps lacked appropriate evaluations from clinical and legal viewpoints, which is considered to be a significant gap.[217, 218]

The findings of the research described in this thesis provide a potential solution to address suboptimal medication adherence in people taking antidepressant medicines for the management of unipolar depression. The integration of the findings from Chapter Six, the conceptual framework of medication adherence, may be used by health care professionals to improve medication adherence (Chapters Four and Five). If combined with the use of appropriate adherence measures for the specific phases of adherence, this may improve overall medication adherence in consumers with unipolar depression.

7.5 Strength and limitation of this thesis

This is a preliminary study of the framework developed to better understand medication-taking behaviour in people living with unipolar depression. A pilot test of the face and content validity of the proposed framework was conducted among health care professionals, via an internet-based survey using an expert panel. In order to balance the framework, the addition of a non-professional panel into the validation process could be considered. Accordingly, the revision of the framework subcomponents as well as pilot testing of the implementation of the framework among the intended users and health care professionals might improve the likelihood of the uptake of this model in practice.

This thesis has a number of strengths, which are stated below:

Firstly, this is the first study to establish a comprehensive framework of medication adherence which adopted the ABC taxonomy for greater understanding of medication-taking behaviour in people with unipolar depression. The framework highlighted the need for receiving specific, individualised support at different phases of adherence for people living with unipolar depression. It can be applied not only to address non-adherence to antidepressant medicine, but also can be used as a guidance for various stakeholders, when health policy related to this area is reviewed.

Secondly, this framework presents a practical model which specifically endorses the creation of a healthcare system in which the dispensing function is separated from the prescribing function. On the other hand, it may not be suitable for a health care system in which the dispensing function is integrated with the prescribing function or in a one-stop service setting.

Lastly, rigorous methods in accordance with the standard approach to conduct research (the PRISMA statement for a systematic review and the COREQ for reporting qualitative research) were employed in the research described in this thesis to ensure the comprehensiveness and appropriateness of the body of the work. In addition, the

triangulation process of multiple sources of information was used for the framework development. These procedures affirmed that solid work has been done.

Despite these strengths, there are some limitations, which are discussed below:

Firstly, this framework does include consumers who apparently fail to recognise depression as a disease or diagnosis, failed to treat depression, or those who do not believe in the doctor. This is including those who could not access or were denied access to health care professionals and the health care system. Given this, the implementation of the framework is limited to people who can or are willing to access health care professionals and the health care system. Therefore, both the interpretation and implementation of the findings must be done carefully. Additionally, the framework was created for primary care where most of people living with unipolar depression are managed. Therefore, the implementation of the framework in other practice settings has not been established.

Secondly, with regard to the validation process via internet-based survey using an expert panel, the researchers acknowledged the value of a non-professional panel arm in this study as it balanced the findings and confirmed potential factors at specific phases from another viewpoint. In addition, increasing the number of expert panel members generally enhances the credibility of results; hence, it must be considered. We also acknowledge that the preliminary framework requires greater clarity with respect to the framework's subcomponents , perhaps in accordance with the Plan-Do-Check-Act cycle (PDCA cycle), a quality improvement methodology that may be used for the continuous quality improvement of processes or elements within the health care system.[219] For this reason, the content validation process was undertaken. In addition, a non-health care professional panel could be recruited to conduct the next stage of validation of the framework subcomponents (influencing factors at particular phases of medication taking behaviour), contributing to increased external validity. In addition, the framework did not explicitly consider the specific competence of health care professionals, which may also influence adherence to medicine.

CHAPTER EIGHT – Conclusions and future directions

8.1 Conclusions

Understanding potential factors influencing medication adherence and non-adherence from the consumer perspective throughout the process of medication taking is a crucial principle of adherence improvement in people living with unipolar depression. The conceptual framework developed and presented in this thesis is the first that has been attempted to unpack and better understand the complicated process of medication adherence in people taking an antidepressant medicine for unipolar depression. Furthermore, it is the first to have used the ABC taxonomy as the broad framework. The framework focused on facilitators of and barriers to medication adherence at the three distinct phases of adherence: initiation, implementation, and discontinuation of therapy. The framework employed the core concept of patient-centeredness which highlights the notion of patients' preferences, patient empowerment, patient autonomy, and shared-decision making approach in health care. As can be seen, informed understanding of consumers' beliefs about medicines, self-motivation, and medication self-management are central to improving medication adherence in people living with depression. In turn, this approach may contribute to improved health outcomes via improved medication adherence in consumers with unipolar depression. This patient-centred approach is aligned with a broader global health approach which has seen a movement from a health care professionals focus to a consumer-centred focus.

The proposed framework attempts to bridge the gap between health care professionals and patients as it aids health care professionals to better understand their patients from the consumer's perspective. It is noteworthy that the underpinning purpose of the proposed framework was for it to be useful for clinical practice, hence the rigorously developed but pragmatic approach to its development.

Specifically, this framework may be used as a guide to inform health professionals to tailor and convey effective strategies to improve medication adherence for individuals with unipolar depression. The integration of tailored and multifaceted interventions in conjunction with proactive care management and the involvement of mental health specialist should be employed in clinical settings for the enhancement of medication adherence. In addition, regular follow-up across the different phases of medication taking behaviour is recommended, coupled with the use of a validated measure/s of medication adherence. Such an approach may improve the effectiveness of antidepressant medicine use in people with unipolar depression which in turn may improve health outcomes.

8.2 Future directions

In light of the proposed framework, it can now undergo feasibility and pilot testing in clinical practice in primary care. Modifications and further validity testing with non-health care professionals would also improve the utility of the framework. Ultimately this framework might be used routinely in clinical practice to assist health care professionals and individuals being treated with antidepressant medicines for unipolar depression.

The proposed framework may also be used as a prototype to develop tailored interventions for other chronic conditions.

Future enhancements of the framework may be included and supported by technology, such as the development of a health application for people with unipolar depression.

This research found that few studies focused on the initiation of antidepressant medicines. This is an important area for future research as little is known about primary non-adherence in people with unipolar depression. This is likely to be of importance given the stigma which surrounds mental illnesses including unipolar depression.

APPENDICES

APPENDIX ONE – Description of journals

Research in Social and Administrative Pharmacy

Research in Social and Administrative Pharmacy (RSAP) is a bi-monthly publication featuring original scientific reports and comprehensive review articles in the social and administrative pharmaceutical sciences. Topic of interest include outcomes evaluation of products, programs, or services; pharmacoepidemiology, medication adherence, direct-to-consumer advertising of prescription medication; disease state management; health systems reform; drug marketing; medication distribution systems such as e-prescribing; web-based pharmaceutical/ medical services; drug commerce and re-importation; and health professions workforce issues.

Journal impact factor: 2.403

Patient Preference and Adherence

An international, peer reviewed, open access journal that focuses on the growing importance of patient preference and adherence throughout the therapeutic continuum. The journal is characterized by the rapid reporting of reviews, original research, modelling and clinical studies across all therapeutic areas. Patient satisfaction, acceptability, quality of life, compliance, persistence and their role in developing new therapeutic modalities and compounds to optimize clinical outcomes for existing disease states are major areas of interest for the journal.

Journal Impact Factor: 1.798 (5 year impact 1.831)

APPENDIX TWO – Letters of ethics approval

Research Integrity
Human Research Ethics Committee

Tuesday, 30 June 2015

Assoc Prof Timothy Chen
Pharmacy; Faculty of Pharmacy
Email: timothy.chen@sydney.edu.au

Dear Timothy

Your request to modify the above project submitted on 3rd June 2015 was considered by the Executive of the Human Research Ethics Committee at its meeting on 23rd June 2015.

The additional information provided was reviewed by the Ethics Office on **30th June 2015.**

The Committee had no ethical objections to the modification/s and has approved the project to proceed.

