Improving our Understanding of Patient Adherence in Gout

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*A thesis submitted in fulfilment of the requirements for the degree of Doctor of Philosophy in **Health Psychology**, the University of Auckland, 2023.*

Abstract

Medication adherence remains problematic in gout management. Previous work demonstrates that adherence can be classified into intentional and unintentional adherence. Intentional nonadherence is driven by patients' beliefs and offers the opportunity for early interventions.

This thesis aimed to extend the current literature by addressing several aims. The first study (described in Chapter Three) aimed to examine the Intentional Non-Adherence Scale (INAS) for assessing medication adherence in gout. This scale was found to be a reliable and valid tool for identifying people at heightened risk for nonadherence in gout. The second study (described in Chapter Four) aimed to explore the main motives behind medication nonadherence, using the INAS. This study concluded that the desire to lead a normal life and the strategy of testing the treatment limits were the main motives of nonadherence. The third study (described in Chapter Five) aimed to provide further understanding of how medication adherence is addressed in online gout educational resources, with a specific focus on main motives of nonadherence. The findings indicated limited adherence coverage and a narrow range of strategies, with a significant portion of resources failing to address the main motives of nonadherence. The fourth study (described in Chapter Six) aimed to investigate the feasibility and acceptability of using smartphone notifications to improve medication adherence through targeting the main motives of nonadherence. The findings showed that the intervention is highly implementable in clinical settings.

In conclusion, this thesis provides more information on intentional nonadherence among people with gout. The research demonstrated that the INAS can serve as an effective tool to assess intentional nonadherence in gout and to understand the main motives behind this behaviour, providing potential targets for designing more tailored interventions and strategies. This research also provides practical guidance for educational content creators. Furthermore, this thesis suggests that smartphone-based intervention holds potential as a patient-centered approach to enhance medication adherence in gout.

Acknowledgements

Here I am at the end of the tunnel, and I would like to thank all those who have been the guiding light throughout this journey.

To my supervisor, Professor Keith J. Petrie, thank you for your guidance and support throughout these years. I have gained a wealth of knowledge under your mentorship. Thank you also to my co-supervisor, Professor Nicola Dalbeth, for her insights, constructive feedback, and words of encouragement, and being a source of inspiration.

To Kamran, without you, this journey would never have been possible. During this whirlwind of life, you've been the reason I've found the strength to keep pushing forward. Your belief in me, just as I believe in you, has been an endless source of strength and determination.

To my beautiful children, Hana and Uhana, you have been my constant source of joy and motivation. Through every moment of exhaustion, your smiles and encouragement have been my determination to keep going. You are the shiniest stars of my world, and my heart brims with love and thankfulness for each of you.

To my parents, Zahra and Farid, who have been my anchor in the storm of life. You have been the light in my darkest hours and the warmth in the coldest moments. Thank you also to my brothers, Ehsan and Vahid, whose love I have always felt, even from miles away.

To my incredible friends, Maryam, Aida, Galia, Julia, Erica, Jean, Valentina and Fatemeh, thank you for being the best source of support throughout this journey, and making my days happier.

To Associate Professor Phillipa Malpas, thank you for your support during the challenging times of the pandemic, and helping me navigate those difficult circumstances. Thank you also to Professor Nathan Consedine for giving me hope when I needed it most. A special thank you to Ranjeeni for her constant support and beautiful smile.

I also thank Hamish Franklin and Tayla Eveleigh from Artilect Limited for their support in developing the smartphone application used in this research.

I am thankful for the love, support, and encouragement I have received from each and every one of you. Your contributions have been immeasurable in helping me reach this milestone in my academic journey.

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List of Abbreviations

ANOVA	Analysis of Variance
ABC	Ascertaining Barriers to Compliance
BCTO	Behaviour Change Technique Ontology
CI	Confidence Interval
df	Degree of Freedom
HMMA	Hierarchical Model for Medication Adherence
INAS	Intentional Non-Adherence Scale
mHealth apps	Mobile Health Applications
SD	Standard Deviation
SE	Standard Error
SU	Serum Urate
SPSS	Statistical Package for the Social Sciences
TAM	Technology Acceptance Model
TSQM	Treatment Satisfaction Questionnaire for Medication
ULT	Urate-Lowering Therapy
WHO	World Health Organisation

Publisher Approvals

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List of Manuscripts and Co-Authorship Forms

1. Emad, Y., Petrie, K. J., Weinman, J., Stamp, L., Horne, A., Gamble, G., Drake, J., Haslett, J., & Dalbeth, N. (2023a). *Assessing medication adherence in gout: utilising the Intentional Non-Adherence Scale (INAS)* [Unpublished Manuscript]. Department of Psychological Medicine, University of Auckland.
2. Emad, Y., Dalbeth, N., Weinman, J., Chalder, T., & Petrie, K. J. (2022). Why do patients with gout not take allopurinol?. *Journal of Rheumatology*, *49*(6), 622-626. https://doi.org/10.3899/jrheum.210950
3. Emad, Y., Derksen, C., Petrie, K. J., & Dalbeth, N. (2024). A content analysis of medication adherence material in patient educational resources about gout. *Rheumatology Advances in Practice*, 8(2), rkae042. https://doi.org/10.1093/rap/rkae042
4. Emad, Y., Dalbeth, N., Weinman, J., Chalder, T., & Petrie, K. J. (2024). Can smartphone notifications help with gout management? A feasibility study. *Journal of Rheumatology*, 51(2), 189–196. https://doi.org/10.3899/jrheum.2023-0711

Chapter One

Topic Introduction and Thesis Overview

Introduction of Thesis Topic

Medication nonadherence is a critical challenge in managing chronic diseases, impacting the effectiveness of treatments and the overall burden of these conditions on a global scale. Chronic diseases affect a substantial proportion of the population, with an estimated 2.1 billion people having at least one chronic condition (World Health Organisation, 2023). In New Zealand, gout is one of the prevalent chronic conditions, affecting 6% of the population aged 20 and above. Certain ethnic groups, such as Māori and Pacific Islanders in New Zealand, have a prevalence more than twice that of other ethnic groups (Health Quality & Safety Commission, 2022).

Gout is a progressive disease characterized by high urate levels in the blood, leading to the formation of painful crystals in the joints and subsequent joint damage. Risk factors for gout include genetics, diet, obesity, and comorbid conditions such as hypertension and diabetes (Dalbeth et al., 2016). If not effectively managed, gout can lead to severe complications, including chronic arthritis, kidney stones, and cardiovascular disease (Richette & Bardin, 2009). These complications not only reduce the quality of life for patients but also impose a significant burden on healthcare systems. New Zealand has a publicly funded healthcare system that provides universal health coverage (Ministry of Health NZ, 2023). However, challenges such as medication adherence continue to affect the management of chronic diseases including gout.

Despite the availability of effective urate-lowering treatments for gout management, studies have shown that a considerable number of people with gout do not adhere to their prescribed medication (Scheepers et al., 2018a). This compromises effective management of the illness and causes unnecessary disability. Why patients make a deliberate decision to not take their gout medication remains relatively understudied. This thesis aims to reduce this gap in literature by focusing on intentional nonadherence to urate lowering medications in people with gout.

Research Aims

The broad aim of this thesis is to provide a better understanding of nonadherence to urate lowering medications in people with gout, with a particular focus on allopurinol. Specifically, this thesis

evaluates the effectiveness of the Intentional Non-Adherence Scale (INAS) for assessing medication adherence in this population and investigates the main reasons behind this behaviour. This thesis explores how medication adherence is addressed in online gout educational resources and provides further evidence for the feasibility of utilising smartphone notifications to enhance medication adherence among people with gout who are taking urate lowering medications, specifically allopurinol.

Thesis Outline

The focus of this thesis is to extend the current understanding of nonadherence behaviour among people with gout, examining a broad range of factors that lead to intentional nonadherence to urate lowering medications. Chapter Two provides a theoretical overview of the current literature relating to medication adherence in gout management and explores evidence that suggests targeting intentional nonadherence could impact the effectiveness of gout treatment strategies. This chapter also outlines a working definition for different types of nonadherence as employed within this thesis and underscores the gaps within the existing literature that this research seeks to bridge.

As shown in Figure 1, the subsequent chapters of the thesis are organised into two distinct sections. Chapters Three and Four aim to deepen our understanding of intentional nonadherence to urate lowering medications, in particular allopurinol. Chapter Three presents the results of a pre-specified cross-sectional analysis of a 12- month randomised clinical trial investigating the concurrent validity of the Intentional Non-Adherence Scale (INAS) in assessing medication adherence. This study determines the associations of INAS scores with medication adherence in people with gout taking allopurinol, while considering clinical and demographic factors. This measure assesses patient's motivations for deviating from their prescribed regimen, thereby highlighting those individuals who may report higher incidents of medication nonadherence. Medication adherence was measured using serum urate levels and number of missed dose(s) within a month. Chapter Four presents the results of a cross-sectional study investigating intentional nonadherence in people with gout by utilising the Intentional Non-Adherence Scale (INAS) scores. This study looks at the main reasons people with gout gave for not taking allopurinol through ranking each INAS item by the percentage of participants agreeing with each statement. This research also aims to examine differences in intentional nonadherence for individuals with and without serum urate at treatment target and to explore any demographic differences in terms of INAS scores.