Details of the approval are as follows:

Project No.: **2014/967**

Project Title: **Factors influencing patients' adherence to antidepressant medicines in unipolar depression: a qualitative study**

Approved Documents:

DATE	TYPE	DOCUMENT NAME
03/06/2015	Other Type	attachment 1 Research data for market research company
03/06/2015	Other Type	attachment 2 Antidepressant lists in Australia version 1
03/06/2015	Participant Info Statement	Appendix 1 Participant information statement version 2
17/11/2014	Advertisements/Flyer	Flyer
17/11/2014	Participant Consent Form	Participant consent form
17/11/2014	Interview Questions	Interview guide
17/11/2014	Other Type	Background information questionnaire
17/11/2014	Telephone Scripts	Telephone script
17/11/2014	Participant Info Statement	Participant information statement
17/11/2014	Other Type	Reserarch reference

Special Conditions:

- Please correct 'anindividual' under point three of your PIS

Please do not hesitate to contact Research Integrity (Human Ethics) should you require further information or clarification.

Yours sincerely

[redacted]

Dr Stephen Assinder
Chair
Human Research Ethics Committee

This HREC is constituted and operates in accordance with the National Health and Medical Research Council's (NHMRC) National Statement on Ethical Conduct in Human Research (2007), NHMRC and Universities Australia Australian Code for the Responsible Conduct of Research (2007) and the CPMP/ICH Note for Guidance on Good Clinical Practice.

Research Integrity & Ethics Administration
Human Research Ethics Committee

Wednesday, 8 March 2017

Assoc Prof Timothy Chen
Pharmacy; Faculty of Pharmacy
Email: timothy.chen@sydney.edu.au

Dear Timothy

The University of Sydney Human Research Ethics Committee (HREC) has considered your application.

After consideration of your response to the comments raised your project has been approved.

Approval is granted for a period of four years from **08 March 2017** to **08 March 2021**

Project title: **Face and content validity of medication adherence conceptual framework: factors influencing patients' adherence to antidepressant medicines in unipolar depression**

Project no.: **2016/965**

First Annual Report due: **08 March 2018**

Authorised Personnel: **Chen Timothy; Srimongkon Pornchanok; Aslani Parisa;**

Documents Approved:

Date Uploaded	Version number	Document Name
20/02/2017	Version 2	Telephone script-Clean version
20/02/2017	Version 2	Invitation e-mail-clean version
07/11/2016	Version 1	Survey
07/11/2016	Version 1	Participant Information Statement

Condition/s of Approval

- Research must be conducted according to the approved proposal.
- An annual progress report must be submitted to the Ethics Office on or before the anniversary of approval and on completion of the project.
- You must report as soon as practicable anything that might warrant review of ethical approval of the project including:
  - Serious or unexpected adverse events (which should be reported within 72 hours).
  - Unforeseen events that might affect continued ethical acceptability of the project.
- Any changes to the proposal must be approved prior to their implementation (except where an amendment is undertaken to eliminate *immediate* risk to participants).
- Personnel working on this project must be sufficiently qualified by education, training and experience for their role, or adequately supervised. Changes to personnel must be reported and approved.

- Personnel must disclose any actual or potential conflicts of interest, including any financial or other interest or affiliation, as relevant to this project.

- Data and primary materials must be retained and stored in accordance with the relevant legislation and University guidelines.

- Ethics approval is dependent upon ongoing compliance of the research with the *National Statement on Ethical Conduct in Human Research*, the *Australian Code for the Responsible Conduct of Research*, applicable legal requirements, and with University policies, procedures and governance requirements.

- The Ethics Office may conduct audits on approved projects.

- The Chief Investigator has ultimate responsibility for the conduct of the research and is responsible for ensuring all others involved will conduct the research in accordance with the above.

This letter constitutes ethical approval only.

Please contact the Ethics Office should you require further information or clarification.

Sincerely

Associate Professor Michael Skilton
Chair
Health Review Committee

The University of Sydney HRECs are constituted and operate in accordance with the National Health and Medical Research Council's (NHMRC) National Statement on Ethical Conduct in Human Research (2007) and the NHMRC's Australian Code for the Responsible Conduct of Research (2007).

APPENDIX THREE – Study instruments for qualitative study (Chapter Four and Five)

Figure A: Poster for the recruitment process

INTERVIEW GUIDE

Factors influencing adherence to anti-depressants in unipolar depression: a qualitative study

This project aims to:

1. To explore the strategies or positive influencing factors which promote medication adherence (at the three stages of adherence: Initiation, Continuation and Discontinuation) in unipolar depression from the consumer's perspective.
2. To explore the barriers or negative influencing factors which reduce medication adherence (at the three stages of adherence: Initiation, Continuation and Discontinuation) in unipolar depression from the consumer's perspective.

The identified strategies or positive factors that encourage consumers to take their antidepressant medicines, and negative factors or barriers to medication adherence, will be used to inform the development of innovative and tailored interventions to promote adherence in our target population.

<u>Factors affecting antidepressant adherence.</u>

1) **Patient related factors** (*Insight* and beliefs:* The specific components of Insight including awareness of present illness, awareness of sign and symptoms related to illness, attribution of current signs and symptoms to the illness, understanding the usefulness of treatment.;Impact of depression, Substance abuse/ comorbidity, Perceived benefits/ costs)
    a. Can you tell me a bit about your experiences of depression?
        i. How long have you been diagnosed with depression?
        ii. How long have you taken antidepressant medicines?
    b. Can you tell me how your depression has affected your life and daily activities?
2) **Condition related factors** (*illness related, severity of symptom, the availability of effective treatment, drug and alcohol abuse, co-morbidities)*
    a. How effective do you find antidepressant medicines for managing the symptoms of depression?
    b. How effective do you find antidepressant medicines for the prevention of episodes of depression?
3) **Clinician related factors** or Health care team and system-related factors*(Therapeutic alliance, support, frequency of visits, clinician perception/preferences, power of suggestion, simplicity of explanation)*
    a. Can you describe to me the relationship you have with your doctor?
    b. How does your doctor or other health care professional encourage or help you to take your antidepressant medicines?
    c. How often do you visit your doctor or other health care professionals?
    d. What do you think about health care team in terms of the support, it provides you to take antidepressant medicines?
    e. What is your opinion about health care system including health insurance groups/ companies in terms of support you to take antidepressant medicines?
4) **Medication related factors***(Efficacy, side effects, frequency, route of administration, polypharmacy, cost)*

a. Can you tell me about your experiences of taking antidepressant medicines?
    i. Do you take your antidepressant medicines as prescribed?
    ii. If not: Why?
b. What are your thoughts about how well your antidepressant medicines have worked for you? (Do you believe in the effectiveness of antidepressant medicines?) Can you tell me a little bit more about that?
c. What do you think about treatments options or medicines for people who have depression?
d. Have you had any side effects from your antidepressant medicines? (such as sexual dysfunction, weight gain, sleep disturbances)
    i. If yes: Can you tell me a bit about that?
    ii. If yes: How did you handle it?
e. Can you tell me about what other people (such as friends, family, work colleagues) think about your using antidepressant medicines?

Antidepressant Medicines:

a. Can you tell me what motivates you to take your antidepressant medicines?
b. What/why made you start your antidepressant medicines?
c. Can you tell me what made you continue your antidepressant medicines?
d. What are some of the steps you take every day to help you in making sure that you take your antidepressant medicines?
e. In an ideal world what sort of help would encourage and help you and other people with depression to take antidepressant medicines on a regular basis?
f. Have you stopped taking antidepressantmedicines for a while? Can you explain more about that?
g. What or who supported you to restart your antidepressant medicines?
h. How often have you stopped taking your antidepressant medicines?

5) **Environmental related factors** or Social and Economic factors*(Family support and beliefs, Access, Formulary considerations, Role of internet/ advertising, financial burden)*
    a. Do you belong to any support group?
        i. If yes: Can you tell me about that? How helpful is the group?
        ii. If no: Would you consider joining such a group?
    b. How well would you say your family (partner, parents, friends, colleagues) support you? What are some of the ways that they support you?
    c. What do you think about the cost of antidepressant medicines?
6) Can you tell me what stops you or gets in the way of youtaking your antidepressant medicines?
7) In your view, what could be the barriersfor people with depression who are trying to take their antidepressant medicines on a regular basis?
8) Can you tell me whether you drink alcohol? Does it impact on your medicine taking?
9) How can you tell me whether you smoke cigarettes? Does it impact on your medicine taking?
10) Do any lifestyle factors impact on your medicine taking?