The second part of the thesis encompasses results from two studies looking at potential strategies for improving medication adherence in gout. Chapter Five shifts focus to the online informational resources available to people with gout. This chapter includes a cross-country content analysis of patient educational materials, and investigates how medication adherence is addressed in online gout educational resources. By investigating the alignment between the content of resources and the reasons for nonadherence identified in Chapter Four, this study provides insights into the potential impact of patient education strategies and the gaps that exist in current online information for patients. Chapter Six reports the results from a randomised controlled feasibility study investigating the feasibility, acceptability, and potential effectiveness of utilising smartphone notifications to enhance medication adherence in people with gout taking allopurinol though targeting the main reasons of nonadherence identified in Chapter Four. The primary outcome measure was medication adherence, measured using serum urate levels and number of missed dose(s) within a month.

Chapter Seven serves as a comprehensive discussion, synthesising the main outcomes of this thesis. This involves integrating these findings with the current literature on medication adherence, evaluating the strengths and limitations of the research, considering the clinical implications for improving medication adherence, and proposing potential avenues for further research.

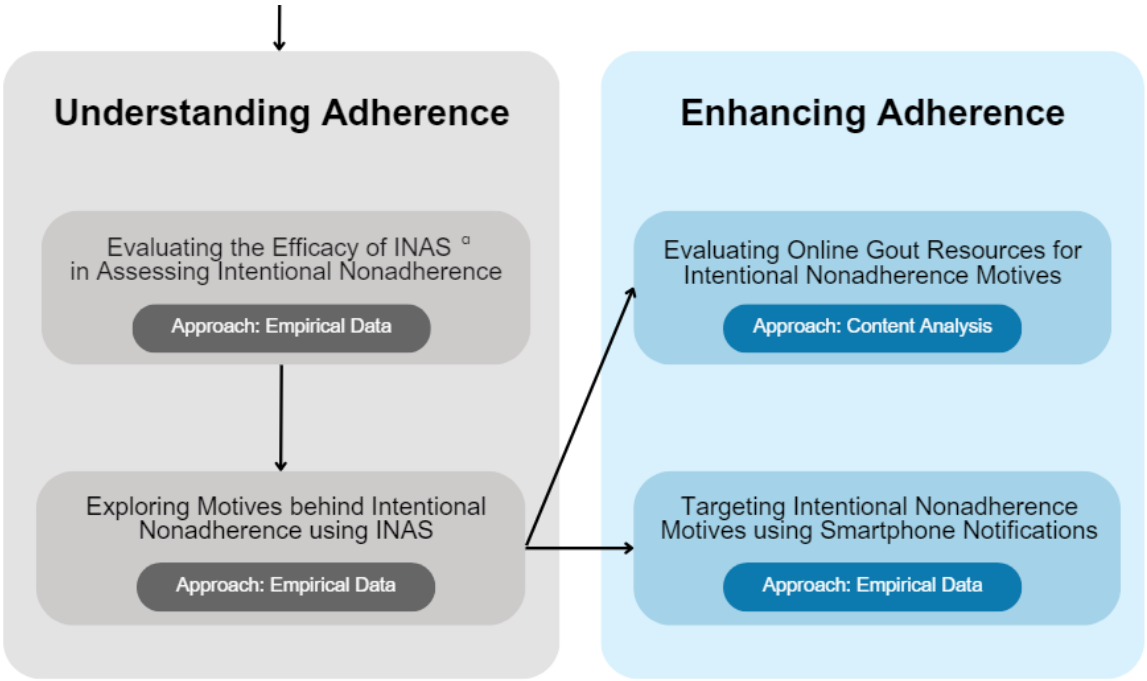

Figure 1. *Conceptual framework; INAS[a]: Intentional Non-Adherence Scale.*

Research Questions

This thesis addresses the following key research questions in its respective chapters:

Chapter Two: Does evidence support the effectiveness of targeting intentional nonadherence in improving gout management outcomes?

Chapter Three: How does the Intentional Non-Adherence Scale (INAS) contribute to the assessment of medication adherence in people with gout taking allopurinol?

Chapter Four: What are the main reasons people with gout do not take their allopurinol as prescribed?

Chapter Five: What are the current gaps in existing online gout educational resources around medication adherence?

Chapter Six: How feasible and acceptable are smartphone notifications designed to improve medication adherence for people with gout?

Chapter Two

Nonadherence: Background, Theory, and Relevant Literature

The following chapter examines the current theoretical underpinnings and empirical evidence concerning medication adherence in gout management. This chapter begins by providing a definition of medication nonadherence as used in this thesis. Intentional and unintentional nonadherence are discussed, followed by a theoretical justification of factors influencing intentional nonadherence. This chapter also discusses different phases of adherence and explores various commonly used measures of adherence. Related literature targeting nonadherence to change motivations and clinical outcomes is discussed, including limitations within these previous research paradigms. Finally, gaps within the existing empirical evidence are evaluated and potential directions for future research are highlighted.

Defining Medication Adherence

The effectiveness of medications relies on a patient's adherence to their prescribed regimen. Historically, this concept was known as "compliance" (Gould & Mitty, 2010). Described as the extent to which a patient adheres to the treatment directives provided by a healthcare provider, compliance reflects a perspective where the provider's viewpoint held greater importance than that of the patient (Vrijens et al., 2012). This term further implied the authority of healthcare providers, with patients assumed to merely follow instructions in a passive manner. Additionally, the term compliance implied that any deviation from medication adherence could be seen as a deficiency on the patient's part, disregarding external factors that often affect adherence (Chakrabarti, 2014).

As healthcare shifted towards a more patient-centered approach, the language used to depict medication-taking behaviour has also changed, transitioning from the notion of "compliance" to the concept of "adherence." This shift is an effort to emphasise the engagement of patients in the process of health decisions (Vahdat et al., 2014; Scholl et al., 2014). According to the World Health Organisation (WHO), adherence is described as follows: "Adherence encompasses the extent to which an individual's actions, including medication consumption, adherence to dietary guidelines, and integration of lifestyle adjustments, align with mutually agreed-upon recommendations from healthcare providers" (Sabate, 2003). This definition of "adherence" not only underscores the crucial significance of the shared understanding established between patients and healthcare providers but

also avoids attributing blame for instances of nonadherence (Brown & Bussell, 2011).

Through shared decision making, patients assume a more active role in their treatment. This more inclusive approach considers patients' thoughts, concerns, and expectations in deciding on a treatment strategy (Arrieta Valero, 2019; NIHCE, 2009; Elwyn et al., 2001). As a result, "adherence" is now used more often than "compliance" to reflect a more equitable and balanced relationship between patients and healthcare providers.

“Concordance” is another term that has been suggested for characterizing adherence behaviours (Stewart et al., 2022; Bell et al., 2007). The term "concordance" signifies the recognition of a cooperative alliance between healthcare providers and patients, wherein crucial medical choices such as starting a new medication are arrived at through joint discussion. This term supports the patient-centric model by highlighting the agreement between the patient and the clinician during decision making (Settineri et al., 2019). However, the term does not accurately describe patient medication-related behaviour and cannot be employed interchangeably with adherence (Horne et al., 2005).

The absence of standardised terminology has given rise to difficulties when it comes to comparing and merging research results from different studies (Ahmed & Aslani et al., 2014; Raebel et al., 2013). For this thesis, adherence to medications is defined as a process through which patients take their medication as prescribed. Throughout this thesis, the term "adherence" was consistently used to refer to this process.

Intentional and Unintentional Non-Adherence

Medication nonadherence can be categorised into intentional, unintentional or a combination of both. Intentional nonadherence is used to describe patient behaviour when they deliberately choose not to follow their prescribed medication regimen, which can involve discontinuing, skipping, or altering the treatment plan (Horne et al., 2005). This commonly represents a patient-driven approach to decision making, linking this form of nonadherence to patients' motivations and beliefs (Hugtenburg et al., 2013).

On the other hand, unintentional nonadherence pertains to instances where patients fail to adhere to their medication schedules due to non-deliberate factors usually beyond their control. Contributors to unintentional nonadherence include forgetfulness, misunderstanding instructions,

difficulty swallowing medications, cognitive limitations, logistic barrier, and treatment cost (Figure 2, Lehane & McCarthy, 2007).

Adherence tendencies are not static; they can vary over time as the contributing factors evolve. Moreover, an individual's engagement in nonadherence behaviour is dynamic, potentially changing over time (Horne, 2005). Recognising the interplay between intentional and unintentional adherence becomes important in devising tailored interventions to effectively tackle medication nonadherence.

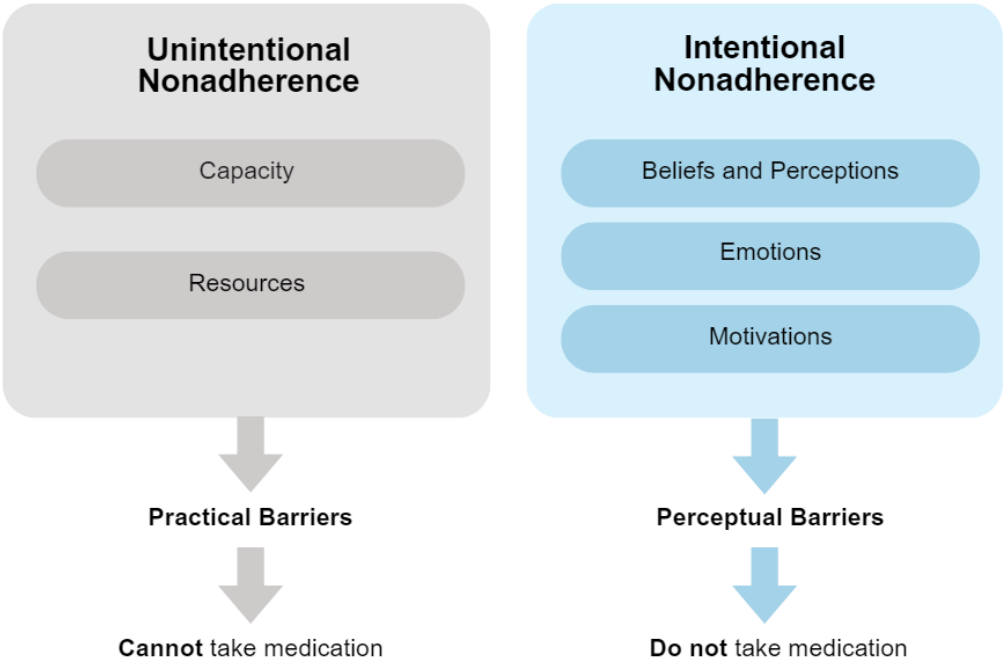

Figure 2. *Intentional nonadherence versus unintentional nonadherence used in Horne et al. (2005).*

Nonadherence in Gout

Gout, which is characterised by the accumulation of monosodium urate crystals, necessitates comprehensive management through urate-lowering therapy (ULT). This therapy is indispensable for managing recurrent gout flares, gout-associated joint damage, and tophaceous gout (FitzGerald et al., 2020). Among ULT options, allopurinol stands as the most commonly used treatment, accounting for over 90% of all administered treatments for gout in the US (Kim et al., 2021). The effective control of gout hinges on maintaining serum urate levels below 0.36mmol/L (6mg/dL) through continuous ULT. If allopurinol fails to achieve target serum urate levels, inadequate response may stem from poor adherence or suboptimal dosing (Stamp et al., 2014).

Gout exhibits significantly low adherence rates (Briesacher et al., 2008). Empirical evidence underscores the concerning trend of low adherence to ULT, with patients often discontinuing

treatment after initiation (De Vera et al., 2014). Previous studies have shown that more than half of patients have stopped taking their prescribed allopurinol after 12 months (Scheepers et al., 2018a). In New Zealand, for example, Martini et al. (2012) reported that 45% of individuals with gout did not adhere to their ULT regimens as prescribed. These rates of nonadherence underline the need to understand the factors contributing to intentional nonadherence to gout therapy and develop better interventions to improve adherence to ULT (Perez-Ruiz & Desideri, 2018).

Measuring Medication Nonadherence

A range of methods have been used for measuring adherence without one being accepted as a definitive assessment method (Van den Bemt et al., 2009). Adherence measurement approaches diverge into two categories: direct and indirect methods. Among indirect methods, self-report scales are the most common and cost-effective assessment used (Nassar et al., 2020). Self-report methods for evaluating medication adherence range from uncomplicated single-item questions about skipped doses to complex questionnaires comprising multiple questions that incorporate motivations behind nonadherence (Stirratt et al., 2015). While capable of evaluating adherence, these methods often fail to capture all potential reasons for intentional nonadherence (Khoiry et al., 2023; Nguyen et al., 2013). Furthermore, while self-report questionnaires are convenient to use (Nassar et al., 2022), they typically overestimate adherence due to social-desirability and self-presentation biases (Horne et al., 2005).

Utilising prescription refill data and pill count to measure medication adherence can also serve as cost-effective indirect strategies for researchers. However, their accuracy can be compromised when patients use multiple pharmacies or when prescription records lack interlinkage within healthcare systems (Lam & Fresco, 2015). Their major weakness is the fact they measure prescription-filling behaviour not medication-taking behaviour.

The most authoritative methods for adherence measurement lie within direct approaches, encompassing biological analysis and observation. In these, blood or urine samples are employed to detect specific drug metabolites from the prescribed medication (Van den Bemt et al., 2012). In the context of gout, serum urate (SU) can be considered as the most important biomarker of gout disease (Cui et al., 2017), and an objective measure of medication adherence (Dalbeth et al., 2017). For example, in a study, Singh et al. (2020) found that lower levels of serum urate were associated with higher odds of adherence to allopurinol and vice versa. In another study, Halpern et al. (2009)

reported a strong association between medication adherence and serum urate levels in people with gout taking allopurinol.

Factors associated with Medication Nonadherence

To comprehend medication adherence, an understanding of the factors influencing patients' adherence behaviour is of great importance (Allemann et al., 2016). The World Health Organisation (WHO) grouped these factors into five main dimensions: patient-related factors, therapy-related factors, condition-related factors, socioeconomic factors, health team/system-related factors (Sabate, 2003). In this thesis, the primary focus is on patient-related factors, in particular medication beliefs, and their impact on adherence to urate lowering medications, while also considering how various other factors influence this relationship.

Patient-related factors include understanding one's medical conditions, beliefs about medications, concerns about potential side effects, and perceptions and anticipations regarding treatment outcomes (Sabate, 2003). These factors offer an understanding of decision-making processes, which forms the basis of intentional nonadherence (Ng et al., 2014; Horne et al., 2013).

Research has demonstrated a strong connection between medication adherence and individuals' beliefs about their medications (Uhlig et al., 2023; Chua et al., 2018; Uhlig et al., 2018), These beliefs are influenced by perceptions regarding the necessity of the prescribed medicines and concerns about their potential adverse effects (Horne & Weinman, 1999). In other words, patients who strongly believe in the need for a particular treatment are more likely to adhere to their prescribed regimen. Conversely, when patients are concerned about potential side effects of the medications, their adherence to the treatment plan tends to decrease (Horne et al., 2013). For example, a recent study by Spragg et al. (2023) revealed that a strong belief in the efficacy and essentiality of allopurinol could significantly enhance adherence during its initiation among individuals with gout. Conversely, the rates of discontinuation were notably higher when individuals perceived allopurinol as ineffective or unnecessary.

Illness perception is another patient-related factor contributing to medication adherence through medication beliefs (Zhao et al., 2022; Pereira et al., 2019). Illness perception encompasses the mental concepts individuals hold regarding a particular illness (Broadbent et al., 2015). These perceptions are constructed around five fundamental aspects: beliefs about the nature of the illness, its causal factors, the potential consequences, its duration and cyclical patterns, and the degree of

control one might have over the illness (Petrie & Weinman, 2012). Previous studies found that individuals who perceive their disease as a long-term chronic condition that can be controlled through continuation of treatment tend to hold stronger beliefs in the necessity of consistent medication use, resulting in higher rate of adherence (Figueiras et al., 2012). For example, Walsh et al. (2016) found that patients who perceived gout to be a chronic condition that can be managed with treatment reported higher rates of adherence to urate lowering medications.

Medication adherence may also be influenced by the effects of treatment-related factors on medication beliefs (Sabate, 2003). These effects are more evident in association between medication adherence and treatment satisfaction (Yin et al., 2023), where individuals evaluate the process of taking the medication and the outcomes associated with the medication (Shikiar & Rentz, 2004). For example, people with gout experiencing side effects after taking allopurinol are more likely to discontinue taking it (Cheen et al., 2019). This happens because when people experience side effects, they often become more concerned about the medications and less satisfied with them, which ultimately influences their decision not to adhere to the treatment (Unni & Bae, 2022; Rai et al., 2018; Barbosa et al., 2012). Similarly, Aung et al. (2017) found patients' concern about ULT side effects and drug interaction to be a major challenge in terms of medication adherence.

In another study, Choi et al. (2022) revealed that experiencing flare-ups after initiating urate lowering medications is associated with lower rates of adherence. During the early stages of ULT, it is common to anticipate flare-ups. This happens because the reduction in serum urate levels can trigger the release of urate crystals from joints and tissues, leading to flare-ups (Latourte et al., 2014). These findings imply that the discomfort and distress caused by these flare-ups might affect patients' confidence in the effectiveness of the treatment, potentially leading to treatment dissatisfaction and skepticism about the medication's overall benefit. As a result, patients who experience flare-ups after initiating ULT may tend more to deviate from their prescribed regimen (Singh et al., 2020).