What other comments do you have that we have not addressed so far?

THE UNIVERSITY OF SYDNEY

INTERVIEW GUIDE FOR PARTICIPANTS

TITLE: Factors influencing adherence to anti-depressants in unipolar depression: a qualitative study

We would like to ask you about…

1) Your experience with depression.
2) Effectiveness of antidepressants.
3) A relationship with your doctor and healthcare professional.
4) Your experience of taking antidepressants and side effects.
5) The environments and people who support you taking your antidepressants.
6) Alcohol consumption, smoking behavior and your lifestyle.

Factors influencing patients' adherence to antidepressant medicines in unipolar depression: A qualitative study

Please place a tick (√) in the box to provide your background details.

1. Gender: ☐ Male ☐ Female ☐ Transgender ☐ Prefer not to respond

2. In what year were you born? _____

3. Ethnicity:
   How do you describe your ethnicity? (please check the one option that best describes you)
   ☐ Oceania and Antarctica (Australia, New Zealand, Melanesia, Micronesia, Polynesia and Antarctica)
   ☐ North-West Europe
   ☐ Southern and Eastern Europe
   ☐ North Africa and Middle East
   ☐ South-East Asia
   ☐ North-East Asia
   ☐ Southern and Central Asia
   ☐ Americas
   ☐ Sub-Saharan Africa
   ☐ Multiracial
   ☐ Other (please specify) _____
   ☐ Prefer not to respond

4. Education: What is the highest degree or level of school you have completed? If currently enrolled, mark the previous grade or highest degree received.
   ☐ No schooling completed
   ☐ Pre-primary education
   ☐ Primary education
   ☐ Secondary education
   ☐ Certificate level
   ☐ Advanced diploma or Diploma level
   ☐ Bachelor degree level (including honours)
   ☐ Graduate Diploma or Graduate certificate level
   ☐ Postgraduate degree level
   ☐ Others (please specify) _____
   ☐ Prefer not to respond

5. What is your marital status?
   ☐ Now married ☐ Separated
   ☐ Widowed ☐ Never married
   ☐ Divorced ☐ Living with a partner in a de facto relationship
   ☐ Prefer not to respond

6. Which of the following are applicable to your living situation? (Check all that apply)
   - ☐ I live alone.
   - ☐ I live with roommates/housemates
   - ☐ I live with parents(s), relative(s), or guardian(s)
   - ☐ I live with a husband/wife/domestic partner/significant other
   - ☐ I live with my child/children
   - ☐ Other (please specify) _____
   - ☐ Prefer not to respond

7. Employment status: Are you currently…?
   - ☐ Employed
   - ☐ Self-employed
   - ☐ Out of work and looking for work
   - ☐ Out of work and not currently looking for work
   - ☐ Other (please specify) _____
   - ☐ Prefer not to respond
   - ☐ A homemaker
   - ☐ A student
   - ☐ Retried
   - ☐ Unable to work

About your health status:

8. Please provide some information about your current medical conditions:
   - 8.1 Depression:
     - 8.1.1 How long have you been diagnosed with depression?
       _____
     - 8.1.2 How long have you taken antidepressant medicines?
       _____
     - 8.1.3 Please write down the name of the antidepressant medicine/s you are currently taking.
       _____
       _____
       _____
       _____
   - 8.2 Other medical conditions:
     - 8.2.1 Do you have any other medical conditions?
       ☐ Yes. Please specify _____
       ☐ No.
     - 8.2.2 What medicines are you taking for these conditions?
       _____
       _____
       _____
       _____

APPENDIX FOUR – Study instruments for the conceptual framework study (Chapter Six)

Table A: Initial items retrieved from previous qualitative research study and review literature.

Dimensions	Sub-dimensions	Factors influencing to medication adherence and related references
1. Factors relating to healthcare providers	1.1 Healthcare professionals (HCPs) influence to medication adherence	- HCPs role as a facilitator[87] - Qualitative study conducted by the researchers
	1.2 Relationships between HCPs and patients	- Good relationship[17, 35, 62, 78, 80, 81] - Rapport established[80] - Lack of attention to the patient[80] - Apparent dismissive reaction[80] - Superficial or glib responses from doctors to patients[80] - Unsatisfactory interaction with HCPs[78] - Disconnected relationship[78] - Patient fear of HCPs[36] - HCPs-patient interaction[66] - Qualitative study conducted by the researchers
	1.3 Support from HCPs/ helpfulness of HCPs visits	- Rating GP visits as moderately to extremely helpful[60] - Support from HCP[37, 80] - Qualitative study conducted by the researchers
	1.4 Stigma about depression in HCPs	- Qualitative study conducted by the researchers
	1.5 Experienced HCPs	- Qualitative study conducted by the researchers
	1.6 Collaboration between HCPs (GPs, psychiatrists, and pharmacists) in a mental health care team	- Multiple prescribers[36] - Qualitative study conducted by the researchers
	1.7 Interactive communication and open dialogues between HCPs and patients	- Communication[60, 78, 88] - Two-way communication/ being listened too[80] - Shared decision-making[80] - Early discussion[62] - Problems communicating with HCPs[36]

Dimensions	Sub-dimensions	Factors influencing to medication adherence and related references
		- Qualitative study conducted by the researchers
	1.8 Adequate information about depressive treatment from HCPs	- Adequate information[38, 62, 80] - Patients are expected to be informed about medicines before treatment initiation[78] - Required more information from their doctors before taking the first dose[80] - Sufficient information form HCPs[37, 81] - Knowledge about the causes of depression and mechanism of antideprssants[37] (and other relevant issues[51]) - Qualitative study conducted by the researchers
	1.9 Adequate time to see the doctor/ length of GP visit	- GP visits longer than 20 mins[60] - Sufficient time during the consultation[17, 78, 80] - No obligation to rush[62] - Qualitative study conducted by the researchers
	1.10 Belief about the efficacy of antidepressant medicine among HCPs	- Qualitative study conducted by the researchers
2. Factors relating to the healthcare system	2.1 Accessibility to the health care providers/ Access to practice	- Accessible[36, 60] - Qualitative study conducted by the researchers
	2.2 Mental health organisations role	- Qualitative study conducted by the researchers
	2.3 Private health insurance	- Qualitative study conducted by the researchers
	2.4 Accessibility of antidepressant medicines/ access to medication	- Qualitative study conducted by the researchers
	2.5 The continuity of care in public system/ health system	- Continuity of care[60] - Qualitative study conducted by the researchers
	2.6 Management issue	- Long waiting time at the clinic[36] - Frequent medication refills[36] - Frequent clinic visits[36] - No supply of medications[36] - Qualitative study conducted by the researchers
	3.1 Patient self-motivation	-'will power'[62] - Wish for complete recovery[36]

Dimensions	Sub-dimensions	Factors influencing to medication adherence and related references
3. Factors relating to patients and carers		- Fear of relapse[36] - The ownership of the decision[37] - Qualitative study conducted by the researchers
	3.2 Acknowledgement of their depression condition	- Accepted their health conditions[78]/diagnosis[62] - Qualitative study conducted by the researchers
	3.3 The involvement of the patients in treatment decision-making process	- Qualitative study conducted by the researchers
	3.4 Previous experience of antidepressant treatment, either favourable or unfavourable	- Previous experience of antidepressant treatment[35, 39, 78] - Personal or family experience of antidepressant medicine, frequently negative[62] - Qualitative study conducted by the researchers
	3.5 Family support	- Family's attitude toward medication[61] - Family support (family/spouse/friends)[36] - Cultural beliefs[36] - Qualitative study conducted by the researchers
	3.6 Peer support	- Trusted friends[62] - Social support[36, 81, 89] - Similar experience sharing/ support from people with depression[79] - Qualitative study conducted by the researchers
	3.7 Patient regular activities	- Such as taking with a meal[36] - Qualitative study conducted by the researchers
	3.8 Stigma about depression/ self-stigma/ antidepressant	- Stigma related to perceived drug dependency[80] - Strong self-stigma attached[80] - 'Felt' Stigma[79] ; refers principally to the fear of discrimination on the basis of perceived unacceptability or inferiority, as opposed to actual instances of discrimination. - Self-stigma[35, 65] - Qualitative study conducted by the researchers
	3.9 Mental health stigma from family members or carers	- Qualitative study conducted by the researchers
	3.10 Stigma in society	- Societal stigma[39]