Factors related to the specific medical condition such as disease duration, disease severity, presence of symptoms and existence of comorbidities, can also influence medication beliefs and subsequently medication adherence. For example, rate of adherence among patients with less severe and prolonged diseases are found to be lower (DiMatteo et al., 2007). This suggests that when a medical condition is perceived as less urgent, patients might not consider the medication as

necessary and might overlook the consequences of not taking their medications, resulting in nonadherence.

Previous research shows that asymptomatic conditions can also be important factors contributing to nonadherence. For example, Perez-Ruiz and Desideri (2018) found that in many conditions, medication adherence frequently declines over extended periods. This tendency is particularly notable in cases of well-controlled gout, where patients experience minimal to no symptoms. When patients do not feel the immediate threat of gout flares, they may not take their prescribed urate lowering medications as seriously, underestimating the potential future consequences of unmanaged serum urate levels.

The presence of comorbidities has been also considered a predisposing factor associated with medication adherence in gout (Singh et al., 2020). Medical comorbidities such as hypertension, renal disfunction, cardiovascular diseases and diabetes mellitus are more common in people with gout (Singh, 2017). Hence, the treatment protocols for these individuals often involve a combination of medications, each with specific dosages, timing requirements, and potential interactions. Negotiating these complexities can become challenging, potentially resulting in a decrease in adherence as patients strive to manage the demands of their comprehensive drug regimens (Ortiz-Uriarte et al., 2023; Hu et al., 2022). However, the relationship between allopurinol adherence and presence of comorbidities has been conflicting across different studies. For instance, Singh et al., (2020) found that odds of allopurinol adherence were higher in people with comorbidities compared to those with no comorbidities. In another study, Chua et al., (2018) found a positive relationship between number of comorbidities and medication adherence. These individuals seem to have a greater awareness of the negative effects of not following their medication regimen on their overall health compared to those without comorbidities (Scheepers et al., 2018a).

It is important to note that social and economic factors play an important role in shaping adherence behaviours. The impact of age on medication adherence is multifaceted, revealing a complex relationship between chronological age and medication adherence. The available body of research suggests that the elderly and younger individuals often demonstrate lower adherence rates to their prescribed medications compared to the middle age groups (Gast & Mathes, 2019; Harrold et al., 2009). Among people with gout, the elderly tend to have multiple chronic health conditions, leading to more complex medication schedules, and they may also face greater physical and

cognitive limitations compared to younger individuals, leading to lower rate of adherence (Liu et al., 2023; Hughes, 2004). On the other hand, younger people with gout may adopt an experimental approach to their treatment regimens, potentially seeking to reduce or stop their medication intake to see if they really need the medication (Emad et al., 2022).

Gout often has been seen as a disease predominantly affecting older men (Petrie & Weinman, 2012). However, this perception seems not to fit younger patients, who are more likely to test treatment necessity, possibly because they don't quite match the usual image of someone with gout due to their younger age (Emad et al., 2022). Research findings from Kleinstauber et al. (2020) support these observations, revealing that gout, much like other chronic medical conditions, tends to occur later in life. This temporal progression leads to a shift in the normative perception of the illness, potentially mitigating the stigma often associated with it in older age groups.

Ethnicity is another socioeconomic factor found to be associated with medication adherence, particularly in gout (Roman, 2022). The prevalence of gout varies among different ethnic groups; for example, Māori and Pasifica populations exhibit higher rates compared to other ethnicities (Te Karu et al., 2021). This distinction underscores the importance of recognising ethnicity as a critical determinant in adherence behaviours. However, there are several knowledge gaps related to such disparities in gout. Socioeconomic health disparities may explain the observed ethnic differences. For instance, previous studies show that Māori and Pasifica are less likely to receive appropriate care than non-Māori often face barriers to healthcare access (Te Karu et al., 2020). It also remains unclear whether the elevated gout risk among specific ethnic groups is linked to variations in risk factors such as renal disease, heart failure and obesity, or if genetic distinctions tied to polymorphisms in genes governing urate production and elimination play a defining role (Singh, 2013). Furthermore, the interaction between genetics and environmental factors influencing variations in gout epidemiology across different ethnic groups is still relatively unexplored.

In addition, levels of education and health literacy are other factors that can contribute to medication adherence outcomes (Fernandez-Lazaro et al., 2019; Geboers et al., 2015). Previous studies emphasised the profound impact of these factors on patients' understanding regarding their treatment regimens and their ability to navigate the complexities of healthcare information, affecting medication adherence (Fields & Batterman, 2018; van Onna et al., 2015).

Lastly, several factors within the healthcare system have been demonstrated to impact medication adherence through medication beliefs. For example, the information available on patient educational resources provided by the healthcare system can affect medication beliefs and consequently medication adherence. For instance, if gout resources offer clear, accurate and patient-centred information that addresses common knowledge gaps, such as misconceptions about ULT and increased risk of gout flares upon initiation of ULT, it can help build their health literacy and reshape patients' medication beliefs regarding the medication effectiveness, resulting in improved adherence. It is important to note that other healthcare system factors such as insurance coverage, co-payment models, and access to healthcare services also influence medication adherence. These factors can influence patients' ability to afford medications and access necessary treatments, further impacting their adherence to prescribed regimens.

Medication Adherence Phases: The ABC Taxonomy

To better understand the complexity of medication adherence, Vrijens et al. (2012) proposed the Ascertaining Barriers to Compliance (ABC) taxonomy, where medication adherence encompasses three essential phases: initiation, implementation, and discontinuation. The initiation phase is defined as consumption of the first dose of a prescribed medication. The implementation phase is defined as the extent to which patients adhere to the prescribed dosing regimen from initiation until the last dose of the medication (period of persistence). The discontinuation phase is defined as the cessation of the prescribed medication for any given reason (period of non-persistence). Persistence refers to the time that patients remain on the prescribed drug regimen from initiation until discontinuation (Figure 3).

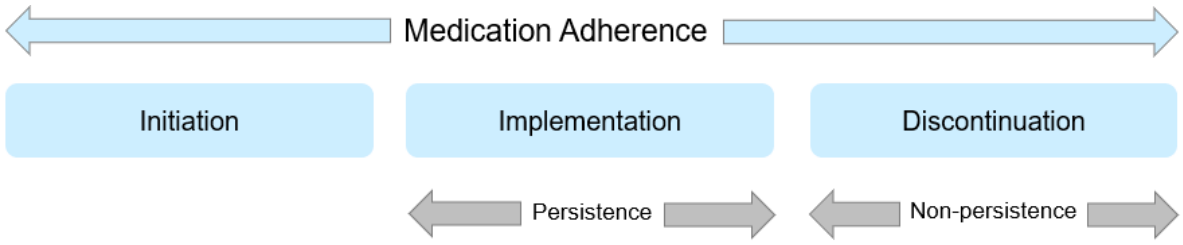

Figure 3. *Medication adherence phases [adapted from Spragg et al. (2023)].*

The initiation phase is where concerns may arise regarding the necessity of the medication or potential side effects. While these concerns are important, they crystallise fully during the implementation phase, where the decision to continue medication has been found to be influenced by individuals' experiences with medication. During this phase, patients balance their positive

experiences (benefits) against negative experiences (concerns) to decide on continuing medication. When the expected benefits aren't realised or if the adverse effects become more frequent or severe and outweigh the perceived benefits, nonadherence is expected. The discontinuation phase emerges when patients decide to prematurely halt their medication. Here, beliefs formed during the implementation phase continue to echo (Khan & Aslani, 2021). For example, if patients perceive ULT as ineffective because gout flares continued despite taking allopurinol, or unnecessary because gout flares were infrequent (or absent), they may choose to discontinue treatment, underscoring the enduring impact of beliefs and perceptions (Spragg et al., 2023).

While all three phases are important to fully understanding medication adherence, this thesis primarily focuses on the implementation phase, emphasising how patient beliefs and perceptions influence adherence to ULT in people with gout. Previous studies show that adherence involves a dynamic process of learning about the medication's efficacy, necessity, and tolerability through experience (Rottman et al., 2017). By focusing on the implementation phase, this thesis aims to identify and address medication beliefs shaped through patients' experiences with the medications, which could lead to discontinuation later on in treatment. This approach adopts a preventative strategy, aiming to establish robust adherence behaviours before potential issues escalate, thereby optimising long-term treatment outcomes.

Theoretical Frameworks of Nonadherence

A number of theoretical frameworks have been developed to explain nonadherence behaviour, providing a structured lens through which we can analyse and understand the interaction of factors contributing to medication adherence. Some of the most relevant theoretical frameworks are the necessity-concern framework, the COM-B model and the hierarchical model for medication adherence. While these theories provide insights into nonadherence behaviour, we primarily focus on the hierarchical model for medication adherence in this thesis. We specifically target medication beliefs and main motives of nonadherence, exploring how these factors can be identified and effectively addressed in gout educational resources and adherence-promoting interventions.