Dimensions	Sub-dimensions	Factors influencing to medication adherence and related references
		- This type of stigma was connected to the view that psychotropic medication would affect cognitive functions. It was based on actual discriminatory remarks by others and can therefore be interpreted as 'enacted' stigma.[79] - Public opinion about depression and its treatment reveals reluctant to consult practitioners about depressive symptoms, and evidence that counselling is favoured over antidepressant treatment.[62] - Stigma in society[36] - Qualitative study conducted by the researchers
	3.11 Belief in antidepressant	- Belief/ perception [16, 36, 62, 63, 90] - Faith[81] - Beliefs and attitudes to depression and antidepressant[35] - Qualitative study conducted by the researchers - Attitudes toward antidepressant[35, 78, 81]
	3.12 The ability to self-manage on medication taking	- (more) self-help practices[60] - Qualitative study conducted by the researchers
	3.13 Concern about the effect of stopping antidepressant therapy	- Experiencing symptoms worsening when they weren't regularly taking antidepressant[39] - Fear of withdrawal symptoms[87] - Fear of relapse[87] - Uncertainty about what would be like without antidepressants[87] - Qualitative study conducted by the researchers
	3.14 Clinical improvement/ feeling better	- Welcoming effects of antidepressant[78] - Recovery[62, 79] - Early treatment response[81] - Feeling better[55] - Treatment outcome[35] - Qualitative study conducted by the researchers
	3.15 Patients who have trust in their HCPs	- Trust in HCPs[36, 78, 80] , Trust in GPs[60] - They believe that 'doctor knows best'[80] - Qualitative study conducted by the researchers
	3.16 Knowledge about depression and antidepressant medicine	- Knowledge [78, 80] - Lack of knowledge about the use of antidepressant, the effect of antidepressant[36] - Qualitative study conducted by the researchers

Dimensions	Sub-dimensions	Factors influencing to medication adherence and related references
	3.17 Forgetfulness	- Forgetfulness[36, 39] - Including: having a busy schedule, being away from home, simply forgetting to take their antidepressant[36] - Qualitative study conducted by the researchers
	3.18 Perceive drug dependency and addiction	- Fear of drug dependency and/or addiction[80] - Fear of drug dependence[36, 55] (erroneous belief, misconceptions about depression and/or antidepressant)[36] - Qualitative study conducted by the researchers
	3.19 Patient perceive and belief about illness (depression)	- Perceive and belief about depression[78, 80] - Qualitative study conducted by the researchers
	3.20 Patient concerns about sense of self while using antidepressant medicines	- Sense of self[80], not feeling like oneself[39] - Worries about the feeling 'fluffy' or 'out of control' when use antidepressant[80] - Sense of self control[55] - Self-reliance[39] - Qualitative study conducted by the researchers
	3.21 Patient belief about the need of antidepressant	- Belief about the need of antidepressant[66, 78, 80] - Awareness about the need to take antidepressant[36] - Uncertainty about the benefits of and the need for antidepressant[87] - Qualitative study conducted by the researchers
	3.22 Patient beliefs about the efficacy of antidepressant medicines	- Beliefs about efficacy of antidepressant[78] - Qualitative study conducted by the researchers
	3.23 Attitudes towards antidepressant	- Negative attitude such as a dislike for the pill[36] - Attitudes towards antidepressant[37] - Qualitative study conducted by the researchers
	3.24 Reminders	-Such as using pillboxes, reminder form family members, keeping medications in visible places[36] - Qualitative study conducted by the researchers
4. Demographic and socioeconomic factors	4.1 Level of education	- Higher level of education predicted the correct intake of antidepressant[81] - Education level[61]
	4.2 Living status/ marital status	- Marital status[60, 61, 92]

Dimensions	Sub-dimensions	Factors influencing to medication adherence and related references
	4.3 Cost of antidepressant medicines/ affordable antidepressant medicines	- Cost of antidepressant[36] - Qualitative study conducted by the researchers
	4.4 Cost of health care	- Qualitative study conducted by the researchers
	4.5 Benefits as main source of income	- Benefits as main source of income[60] - Qualitative study conducted by the researchers
	4.6 Family income	- Low family income[35]
5. Disease and medicine factors	5.1 The severity of depressive symptoms	- Severity of depression[60, 62-66] - Qualitative study conducted by the researchers
	5.2 Depressive symptoms itself such as lack of motivation, lethargy, forgetfulness	- Clinical features of depression[6, 7, 9, 35] - Qualitative study conducted by the researchers
	5.3 Chronic conditions itself that requires long-term treatment	- Chronic condition of depression which requires long-term treatment[60, 78]
	5.4 Recurrent episode	- Recurrent of depressive episode[60, 61]
	5.5 Comorbidity	- Comorbidity[35, 36, 60, 65, 80, 90-92] - Including alcohol dependence[36] and substance abuse[90]
	5.6 Length of depressive illness	- Length of previous illness[62] - Longer onset of depression[81] - Treatment duration[36]
	5.7 Patient concerns about possible adverse drug reactions	- Concern about possible adverse drug reactions[78, 80] - Qualitative study conducted by the researchers
	5.8 The effectiveness of antidepressant medicines	- Lack of therapeutic response[38] - Lack of efficacy[36, 37, 39, 55, 66] - Qualitative study conducted by the researchers
	5.9 Category of antidepressant used	- Category of antidepressant used[60]
	5.10 Other medicines used	- Pill burden[36] - Qualitative study conducted by the researchers
	5.11 Experiencing ADR	- Experiencing ADRs[35-39, 55, 64, 78, 81] - Concern about the potential ADRs[39]

Dimensions	Sub-dimensions	Factors influencing to medication adherence and related references
		- Qualitative study conducted by the researchers
	5.12 Medication duration of treatment	- Medication duration of treatment[61]
	5.13 Medication onset	- Pharmacological factors[35]

Face and content validity of a medication adherence conceptual frameworks -- Electronic platform

Face and content validity of a medication adherence conceptual framework: factors influencing consumers' adherence to antidepressant medicines in unipolar depression

What is this study about?

Various terms have been used to describe medication taking behaviour of patients including "compliance", "persistence", and "adherence". Recently, a European consortium working group - The Ascertaining Barriers to Compliance project or ABC project[1] - established a new taxonomy for describing different phases of medication taking behaviour. Specifically they conceptualised medication adherence into three distinct phases: initiation, implementation, and discontinuation of therapy.

Based on this framework (initiation, implementation, and discontinuation of therapy), in-depth interviews conducted with the consumers and a review of the literature, we have identified factors known to influence medication taking behaviour at each of these three phases of medication taking, for consumers with depression.

Therefore, the aim of this study is to assess the face and content validity of factors which may facilitate and hinder medication adherence at each of the three phases of medication taking behaviour (i.e. initiation, implementation, and discontinuation of therapy).

There are 3 parts in this questionnaire.
1. Part 1: The influencing factors at the initiation phase of adherence
2. Part 2: The influencing factors at the implementation phase of adherence
3. Demographic data

You will be asked to evaluate the factors influencing (listed statements) each phase of adherence. Specifically, you will be asked to assess relevance to practice and importance of the factor, on 5-point scales. This questionnaire requires about 20-30 minutes to complete.

If you would like to clarify any items prior to rating them, please contact Pornchanok Srimongkon via mobile (0449 761 980) or email psri6621@uni.sydney.edu.au.

Thank you for participating in our survey. Your feedback is important.

Reference

[1] Vrijens, B., et al., A new taxonomy for describing and defining adherence to medications. Br J Clin Pharmacol, 2012. 73(5): p. 691-705.

THE UNIVERSITY OF SYDNEY

Discipline of Pharmacy Practice
Faculty of Pharmacy

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Face and content validity of medication adherence conceptual framework: factors influencing patients' adherence to antidepressant medicines in unipolar depression

PARTICIPANT INFORMATION STATEMENT

(1) What is this study about?

You are invited to take part in a research study about evaluating the face and content validity of a medication adherence conceptual framework in people with unipolar depression. Our research plans to develop a conceptual framework of the facilitators of and barriers to medication adherence in people with unipolar depression. Knowledge of these factors may inform strategies to facilitate medication adherence by consumers with unipolar depression. The conceptual framework is based on a review of the literature, previous qualitative research findings, and an adherence model proposed by a European consortium (Vrijens et al 2012). The purpose of this study is to measure the face and content validity of facilitators of and barriers to medication taking behaviour at the different stages of adherence (initiation, implementation and discontinuation of therapy). It is anticipated that this framework may provide a foundation to create individualised strategies to facilitate medication adherence in consumers with unipolar depression.

You have been invited to participate in this study because of your experience in unipolar depression and/or medication adherence. The insights and information you provide will help create strategies to assist consumers with unipolar depression to take their medicines regularly.

This Participant Information Statement tells you about the research study. Knowing what is involved will help you decide if you want to take part in the research. Please read this sheet carefully and ask questions about anything that you don't understand or want to know more about.

Participation in this research study is voluntary. So it's up to you whether you wish to take part or not.

By giving your consent to take part in this study you are telling us that you:

- ✓ Understand what you have read

- ✓ Agree to take part in the research study as outlined below
- ✓ Agree to the use of your personal information as described.

You will be given a copy of this Participant Information Statement to keep.

(2) Who is running the study?

The study is being carried out by the following researchers:

- Timothy F. Chen, Associate Professor, Faculty of Pharmacy, The University of Sydney
- Parisa Aslani, Associate Professor, Faculty of Pharmacy, The University of Sydney
- Pornchanok Srimongkon, PhD candidate, Faculty of Pharmacy, The University of Sydney

Pornchanok Srimongkon is conducting this study as a part of her research for the degree of Doctor of Philosophy. This research will take place under the supervision of Associate Professors Timothy F. Chen and Parisa Aslani.

(3) What will the study involve for me?

Based on your experience in the treatment of unipolar depression, you will be asked to rate your level of agreement with a number of specific statements which relate to different aspects of medication taking behaviour. You will be provided with descriptions of terms that have been used in this study. You will receive the survey and supporting documents by email (containing a survey link or e-mail attachment) or mail (if preferred). If you do prefer to complete a hard copy of the survey, we will post the survey or send it as an e-mail attachment. We ask that you return the survey within two weeks. We will consider completion and return of the on-line or hard copy survey as your consent for participation in this study. We plan to analyse the extent of agreement between you and other participants, noting that there are no right or wrong answers. Our goal is to have a high level of agreement between participants. This may require one or more rounds of the survey to be completed by you.

(4) How much of my time will the study take?

The expected time to complete the rating scale is about 15 to 20 minutes per round; and up to 60 minutes if you participate in three rounds.

(5) Who can take part in the study?

This study requires experts who have experience in unipolar depression and or medication adherence. The participants may be based in or outside of Australia and may include healthcare professionals (e.g. general practitioners, psychiatrists, and pharmacists) and academics.

(6) Do I have to be in the study? Can I withdraw from the study once I've started?

Being in this study is completely voluntary and you do not have to take part. Your decision whether to participate will not affect your current or future relationships with the researchers or anyone else at the University of Sydney.

If you decide to take part in the study and then change your mind later, you are free to withdraw at any time. You can do this by contacting Pornchanok Srimongkon (psri6621@uni.sydney.edu.au or phone number +61 449 761 980). You are free to stop participating in the study at any time.

If you decide to withdraw from the study, we will not collect any more information from you. Any information that we have already collected will be deleted once you withdraw from the study.

(7) Are there any risks or costs associated with being in the study?

Aside from giving up your time, we do not expect that there will be any risks or costs associated with taking part in this study.

(8) Are there any benefits associated with being in the study?

We cannot guarantee that you will receive any direct benefits from being in the study.

(9) What will happen to information about me that is collected during the study?

Your scores for each part of the questionnaire will be used to determine the face and content validity of items based on the level of agreement between participants. Your responses will remain confidential and will not be identified in any publications or reports. Only the involved researchers in this project will have access to the data. No third parties will be granted access to the results of this study. The results of this study may be published in peer-reviewed journal and you will be notified when it is published. Paper survey instruments will be stored in a locked filling cabinet in a locked research laboratory in the Pharmacy and Bank Building A15 (Room N507). The data will be retained in an unidentifiable format in the same location for 5 years after completion of the study.

By providing your consent, you are agreeing to us collecting personal information about you for the purposes of this research study. Your information will only be used for the purposes outlined in this Participant Information Statement.

(10) Can I tell other people about the study?

Please don't talk to other people about the study, because the new conceptual framework is still under the development and testing stages.

(11) What if I would like further information about the study?

When you have read this information, A/Prof Timothy F Chen and Miss Pornchanok Srimongkon will be available to discuss it with you further and answer any questions you may have. If you would like to know more at any stage during the study, please feel free to contact Miss Pornchanok Srimongkon by email: psri6621@uni.sydney.edu.au; or A/Prof Tim Chen: timothy.chen@sydney.edu.au; or A/Prof Parisa Aslani: parisa.aslani@sydney.edu.au.

(12) Will I be told the results of the study?

You have a right to receive feedback about the overall results of this study. A brief summary of the findings of this research will distribute to participants at the conclusion of the study.

(13) What if I have a complaint or any concerns about the study?

Research involving humans in Australia is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this study have been approved by the HREC of the University of Sydney *protocol number 2016/965.* As part of this process, we have agreed to carry out the study according to the *National Statement on Ethical Conduct in Human Research (2007).* This statement has been developed to protect people who agree to take part in research studies.

If you are concerned about the way this study is being conducted or you wish to make a complaint to someone independent from the study, please contact the university using the details outlined below. Please quote the study title and protocol number.

The Manager, Ethics Administration, University of Sydney: **Telephone:** +61 2 8627 8176, **Email:** ro.humanethics@sydney.edu.au, **Fax:** +61 2 8627 8177 (Facsimile)

This information sheet is for you to keep

Face and content validity of a medication adherence conceptual framework: factors influencing consumers' adherence to antidepressant medicines in unipolar depression

Definition of terms used in this study

1. Medication adherence[1]: The process by which consumers take their medicines as prescribed. Medication taking may be divided into three phases: initiation, implementation and discontinuation of therapy.

1.1 Initiation occurs when the consumer takes the first dose of a prescribed medicine[1].

i. Facilitators of initiation of therapy: factors that encourage consumers to take the first dose of an antidepressant medicine.

ii. Barriers to initiation of therapy: factors that discourage consumers from taking the first dose of an antidepressant medicine.

1.2 Implementation is the extent to which a consumer's actual dosing corresponds to the prescribed dosing regimen, from initiation until the last dose is taken[1].

i. Facilitators of implementation of therapy: factors that encourage consumers to keep taking their antidepressant medicine.

ii. Barriers to implementation of therapy: factors that discourage consumers from taking their antidepressant medicine.

1.3 Discontinuation occurs when the consumers stop taking their prescribed medicine, for any reason(s)[1].

2. Healthcare provider refers to general practitioners (GPs), psychiatrists, pharmacists, and mental health workers.

Reference

[1] Vrijens, B., et al., A new taxonomy for describing and defining adherence to medications. Br J Clin Pharmacol, 2012. 73(5): p. 691-705.

Figure 1: The conceptual framework for this study

Face and content validity of a medication adherence conceptual framework: factors influencing consumers' adherence to antidepressant medicines in unipolar depression

Part 1: The influencing factors at the initiation phase of adherence.

Please read the following statements and indicate the extent to which you agree or disagree with them.

The operational definitions of these terms are reported below.

- **Relevance**: The extent to which the statement (influencing factor) is relevant to practice at the specified phase of medication adherence.

- **Importance**: The extent to which the statement (influencing factor) is important for the specified phase of medication adherence.

If you would like to add, delete or modify any item, please record your suggestions in the comments section below the item.