The Necessity-Concern Framework

The necessity-concern framework is a multidimensional theory that focuses on the relationship between patients' necessity beliefs and concerns regarding medication and how these beliefs influence medication adherence (Horne & Weinman, 1999). According to this framework, patients

weigh the perceived benefits (necessity beliefs) of taking a medication against their concerns (potential drawbacks or side effects) when deciding whether to adhere to a prescribed regimen (Phillips et al., 2014). The necessity-concern framework predicts that higher adherence is likely when patients perceive the necessity of the medication as outweighing their concerns (Foot et al., 2016). This framework has been studied and supported in various medical contexts including gout.

Regarding gout, a necessity-concern framework suggests that patients' perceptions of the necessity of ULT and their concerns about potential drawbacks play an important role in determining adherence behaviour (Uhlig et al., 2023). Patients who recognise the necessity of ULT in preventing flares, reducing long-term complications, and improving their overall quality of life are more likely to adhere to their treatment regimens (Horne et al., 2013). However, concerns about potential side effects, interactions with other medications, and the inconvenience of long-term therapy can act as barriers to adherence (Singh, 2014). The balance between patients' necessity beliefs and concerns regarding ULT aligns with the core principle of the necessity-concern framework, where adherence is predicted to be higher when the perceived benefits outweigh the perceived drawbacks (Yin et al., 2023). Recent studies applying the necessity-concern framework to the context of gout have provided insights into how these factors influence nonadherence and have underscored the need to address patients' beliefs and concerns to enhance ULT adherence and improve gout management outcomes (Uhlig et al., 2023; Spragg et al., 2023; Huang et al., 2022).

While the simplicity of the necessity-concern framework is an advantage, it can also be a limitation when dealing with nonadherence behaviours. For instance, a patient with gout may have strong beliefs about the necessity of ULT but still struggle with adherence due to logistic barriers, such as difficulty accessing medications or inadequate support from healthcare providers in managing their condition. In such cases, the necessity-concern framework alone may not provide a comprehensive understanding of the nonadherence problem. Moreover, much of the evidence on the necessity-concern framework is cross-sectional in nature, capturing patients' beliefs and concerns at a single time point. Hence, the existing evidence does not adequately address how medication beliefs may change over time or in response to treatment experiences.

The COM-B Model

The COM-B model provides a framework for comprehending nonadherence, particularly in the context of ULT in gout treatment. This model breaks down behaviour change into three components:

capability, opportunity, and motivation. In gout management, capability refers to a patient's comprehension of their ULT regimen and their ability to adhere to it. Opportunity encompasses external variables, including access to necessary medications and healthcare resources, which significantly influence a patient's adherence to ULT. Motivation refers to the multifaceted reasons underpinning a patient's commitment to their treatment, encompassing both conscious and subconscious cognitive processes (Michie et al., 2011; Figure 4).

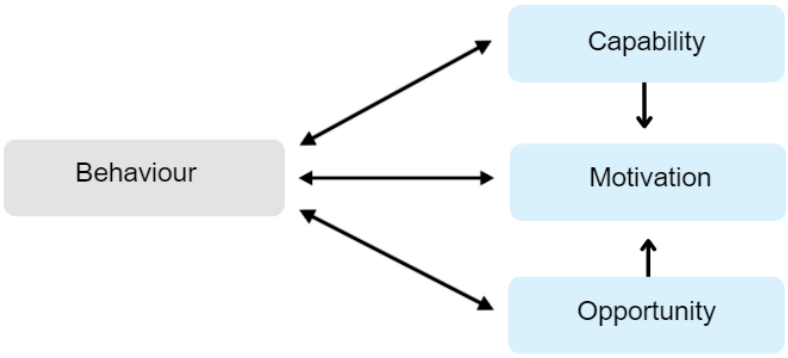

Figure 4. *The COM-B model used in Michie et al. (2011).*

Applying the COM-B model to medication nonadherence in gout offers valuable insights into the barriers some patients face when following their prescribed treatment plans. Capability-related challenges might emerge if patients lack a comprehensive understanding of the significance of their medications or the importance of dietary modifications alongside the treatment. Opportunity-based obstacles could arise due to challenges in obtaining medications or accessing crucial medical appointments for monitoring. Motivation-based hurdles might encompass limited awareness of the long-term benefits of adhering to prescribed regimens or emotional factors impacting a patient's dedication to managing their condition effectively (Michie et al., 2011).

As another example, when examining nonadherence to ULT, a significant factor to consider is the occurrence of flare-ups following the initiation of treatment (Choi et al., 2022; Aung et al., 2017). As highlighted in the previous section, flare-ups which are characterised by sudden and severe joint pain, can lead to nonadherence as patients might become discouraged by the perceived ineffectiveness of treatment during such episodes (Wortmann et al., 2010). This challenge intersects with both capability and motivation within the COM-B model. Capability is impacted as patients might find it difficult to persist with treatment when it doesn't seem to alleviate immediate symptoms. Motivation, on the other hand, can be hindered as patients feel the frustration of experiencing unexpected flare-ups despite their adherence efforts. Additionally, opportunity-related barriers can

emerge if patients are not provided with adequate information on managing these flare-ups or if they face difficulties in promptly accessing medical support during such occurrences.

The COM-B framework also provides a roadmap for designing targeted interventions to enhance adherence in patients undergoing long-life treatments (Xu et al., 2020). Tailoring strategies to enhance patient education, streamline medication accessibility, and address patient's motivations holds potential to enhance medication adherence (Beauvais, 2019; Reach, 2011).

However, one notable weakness encountered in the application of the COM-B framework is the ambiguity in classifying certain behavioural determinants (Whittal et al., 2021). For example, consider the determinant 'self-efficacy,' which has been identified as a barrier to medication adherence (Okuboyejo et al., 2018; Oshotse et al., 2018), in particular among people with gout taking urate lowering medications (Yin et al., 2023; Uhlig et al., 2021). 'Self-efficacy' could be categorised as 'psychological capability,' given its association with psychological skills and mental processes. However, it could also be interpreted as a construct linked to 'reflective motivation' since it involves self-evaluation and belief assessment (Michie et al., 2014). This ambiguity in classification introduces uncertainty and challenges in precisely defining the relevant COM-B component for certain determinants, which, in turn, may affect the accuracy of intervention designing and implementation.

Moreover, it is important to note that while the framework recognises the importance of capability, opportunity, and motivation in medication adherence, it does not clearly establish hierarchy among them. Because these factors are intertwined and affect each other (Michie et al., 2011), prioritising and targeting them for interventions can be challenging. Effective change often entails addressing multiple factors to have a meaningful impact on patient behaviour.

The Hierarchical Model for Medication Adherence

Unni and Bae (2022) introduced a new framework to address medication adherence called the Hierarchical Model for Medication Adherence (HMMA). This model suggests that individuals must develop specific skills, beliefs, and behaviours at different levels to achieve optimal medication adherence (Figure 5).

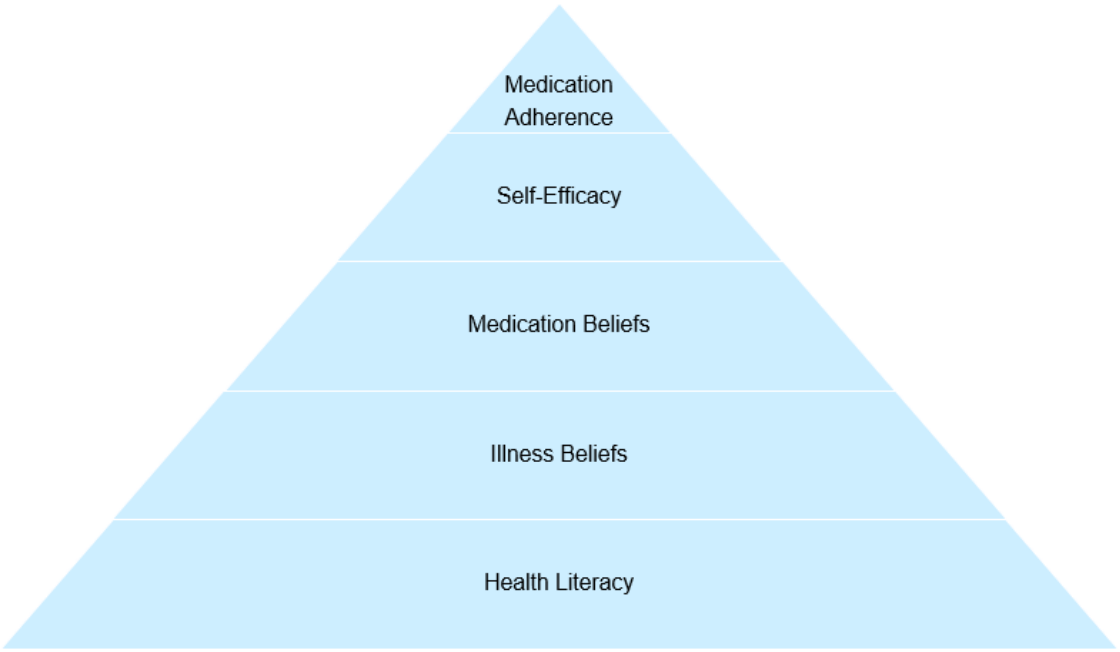

Figure 5. *The hierarchical model for medication adherence used in Unni and Bae (2022).*

Based on this model, every individual should have adequate health literacy as a foundational requirement. Health literacy enables individuals to attain a comprehensive understanding of their disease and the prescribed treatment regimen (Unni & Bae, 2022). For instance, in gout, a patient needs to understand how excess levels of serum urate contributes to joint inflammation and how urate lowering medications mitigate this process. Without this understanding, long-term adherence can become challenging (Sinnappah et al., 2022; Fields & Batterman, 2018). This phase represents an opportunity for enhancing medication adherence through providing accurate and targeted information in patient educational resources, which play an important role in building health literacy (Sørensen et al., 2021).