1. Following the diagnosis of a consumer with depression, GPs can influence whether consumers commence therapy with antidepressant medicines.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The above statement is relevant to practice.	○	○	○	○	○
The above statement describes an important influencing factor for the initiation phase of adherence.	○	○	○	○	○

Please specify any other comments (e.g. Clarity of statement)

2. Following the diagnosis of a consumer with depression, psychiatrists can influence whether consumers commence therapy with antidepressant medicines.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The above statement is relevant to practice.	○	○	○	○	○
The above statement describes an important influencing factor for the initiation phase of adherence.	○	○	○	○	○

Please specify any other comments (e.g. Clarity of statement)

3. Following the diagnosis of a consumer with depression, community pharmacists can influence whether consumers commence therapy with antidepressant medicines.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The above statement is relevant to practice.	○	○	○	○	○
The above statement describes an important influencing factor for the initiation phase of adherence.	○	○	○	○	○

Please specify any other comments (e.g. Clarity of statement)

4. Good relationships between GPs and consumers can influence whether consumers commence therapy with antidepressant medicines.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The above statement is relevant to practice.	○	○	○	○	○
The above statement describes an important influencing factor for the initiation phase of adherence.	○	○	○	○	○

Please specify any other comments (e.g. Clarity of statement)

5. Good relationships between psychiatrists and consumers can influence whether consumers commence therapy with antidepressant medicines.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The above statement is relevant to practice.	◯	◯	◯	◯	◯
The above statement describes an important influencing factor for the initiation phase of adherence.	◯	◯	◯	◯	◯

Please specify any other comments (e.g. Clarity of statement)

Face and content validity of a medication adherence conceptual framework: factors influencing consumers' adherence to antidepressant medicines in unipolar depression

Part 1: The influencing factors at the initiation phase of adherence.

6. Good relationships between community pharmacists and consumers can influence whether consumers commence therapy with antidepressant medicines.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The above statement is relevant to practice.	○	○	○	○	○
The above statement describes an important influencing factor for the initiation phase of adherence.	○	○	○	○	○

Please specify any other comments (e.g. Clarity of statement)

7. Good support from the GPs is critical to whether a consumer with depression commences therapy with an antidepressant medicine.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The above statement is relevant to practice.	○	○	○	○	○
The above statement describes an important influencing factor for the initiation phase of adherence.	○	○	○	○	○

Please specify any other comments (e.g. Clarity of statement)

8. Good support from a psychiatrist is critical to whether a consumer with depression commences therapy with an antidepressant medicine.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The above statement is relevant to practice.	○	○	○	○	○
The above statement describes an important influencing factor for the initiation phase of adherence.	○	○	○	○	○

Please specify any other comments (e.g. Clarity of statement)

9. Good support from the community pharmacist is critical to whether a consumer with depression commences therapy with an antidepressant medicine.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The above statement is relevant to practice.	○	○	○	○	○
The above statement describes an important influencing factor for the initiation phase of adherence.	○	○	○	○	○

Please specify any other comments (e.g. Clarity of statement)

10. Any perceived stigma displayed by health care professionals toward depression can inhibit a consumer from commencing an antidepressant medicine.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The above statement is relevant to practice.	○	○	○	○	○
The above statement describes an important influencing factor for the initiation phase of adherence.	○	○	○	○	○

Please specify any other comments (e.g. Clarity of statement)

Face and content validity of a medication adherence conceptual framework: factors influencing consumers' adherence to antidepressant medicines in unipolar depression

Part 1: The influencing factors at the initiation phase of adherence.

11. GPs beliefs about the efficacy of antidepressant medicines influences whether a consumer commences therapy with an antidepressant medicine.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The above statement is relevant to practice.	○	○	○	○	○
The above statement describes an important influencing factor for the initiation phase of adherence.	○	○	○	○	○

Please specify any other comments (e.g. Clarity of statment)

12. Psychiatrist beliefs about the efficacy of antidepressant medicines influences whether a consumer commences therapy with an antidepressant medicine.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The above statement is relevant to practice.	○	○	○	○	○
The above statement describes an important influencing factor for the initiation phase of adherence.	○	○	○	○	○

Please specify any other comments (e.g. Clarity of statement)

13. Community pharmacist beliefs about the efficacy of antidepressant medicines influences whether a consumer commences therapy with an antidepressant medicine.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The above statement is relevant to practice.	○	○	○	○	○
The above statement describes an important influencing factor for the initiation phase of adherence.	○	○	○	○	○

Please specify any other comments (e.g. Clarity of statement)

14. Self-motivation of a consumer is a factor in whether they commence therapy with an antidepressant medicine.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The above statement is relevant to practice.	○	○	○	○	○
The above statement describes an important influencing factor for the initiation phase of adherence.	○	○	○	○	○

Please specify any other comments (e.g. Clarity of statement)

15. Consumers who acknowledge their depressive condition, tend to commence therapy when prescribed an antidepressant medicine.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The above statement is relevant to practice.	○	○	○	○	○
The above statement describes an important influencing factor for the initiation phase of adherence.	○	○	○	○	○

Please specify any other comments (e.g. Clarity of statement)

Face and content validity of a medication adherence conceptual framework: factors influencing consumers' adherence to antidepressant medicines in unipolar depression

Part 1: The influencing factors at the initiation phase of adherence.

16. Consumers who are involved in the treatment decision-making process are more likely to commence therapy with an antidepressant medicine.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The above statement is relevant to practice.	◯	◯	◯	◯	◯
The above statement describes an important influencing factor for the initiation phase of adherence.	◯	◯	◯	◯	◯

Please specify any other comments (e.g. Clarity of statement)

17. Consumers who have previous unfavourable experiences with antidepressant treatment are less likely to commence therapy with antidepressant medicines.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The above statement is relevant to practice.	◯	◯	◯	◯	◯
The above statement describes an important influencing factor for the initiation phase of adherence.	◯	◯	◯	◯	◯

Please specify any other comments (e.g. Clarity of statement)

18. Consumers who have adequate information about depression and antidepressant medicines are more likely to commence antidepressant therapy.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The above statement is relevant to practice.	○	○	○	○	○
The above statement describes an important influencing factor for the initiation phase of adherence.	○	○	○	○	○

Please specify any other comments (e.g. Clarity of statement)

19. Stigma about depression can be a barrier to a consumer t commencing antidepressant therapy.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The above statement is relevant to practice.	○	○	○	○	○
The above statement describes an important influencing factor for the initiation phase of adherence.	○	○	○	○	○

Please specify any other comments (e.g. Clarity of statement)

20. Consumer beliefs about the efficacy of antidepressant medicines influences whether they commence therapy with an antidepressant medicine.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The above statement is relevant to practice.	○	○	○	○	○
The above statement describes an important influencing factor for the initiation phase of adherence.	○	○	○	○	○

Please specify any other comments (e.g. Clarity of statement)

Face and content validity of a medication adherence conceptual framework: factors influencing consumers' adherence to antidepressant medicines in unipolar depression

Part 1: The influencing factors at the initiation phase of adherence.

21. Concern about possible adverse drug reactions can influence whether a consumer commences therapy with an antidepressant medicine.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The above statement is relevant to practice.	◯	◯	◯	◯	◯
The above statement describes an important influencing factor for the initiation phase of adherence.	◯	◯	◯	◯	◯

Please specify any other comments (e.g. Clarity of statement)

22. Consumers with higher levels of education are more willing to commence antidepressant therapy.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The above statement is relevant to practice.	◯	◯	◯	◯	◯
The above statement describes an important influencing factor for the initiation phase of adherence.	◯	◯	◯	◯	◯

Please specify any other comments (e.g. Clarity of statement)

23. The accessibility of the health care providers affects when a consumer commences therapy with an antidepressant medicine.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The above statement is relevant to practice.	○	○	○	○	○
The above statement describes an important influencing factor for the initiation phase of adherence.	○	○	○	○	○

Please specify any other comments (e.g. Clarity of statement)

24. Private health insurance influences whether a consumer commences therapy with an antidepressant medicine.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The above statement is relevant to practice.	○	○	○	○	○
The above statement describes an important influencing factor for the initiation phase of adherence.	○	○	○	○	○

Please specify any other comments (e.g. Clarity of statement)

25. Consumers who live with a partner are more likely to commence antidepressant therapy.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The above statement is relevant to practice.	○	○	○	○	○
The above statement describes an important influencing factor for the initiation phase of adherence.	○	○	○	○	○

Please specify any other comments (e.g. Clarity of statement)

Face and content validity of a medication adherence conceptual framework: factors influencing consumers' adherence to antidepressant medicines in unipolar depression

Part 1: The influencing factors at the initiation phase of adherence.