According to this framework, once patients understand their condition and treatment, illness beliefs come into play (Unni & Bae, 2022). This aligns with the common-sense model of illness, where a patient's belief in their illness significantly impacts adherence (Leventhal et al., 2016). In gout, if a patient recognises the chronic nature of the condition and the potential consequences of not adhering to ULT, they are more likely to stick to their prescribed medications (Dalbeth et al., 2011). Previous research indicated that individuals who consider their gout as a chronic and manageable disease, were more likely to adhere to ULT (Walsh et al., 2016)

The model's subsequent phase involves beliefs about medications (Unni & Bae, 2022). This aligns with the necessity-concern framework, where patients weigh the necessity of medication

against concerns they might have about their prescribed medications, such as side effects (Horne & Weinman, 1999). This is applicable to people with gout who may experience concerns about the potential adverse effects of medication or have reported a perceived lack of immediate symptom relief from ULT. If they perceive the necessity of treatment to be higher than these concerns, adherence becomes more probable (Yin et al., 2023). This phase can be influenced by a patient's level of satisfaction with their treatment; when individuals are satisfied with their medications, they tend to believe that taking their medications is necessary, resulting in a higher rate of adherence (Unni & Bae, 2022). By addressing these concerns and emphasising the importance of consistent ULT, healthcare providers can promote treatment satisfaction through a balanced perspective where the necessity of long-term serum urate control outweighs short-term concerns.

The pinnacle of the model is self-efficacy, referring to a patient's ability to carry out the required actions. In the context of gout, even with adequate health literacy and positive beliefs, patients still need confidence in managing their medications. This encompasses medication routines, behaviour modification, and recognising potential triggers for nonadherence (Unni & Bae, 2022). Modifying patient knowledge, medication beliefs, and associated behaviour through educational and behavioural interventions can enhance an individual's self-efficacy and their subsequent medication adherence (Ramsubeik et al., 2018; Johnson et al., 2016).

The hierarchical model for medication adherence presents a new framework for understanding medication adherence. This model offers a holistic approach that considers various levels of determinants of medication adherence, allowing for tailored interventions based on individual patient need. However, identifying and addressing factors at multiple levels can be resource-intensive and challenging to implement in real-world clinical settings. The effectiveness of the hierarchical model for medication adherence (HMMA) framework in enhancing adherence within gout management requires further investigation to clarify its applicability, feasibility, and potential impacts on patient behaviour and clinical outcomes. This ongoing exploration will lead to refinements and more tailored strategies that address the distinct challenges among people with gout taking urate lowering medications.

Interventions to Improve Medication Adherence in People with Gout

As defined at the beginning of this chapter, gout is a prevalent form of inflammatory disease characterized by elevated serum urate levels, necessitating consistent medication adherence to

effectively manage its symptoms and prevent recurring flares. Adherence to urate lowering medications is of great importance in achieving optimal outcomes in gout management. However, patients often encounter challenges that hinder their ability to adhere to prescribed ULT regimens. In response, researchers and healthcare providers have explored various interventions tailored to enhancing medication adherence in the context of ULT for gout (Figure 6). This section examines the effectiveness of patient-focused interventions categorised into three main approaches: educational and informational approaches, behavioural and supportive approaches, and technology-based approaches. Each category is tailored to address different dimensions of patient-related factors contributing to adherence.

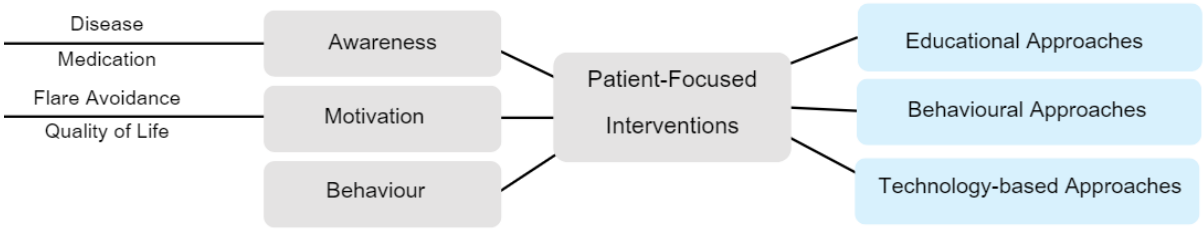

Figure 6. *Patient-related interventions to improve medication adherence in people with gout [adapted from Sabate (2003)].*

Educational and Informational Approaches

Educational interventions that focus on adherence to urate lowering medications have shown promise in fostering patient understanding and motivation (Coleshill et al., 209; Perez-Ruiz & Desideri, 2018). Providing patients with accurate and comprehensive information about gout, the rationale behind adhering to ULT, potential consequences of nonadherence, and benefits of sustained adherence can empower them to make informed decisions (Perez-Ruiz et al., 2020). A meta-analysis by Sinnappah et al. (2022) demonstrated that patients who participated in nurse-led educational sessions regarding gout and ULT exhibited significantly improved adherence rates.

In another review, researchers highlighted that targeted educational interventions addressing specific knowledge gaps have been linked to enhanced adherence to urate lowering medications. For example, a common misconception among people with gout is the belief that they can discontinue ULT once their gout flares subside. This misconception is rooted in the misunderstanding that ULT is only necessary during active gout flares. To address these misconceptions and other barriers to optimal care that vary among individual patients, ongoing discussions are crucial, not only during initial consultations but as part of continuous patient-provider dialogue. In addition, gout patients often

lack awareness regarding the causes and consequences of gout. They may not fully appreciate that poor medication adherence can lead to recurrent gout flares. Furthermore, there is a lack of understanding among patients about the genetic and metabolic factors underlying gout, which can lead to stigmatizing gout and self-blame. These issues can profoundly impact patients' medication adherence (Fields & Batterman, 2018). Therefore, addressing these knowledge gaps and misconceptions though educational and informational interventions is crucial for improving gout management.

While encouraging results have emerged concerning the impact of patient education on medication adherence in people with gout, Rolston et al. (2018) suggest that such interventions for educating people with gout should be tailored to fit their cultural context. This acknowledgment underscores the importance of not only providing educational materials and interventions but also ensuring that they are culturally sensitive and relevant to the specific backgrounds, beliefs, and practices of people with gout. Tailoring educational approaches in this manner is important for fostering more culturally appropriate adherence strategies, emphasising the importance of patient-centred research and practice.

Behavioural and Supportive Approaches

For a comprehensive understanding of behaviour change techniques in medication adherence interventions, researchers often refer to the Behaviour Change Technique Ontology (BCTO; Marques et al., 2023). This ontology provides a structured taxonomy that categorizes behaviour change techniques used in healthcare interventions, facilitating the implementation of effective strategies tailored to specific patient populations, such as those with gout.

Behavioural interventions can help with improving medication adherence to ULT in patients with gout. Strategies such as improving self-management skills, self-monitoring, and habit formation have demonstrated effectiveness (Perez-Ruiz & Desideri, 2018). In a randomized controlled trial by Fontanet et al. (2021), habit formation theory was applied to enhance medication adherence in gout patients. The trial leveraged cues and rewards to encourage daily oral medication adherence. Participants linked medication-taking to daily activities and selected charities to receive rewards upon adherence. The study aimed to evaluate the impact of this behavioural approach on medication adherence over 18 weeks, highlighting its potential to improve gout outcomes.

In a recent meta-analysis, Ramsubeik et al. (2018) focused on interventions led by healthcare providers, aiming to foster behavioural changes among gout patients. Their findings indicated that these interventions led to notable improvements in gout-related outcomes, including enhanced adherence to urate lowering medications, lowered urate levels, improved quality of life, and increased patient satisfaction.

Technology-Based Approaches

Adherence-improving interventions can also utilise technology to deliver their content in a format that is both portable and easily distributable. Smartphone apps, electronic reminders, and telemedicine platforms offer innovative ways to engage patients and promote adherence to urate lowering medications (Fields & Batterman, 2018; Jimenez-Liñan et al., 2017).