26. The cost of antidepressant medicines influences whether a consumer commences taking antidepressant therapy.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The above statement is relevant to practice.	○	○	○	○	○
The above statement describes an important influencing factor for the initiation phase of adherence.	○	○	○	○	○

Please specify any other comments (e.g. Clarity of statement)

27. The cost of health care influences when a consumer commences therapy with an antidepressant medicine.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The above statement is relevant to practice.	○	○	○	○	○
The above statement describes an important influencing factor for the initiation phase of adherence.	○	○	○	○	○

Please specify any other comments (e.g. Clarity of statement)

28. Consumers who have family support are more likely to commence antidepressant therapy.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The above statement is relevant to practice.	○	○	○	○	○
The above statement describes an important influencing factor for the initiation phase of adherence.	○	○	○	○	○

Please specify any other comments (e.g. Clarity of statement)

29. Consumers who have peer support are more likely to commence antidepressant therapy.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The above statement is relevant to practice.	○	○	○	○	○
The above statement describes an important influencing factor for the initiation phase of adherence.	○	○	○	○	○

Please specify any other comments (e.g. Clarity of statement)

30. Any perceived stigma displayed by a family member or carer toward mental health can be a barrier to a consumer commencing antidepressant therapy.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The above statement is relevant to practice.	○	○	○	○	○
The above statement describes an important influencing factor for the initiation phase of adherence.	○	○	○	○	○

Please specify any other comments (e.g. Clarity of statement)

Face and content validity of a medication adherence conceptual framework: factors influencing consumers' adherence to antidepressant medicines in unipolar depression

Part 1: The influencing factors at the initiation phase of adherence.

31. Stigma in society can be a barrier to a consumer commencing antidepressant therapy.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The above statement is relevant to practice.	○	○	○	○	○
The above statement describes an important influencing factor for the initiation phase of adherence.	○	○	○	○	○

Please specify any other comments (e.g. Clarity of statement)

32. Mental health advocacy organizations such as BeyondBlue influence whether a consumer commences therapy with an antidepressant medicine.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The above statement is relevant to practice.	○	○	○	○	○
The above statement describes an important influencing factor for the initiation phase of adherence.	○	○	○	○	○

Please specify any other comments (e.g. Clarity of statement)

33. Consumers who have more severe depressive symptoms are more willing to commence antidepressant medicines.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The above statement is relevant to practice.	◯	◯	◯	◯	◯
The above statement describes an important influencing factor for the initiation phase of adherence.	◯	◯	◯	◯	◯

Please specify any other comments (e.g. Clarity of statement)

Face and content validity of a medication adherence conceptual framework: factors influencing consumers' adherence to antidepressant medicines in unipolar depression

Part 2: The influencing factors at the implementation phase of adherence.

Please read the following statements and indicate the extent to which you agree or disagree with them.

The operational definitions of these terms are reported below.

- **Relevance**: The extent to which the statement (influencing factor) is relevant to practice at the specified phase of medication adherence.

- **Importance**: The extent to which the statement (influencing factor) is important for the specified phase of medication adherence.

If you would like to add, delete or modify any item, please record your suggestions in the comments section below the item.

34. Following the diagnosis of a consumer with depression, GPs can influence whether consumers continue to take antidepressant medicines.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The above statement is relevant to practice.	○	○	○	○	○
The above statement describes an important influencing factor for the implementation phase of adherence.	○	○	○	○	○

Please specify any other comments (e.g. Clarity of statement)

35. Following the diagnosis of a consumer with depression, psychiatrists can influence whether consumers continue to take antidepressant medicines.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The above statement is relevant to practice.	○	○	○	○	○
The above statement describes an important influencing factor for the implementation phase of adherence.	○	○	○	○	○

Please specify any other comments (e.g. Clarity of statement)

36. Following the diagnosis of a consumer with depression, community pharmacists can influence whether consumers continue to take antidepressant medicines.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The above statement is relevant to practice.	○	○	○	○	○
The above statement describes an important influencing factor for the implementation phase of adherence.	○	○	○	○	○

Please specify any other comments (e.g. Clarity of statement)

37. Experienced GPs can influence whether consumers continue to take antidepressant medicines.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The above statement is relevant to practice.	○	○	○	○	○
The above statement describes an important influencing factor for the implementation phase of adherence.	○	○	○	○	○

Please specify any other comments (e.g. Clarity of statement)

38. Experienced psychiatrists can influence whether consumers continue to take antidepressant medicines.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The above statement is relevant to practice.	○	○	○	○	○
The above statement describes an important influencing factor for the implementation phase of adherence.	○	○	○	○	○

Please specify any other comments (e.g. Clarity of statement)

39. Experienced community pharmacists can influence whether consumers continue to take antidepressant medicines.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The above statement is relevant to practice.	○	○	○	○	○
The above statement describes an important influencing factor for the implementation phase of adherence.	○	○	○	○	○

Please specify any other comments (e.g. Clarity of statement)

Part 2: The influencing factors at the implementation phase of adherence.

40. Good relationships between GPs and consumers can influence whether consumers continue to take antidepressant medicines.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The above statement is relevant to practice.	○	○	○	○	○
The above statement describes an important influencing factor for the implementation phase of adherence.	○	○	○	○	○

Please specify any other comments (e.g. Clarity of statement)

41. Good relationships between psychiatrists and consumers can influence whether consumers continue to take antidepressant medicines.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The above statement is relevant to practice.	○	○	○	○	○
The above statement describes an important influencing factor for the implementation phase of adherence.	○	○	○	○	○

Please specify any other comments (e.g. Clarity of statement)

42. Good relationships between community pharmacists and consumers can influence whether consumers continue to take antidepressant medicines.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The above statement is relevant to practice.	○	○	○	○	○
The above statement describes an important influencing factor for the implementation phase of adherence.	○	○	○	○	○

Please specify any other comments (e.g. Clarity of statement)

43. Collaboration between GPs, psychiatrists, and pharmacists in a mental healthcare team can influence whether consumers continue to take antidepressant medicines.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The above statement is relevant to practice.	○	○	○	○	○
The above statement describes an important influencing factor for the implementation phase of adherence.	○	○	○	○	○

Please specify any other comments (e.g. Clarity of statement)

44. Interactive communication and open dialogue between health care professionals and consumers can influence whether consumers continue to take antidepressant medicines.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The above statement is relevant to practice.	○	○	○	○	○
The above statement describes an important influencing factor for the implementation phase of adherence.	○	○	○	○	○

Please specify any other comments (e.g. Clarity of statement)

Face and content validity of a medication adherence conceptual framework: factors influencing consumers' adherence to antidepressant medicines in unipolar depression

Part 2: The influencing factors at the implementation phase of adherence.

45. Lack of adequate information about depressive treatment from health care professional can inhibit a consumer from continuing to take antidepressant medicines.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The above statement is relevant to practice.	○	○	○	○	○
The above statement describes an important influencing factor for the implementation phase of adherence.	○	○	○	○	○

Please specify any other comments (e.g. Clarity of statement)

46. Stigma about depression from health care professionals can inhibit a consumer from continuing to take antidepressant medicines.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The above statement is relevant to practice.	○	○	○	○	○
The above statement describes an important influencing factor for the implementation phase of adherence.	○	○	○	○	○

Please specify any other comments (e.g. Clarity of statement)

47. Consumers who believe in antidepressants are more likely to continue to take antidepressant medicines.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The above statement is relevant to practice.	○	○	○	○	○
The above statement describes an important influencing factor for the implementation phase of adherence.	○	○	○	○	○

Please specify any other comments (e.g. Clarity of statement)

48. Consumers who are more able to self-manage are more likely to continue to take antidepressant medicines.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The above statement is relevant to practice.	○	○	○	○	○
The above statement describes an important influencing factor for the implementation phase of adherence.	○	○	○	○	○

Please specify any other comments (e.g. Clarity of statement)

49. Consumers who are involved in the treatment decision-making process are more likely to continue to take antidepressant medicines.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The above statement is relevant to practice.	○	○	○	○	○
The above statement describes an important influencing factor for the implementation phase of adherence.	○	○	○	○	○

Please specify any other comments (e.g. Clarity of statement)

Part 2: The influencing factors at the implementation phase of adherence.