Electronic reminders to improve medication adherence have been widely reviewed. For example, Bunphong and Narongroeknawin (2018) conducted a study to assess the impact of mobile phone text message reminders on the adherence to allopurinol treatment and serum urate levels in gout patients. The randomised controlled trial involved 82 adult patients diagnosed with gout. The intervention group received daily text reminders to take allopurinol, while the control group received weekly text messages about non-pharmacologic gout treatment. After 12 weeks, the intervention group showed significantly improved adherence (88.1% vs. none in the control group) and a greater reduction in serum urate levels compared to controls. This suggests that mobile phone text reminders can enhance allopurinol adherence and aid in managing serum urate levels in people with gout.

Regarding mobile health applications (mHealth apps), Stamp and Gaffo (2022) suggest that self-monitoring through mobile apps can enhance adherence with urate lowering medications in people with gout. Similarly, in another study by te Kampe et al. (2022), a novel web-based patient-tailored tool was developed and utilised to improve medication adherence in people with gout who have been taking allopurinol. This tool was built upon a foundation of various behavioural theories that influence health-related behaviours through self-management strategies. The study outcomes underscore the efficacy of this web-based patient-tailored tool in improving adherence to allopurinol. By delivering tailored content, providing personalised information about gout management, and addressing knowledge gaps among participants, the tool achieved significant positive impact on medication adherence. Furthermore, the tool effectively enhanced participants' motivation by

specifically targeting their attitudes and self-efficacy, which are core elements in promoting desired behavioural shifts.

Technology was used in another intervention to improve adherence with urate lowering medications (Phang et al., 2020). Through this study, the investigators aimed to optimize gout patient care by employing telemedicine to provide patient education, facilitate remote consultations and adherence support, aligning with the evolving landscape of digital healthcare. Notably, this intervention led to a noteworthy reduction in the timeframe required to achieve target serum urate levels, showcasing a median duration of 19 weeks. While the study's primary focus wasn't solely on adherence evaluation, the outcomes suggest a promising impact on patient adherence to ULT. This implication is further supported by heightened medication satisfaction and expedited achievement of the serum urate target (<360 μmol/L), noted in approximately 57.5% of patients. Particularly encouraging results were observed among those with tophaceous gout, with 36.4% reaching a SU level <300 μmol/L.

While progress has been made in this direction, the demand for tailored interventions remains evident. Yin et al. (2022) accentuates the significance of tailoring mobile health applications specifically to help with gout self-management, taking into account individual patient beliefs and preferences. An exploration of digital health endeavours aimed at enhancing adherence across various rheumatic conditions, including gout, highlights the indispensability of personalised interventions that revolve around the patient (van Mierlo et al., 2015). As the landscape of technology-assisted healthcare evolves, these comprehensive interventions provide a glimpse into a more patient-centric and technologically empowered approach to gout management and the enhancement of medication adherence.

Research Gaps within the Literature

Although empirical work exists within the realm of medication adherence, there are some important gaps in understanding this behaviour among people with gout. Firstly, diverse methodologies were employed in assessing medication adherence. Studies analysing medication adherence show variation in study designs and adherence metrics, resulting in limitations to drawing comprehensive interpretations. The overall quality of reviewed data presents prevalent risks of bias and inconsistency in evaluating intervention effects on adherence, further complicating our insights (Sinnappah et al., 2022). The inconsistency in results from previous studies can be linked to the different ways

researchers used to measure medication adherence. For instance, some studies relied on objective measures such as serum urate levels (Singh et al., 2020), pill counts (Lee & So, 2016) and dispensing records (Rashid et al., 2015), while others used self-reported data (Tan et al., 2016; Singh et al., 2016; Singh et al., 2014). These variations in measurement methods have contributed to the inconsistencies in research outcomes, particularly regarding the relationship between adherence to ULT and contributing patient-related factors. Objective measures including pill count, serum urate level, and dispensing data face limitations in capturing the complex nature of nonadherence - whether intentional or unintentional. On the other hand, methods such as self-administered questionnaires or counting missed doses may be susceptible to recall bias or social desirability.

Moreover, there is a lack of standardised questionnaires or assessment tools targeting intentional nonadherence within the context of gout. Integrating tailored measures within adherence-promoting interventions becomes important, as they can offer insights into the motivations driving intentional nonadherence, for example, such measures could explore patients' beliefs about their urate lowering medications, their perceptions of gout curability, or their concerns about potential side effects. These insights would ultimately facilitate the development of more personalised strategies to enhance medication adherence in gout.

As patients undertake self-assessment of medication necessity and potentially modify treatment without professional consultation, the potential for intentional nonadherence grows (Ng, 2016). Despite active participation by gout patients in treatment decisions and their tendency to seek online health information about their condition and medications (Rai et al., 2018), systematic investigation into the effectiveness of online educational resources in improving medication adherence remains a notable gap (Ramsubeik et al., 2018).

Another significant gap in the existing literature pertains to the absence of technology-based interventions in the domain of gout educational and behavioural strategies. With the rise of digital health tools and mobile applications, there is a gap in the literature regarding the effectiveness of these interventions in improving medication adherence in gout patients on ULT. Given the potential advantages of technology for convenient and accessible support, such as real-time tracking, reminders, and personalised feedback, exploring the feasibility and impact of incorporating these solutions into gout management strategies becomes important to enhance patient outcomes. Tailored Interventions which target the reasons behind intentional nonadherence may improve patient

understanding and be more effective in improving health outcomes. However, work in this area is limited. We are yet to understand what drives intentional nonadherence to urate lowering medications among people with gout in a standardised way.

Considering the potential of online gout resources in empowering individuals to make informed decisions about taking their prescribed medications, future research should evaluate the content and strategies used in these resources, with a particular focus on how effectively they address the primary reasons behind intentional nonadherence to ULT. Lastly, we are yet to understand the potential of utilising smartphone notifications to enhance medication adherence to urate lowering medications in people with gout. There is a need for more trials which develop and assess the aspects of intentional nonadherence using diverse methodological approaches. Such studies would offer an understanding of the potentials and limitations tied to integrating customised interventions into clinical practice. This integration aims to effectively convey health information and enhance medication adherence to urate lowering medications in people with gout.

Summary

Medication adherence is essential for optimal gout management. Despite this, a significant proportion of people with gout do not take their medications as prescribed. Theoretical and empirical evidence demonstrates how educating patients and targeting their medication beliefs and perceptions may enhance adherence to urate lowering medications in gout. The majority of empirical evidence examining medication adherence has utilised general educational and behavioural approaches to change medication-taking behaviour, rather than tailoring interventions to address motives for intentional nonadherence in particular. Targeting underlying reasons behind intentional nonadherence presents a new intervention technique that provides initial evidence for improving medication adherence, by offering more information on how patients' beliefs and perceptions can affect their decision-making process. The current nonadherence to urate lowering medications literature is minimal, and contains clear gaps and limited evidence for change in objective health outcomes. The following chapters of this thesis will address these gaps to broaden understanding of how addressing motives of intentional nonadherence can enhance medication adherence and ultimately improve health outcomes for people with gout.

Chapter Three

Assessing Intentional Nonadherence in Gout

Preface

Gout is a prevalent form of inflammatory disease caused by the accumulation of urate crystals in joints. The effective management of this progressive condition necessitates consistent adherence to prescribed urate lowering medications, in particular allopurinol (Scheepers et al., 2018b). Allopurinol works by reducing the production of urate in the body and is often the preferred first-line urate lowering medication for managing gout (Qurie et al., 2023). Yet, despite its proven efficacy, about half of individuals with gout intentionally decide not to take allopurinol, potentially compromising their health outcomes (Yin et al., 2018).

In order to gain a better understanding of medication adherence in gout, this section introduces a quantitative research study centered on the Intentional Non-Adherence Scale (INAS) (Weinman et al., 2018). As highlighted in Chapter Two, adherence measurement in healthcare is a complex, multifaceted field, often lacking standard measures specifically designed to address intentional nonadherence. The INAS stands out as a unique tool explicitly tailored for assessing intentional nonadherence.

Although the INAS was found to be associated with levels of serum urate in people with gout (Weinman et al., 2018), there is still limited data on the scale's concurrent validity concerning medication adherence among this population. Moreover, there is no data on how associations between INAS scores and medication adherence might be modified by demographic and clinical factors. This section aims to address these gaps in the existing literature and provide a more comprehensive assessment of medication adherence in gout.

Therefore, the primary objective of the following study is to explore INAS efficacy in assessing medication adherence among people with gout taking allopurinol. The study investigated to what extent INAS scores associate with serum urate, an objective measure of adherence to allopurinol, and the self-reported number of missed doses (Emad et al., 2023a).

The findings of this study can help healthcare providers to identify patients at higher risk of nonadherence to allopurinol, thus offering the potential for timely intervention with this group.