50. Consumers who have previous unfavourable experiences with antidepressant treatment are more unlikely to continue to take antidepressant medicines.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The above statement is relevant to practice.	○	○	○	○	○
The above statement describes an important influencing factor for the implementation phase of adherence.	○	○	○	○	○

Please specify any other comments (e.g. Clarity of statement)

51. Consumers who are concerned about the effect of stopping antidepressant therapy are more likely continue to take antidepressant medicines.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The above statement is relevant to practice.	○	○	○	○	○
The above statement describes an important influencing factor for the implementation phase of adherence.	○	○	○	○	○

Please specify any other comments (e.g. Clarity of statement)

52. Consumers who feel better after taking antidepressants tend to continue to take antidepressant medicines.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The above statement is relevant to practice.	○	○	○	○	○
The above statement describes an important influencing factor for the implementation phase of adherence.	○	○	○	○	○

Please specify any other comments (e.g. Clarity of statement)

53. Consumers who have trust in their health care professionals are more likely to continue to take antidepressant medicines.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The above statement is relevant to practice.	○	○	○	○	○
The above statement describes an important influencing factor for the implementation phase of adherence.	○	○	○	○	○

Please specify any other comments (e.g. Clarity of statement)

54. Consumers who have knowledge about depression and antidepressant therapy are more likely to continue to take antidepressant medicines.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The above statement is relevant to practice.	○	○	○	○	○
The above statement describes an important influencing factor for the implementation phase of adherence.	○	○	○	○	○

Please specify any other comments (e.g. Clarity of statement)

Part 2: The influencing factors at the implementation phase of adherence.

55. Forgetfulness can inhibit a consumer from continuing therapy with an antidepressant medicine.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The above statement is relevant to practice.	○	○	○	○	○
The above statement describes an important influencing factor for the implementation phase of adherence.	○	○	○	○	○

Please specify any other comments (e.g. Clarity of statement)

56. Consumers with higher levels of education are more willing to continue to take antidepressant medicines.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The above statement is relevant to practice.	○	○	○	○	○
The above statement describes an important influencing factor for the implementation phase of adherence.	○	○	○	○	○

Please specify any other comments (e.g. Clarity of statement)

57. Consumers who have positive experiences from antidepressant therapy are more likely to continue to take antidepressant medicines.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The above statement is relevant to practice.	○	○	○	○	○
The above statement describes an important influencing factor for the implementation phase of adherence.	○	○	○	○	○

Please specify any other comments (e.g. Clarity of statement)

58. Consumers who have few adverse drug reactions from antidepressant medicines are more likely to continue to take them.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The above statement is relevant to practice.	○	○	○	○	○
The above statement describes an important influencing factor for the implementation phase of adherence.	○	○	○	○	○

Please specify any other comments (e.g. Clarity of statement)

59. Ineffectiveness of antidepressant treatment can inhibit a consumer from continuing therapy with an antidepressant medicine.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The above statement is relevant to practice.	○	○	○	○	○
The above statement describes an important influencing factor for the implementation phase of adherence.	○	○	○	○	○

Please specify any other comments (e.g. Clarity of statement)

Part 2: The influencing factors at the implementation phase of adherence.

60. Consumers who have private health insurance are more likely to continue to take antidepressant medicines.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The above statement is relevant to practice.	○	○	○	○	○
The above statement describes an important influencing factor for the implementation phase of adherence.	○	○	○	○	○

Please specify any other comments (e.g. Clarity of statement)

61. The accessibility of the health care services effects whether a consumer continues to take antidepressant medicines.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The above statement is relevant to practice.	○	○	○	○	○
The above statement describes an important influencing factor for the implementation phase of adherence.	○	○	○	○	○

Please specify any other comments (e.g. Clarity of statement)

62. The accessibility of antidepressant medicines effects whether a consumer continues to take antidepressant medicines.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The above statement is relevant to practice.	○	○	○	○	○
The above statement describes an important influencing factor for the implementation phase of adherence.	○	○	○	○	○

Please specify any other comments (e.g. Clarity of statement)

63. Lack of continuity of care in the public system can inhibit a consumer from continuing therapy with antidepressant medicines.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The above statement is relevant to practice.	○	○	○	○	○
The above statement describes an important influencing factor for the implementation phase of adherence.	○	○	○	○	○

Please specify any other comments (e.g. Clarity of statement)

64. Consumers who live with a partner are more likely to continue to take antidepressant medicines.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The above statement is relevant to practice.	○	○	○	○	○
The above statement describes an important influencing factor for the implementation phase of adherence.	○	○	○	○	○

Please specify any other comments (e.g. Clarity of statement)

Part 2: The influencing factors at the implementation phase of adherence.

65. Consumers who can afford antidepressants are more likely to continue to take antidepressant medicines.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The above statement is relevant to practice.	○	○	○	○	○
The above statement describes an important influencing factor for the implementation phase of adherence.	○	○	○	○	○

Please specify any other comments (e.g. Clarity of statement)

66. Societal stigma about depression can inhibit a consumer from continuing therapy with an antidepressant medicine.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The above statement is relevant to practice.	○	○	○	○	○
The above statement describes an important influencing factor for the implementation phase of adherence.	○	○	○	○	○

Please specify any other comments (e.g. Clarity of statement)

67. Lack of support from family can inhibit a consumer from continuing therapy with an antidepressant medicine.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The above statement is relevant to practice.	○	○	○	○	○
The above statement describes an important influencing factor for the implementation phase of adherence.	○	○	○	○	○

Please specify any other comments (e.g. Clarity of statement)

68. Stigma about depression by family members can inhibit a consumer from continuing therapy with an antidepressant medicine.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The above statement is relevant to practice.	○	○	○	○	○
The above statement describes an important influencing factor for the implementation phase of adherence.	○	○	○	○	○

Please specify any other comments (e.g. Clarity of statement)

69. Mental health organizations such as BeyondBlue influence whether consumers continue to take antidepressant medicines.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The above statement is relevant to practice.	○	○	○	○	○
The above statement describes an important influencing factor for the implementation phase of adherence.	○	○	○	○	○

Please specify any other comments (e.g. Clarity of statement)

Part 2: The influencing factors at the implementation phase of adherence.

70. Consumers who have more severe depressive symptoms are more likely to continue to take antidepressant medicines.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The above statement is relevant to practice.	○	○	○	○	○
The above statement describes an important influencing factor for the implementation phase of adherence.	○	○	○	○	○

Please specify any other comments (e.g. Clarity of statement)

71. Depressive symptoms can inhibit a consumer from continuing therapy with an antidepressant medicine.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The above statement is relevant to practice.	○	○	○	○	○
The above statement describes an important influencing factor for the implementation phase of adherence.	○	○	○	○	○

Please specify any other comments (e.g. Clarity of statement)

72. Long term treatment of depression can inhibit a consumer from continuing therapy with an antidepressant medicine.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
The above statement is relevant to practice.	○	○	○	○	○
The above statement describes an important influencing factor for the implementation phase of adherence.	○	○	○	○	○

Please specify any other comments (e.g. Clarity of statement)

73. Please describe any other factors which can influence adherence to antidepressant medicines.

Face and content validity of a medication adherence conceptual framework: factors influencing consumers' adherence to antidepressant medicines in unipolar depression

Demographic data

74. What is your gender?

- ◯ Male
- ◯ Female

75. What is your health profession?

- ◯ General practitioner
- ◯ Psychiatrist
- ◯ Pharmacist
- ◯ Academic researcher
- ◯ Other (please specify)

76. How many years have you been working as a health care professional?

Thank you very much for your time. Your response is important for us.

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