Abstract

Objective. The objectives of this study were to investigate the utility of the Intentional Non-Adherence Scale (INAS) in assessing adherence to allopurinol, and to examine differences in INAS scores for individuals with and without serum urate (SU) at treatment target (<0.36mmol/L, 6mg/dL). **Methods.** This study was a pre-specified cross-sectional analysis of a 12- month randomised clinical trial of colchicine prophylaxis involving 182 individuals with gout. Allopurinol treatment was initiated at the baseline visit for all participants, using a start-low go-slow treat to target approach. At baseline, participants were randomised 1:1 to colchicine 0.5 mg daily or placebo for the first 6 months of the trial. The current study analysed data collected at the month 12, including the Intentional Non-Adherence Scale (INAS) scores and medication adherence measures (serum urate levels and self-reported number of missed doses). Multiple linear regression analysis was conducted on medication adherence, adjusting for clinical and demographic features. Differences in INAS scores were analysed between individuals who did and did not achieve the treatment target SU. **Results.** Higher scores in the INAS total scale (r = 0.18, *P* = .024), INAS *Testing Treatment* which indicates minimizing medication intake to test treatment limits (r = 0.36, *P* <.001), and INAS *Medicine Sensitivity* which indicates heightened perceived sensitivity to medication effects (r = 0.16, *P* = .040) were associated with a greater number of missed doses within a month. When entered into a linear regression model after controlling for other factors, the INAS *Testing Treatment* scores remained significantly associated with the number of missed doses (F (3,152) = 4.74, *P* <.001). Higher SU levels were significantly associated with higher INAS *Testing Treatment* scores (r = 0.17, *P* = .025), particularly among younger patients (r = 0.25, *P* = .022); with younger individuals being more likely not to take allopurinol as a way of testing if they really needed it. The INAS *Testing Treatment* scores were significantly different between individuals who did and did not achieve the treatment target SU levels [t (160) = -2.43, *P* = .016]. When entered into a linear regression model after controlling for other factors, the INAS total scale scores, the INAS Testing Treatment scores, in conjunction with age, remained significantly associated with SU levels (F (4,155) = 4.59, *P* <.001). **Conclusion.** These findings show the concurrent validity of the INAS in assessing medication adherence in people with gout. By providing a reliable means of identifying intentional nonadherence, these results could support the development of tailored interventions to enhance medication adherence in gout management.

Introduction

Medication nonadherence is a significant concern and a major barrier to treatment success among people with gout, particularly those on urate lowering treatment (ULT) with allopurinol (Koesmahargyo et al., 2020). Allopurinol is the first-line recommended agent of ULT, and it is recommended that allopurinol is dosed to achieve serum urate (SU) concentrations below 0.36mmol/L (6mg/dL; FitzGerald et al., 2020). However, adherence rates to ULT are very low (Scheepers et al., 2018a; Yin et al., 2018). A considerable portion of medication nonadherence to ULT can be attributed to intentional nonadherence (Hill-McManus et al., 2018), where individuals actively decide not to take their medication as prescribed (Huyard et al., 2017).

The quantification of intentional nonadherence has gained increasing recognition in development of self-report questionnaires (Chan et al., 2020). Weinman et al. (2018) developed the Intentional Non-Adherence Scale (INAS) to shed light on different reasons behind intentional nonadherence. The INAS offers four subscales that have been found to inform these motivations (Emad et al., 2022): *Resisting Illness* reflects a desire to avoid reminders of gout and to feel normal; *Testing Treatment* involves minimizing medication intake to test treatment limits; *Drug-specific Concerns* encompass worries about potential consequences of medication intake such as side effects; and *Medicine Sensitivity* indicates heightened perceived sensitivity to medication effects. While the measure was found to be valid and reliable, associating with SU levels as a measure of adherence (Weinman et al., 2018), there is still limited data on its concurrent validity concerning how INAS scores associate with medication adherence in people with gout, and how this relationship might be influenced by clinical features such as presence of tophi and comorbidities (Hu et al., 2022; Rogenmoser & Arnold, 2018) as well as demographic factors (Setyawan et al., 2022; Chua et al., 2018; De Vera et al., 2014). For example, age has been identified as an important contributing factor to nonadherence to ULT in previous studies, with younger people with gout tending more to deliberately deviate from their prescribed regimens (Emad et al., 2022; Perez-Ruiz et al., 2020; Aung et al., 2017).

Despite the acknowledged significance of assessing intentional nonadherence, the concurrent validity of the INAS and its association with adherence to ULT in people with gout remains underexplored. Establishing validity is important for evaluating the scale's effectiveness in assessing intentional nonadherence in gout, enabling development of tailored interventions and support to

improve treatment outcomes and reduce the burden of gout-related complications. Therefore, this study aimed to determine the association of INAS scores with medication adherence in people with gout taking allopurinol, while considering clinical and demographic factors.

Method

Participants

This study was a pre-specified analysis of a 12- month randomised clinical trial of colchicine prophylaxis. 200 participants were recruited from primary care, secondary care and through public advertising. Inclusion criteria were: (1) age of eighteen or over; (2) a rheumatologist-confirmed diagnosis of gout; (3) meeting the American College of Rheumatology (ACR) recommendations for starting ULT (FitzGerald et al., 2020); (4) SU ≥0.36 mmol/L (6 mg/dL) at screening, and (5) English-speaking. People with a history of intolerance or contraindication to allopurinol or colchicine were receiving azathioprine, cyclosporine, or other immunosuppression (due to interactions with allopurinol), had stage 4 or 5 chronic kidney disease (estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2), unstable comorbid health conditions (e.g., New York Heart Association (NYHA) stage 4 heart failure, recent myocardial infarction, advanced cancer) or dementia were excluded. Allopurinol treatment was initiated at the baseline visit for all participants, using a start-low go-slow treat to target approach. At baseline, participants were randomised 1:1 to colchicine 0.5 mg daily or placebo for the first 6 months of the trial. Blood was obtained monthly for SU levels during the trial period. 182 participants completed the final visit at 12 months following the initiation of allopurinol and were included in the per protocol population (Stamp et al., 2023).

The current study analysed data collected at the month 12, including the INAS scores, the SU levels, and the self-reported number of missed doses within a month. We also used the clinical and demographic data collected at the baseline visit in the main trial.

Ethical approval was obtained from the New Zealand Health and Disability Ethics Committee (Ref 18/STH/156), and all patients provided written informed consent.

Measurements

Medication adherence. Adherence to allopurinol was assessed by serum urate levels and the patient-reported number of missed dose(s) at 12 months following the initiation of allopurinol.

Intentional Non-Adherence Scale (INAS). The INAS is a tool used to understand why people choose not to follow their prescribed regimens. This questionnaire consists of 22 items

designed to explore the reasons behind this behaviour (Weinman et al., 2018). The scale asks patients to reflect on their experiences with medication over the past 6 months and indicate how much they agree or disagree with each statement on a 5-point Likert scale from strongly agree (5) to strongly disagree (1). The INAS has four subscales: Firstly, *Resisting Illness*, which refers to the desire of feeling healthy and normal, and not to be reminded of one's illness (e.g., "Because I want to lead a normal life again"). Secondly, *Testing Treatment*, which refers to the patient's attempts for testing the limits of treatment to see if they can get away with less or no treatment (e.g., "To see if I can do without it"). Thirdly, *Drug-Specific Concerns*, which include concerns about not being on the right medication or dosage, the potential side effects, medication effectiveness over time, and worries about developing drug dependency (e.g., "Because I think I am on too high a dose"). Fourthly, *Medicine Sensitivity* which refers to the patient perceiving themselves as highly sensitive to the effects of medicine (e.g., "Because the medicine is harsh on my body"). The overall INAS scores range from 22 to 110 with higher scores indicating a greater tendency toward intentional nonadherence behaviour. INAS subscales showed acceptable internal consistency with Cronbach's alpha ranging from 0.64-0.78 in the current sample. The overall internal consistency of the INAS total scale was 0.87. Participants completed this scale at 12 months following the initiation of allopurinol.

Clinical and demographic features. Using a dedicated demographic and clinical data form, we gathered demographic details, including age, gender, years of education, and ethnicity. We also collected clinical data, which encompassed gout duration, tophus count utilising a tophus diagram (homunculus), and the number of comorbidities, where applicable.

Statistical analysis

All statistical analyses were performed using SPSS version 25.0 (IBM Crop.). Mean with 95% Confidence Intervals (CI) and percentages were used to describe the clinical characteristics of participants. Pearson's correlations and a multiple linear regression analysis using the enter method were used to describe the associations between variables. Independent t-tests were also conducted to investigate differences in outcome measures for males and females as well as for participants who did or did not achieve the treatment target SU levels (<0.36mmol/L or 6mg/dL). We applied one-way ANOVA to examine differences in outcome measures for people from different ethnicities.

All statistical tests were two-tailed, and data outliers were excluded from the analysis. A significance level of .05 was used to determine statistical significance for all analyses. For data

visualization and creating scatterplots, we utilised the R programming language version 4.3.1 (R Core Team, 2021) and the ggplot2 package version 3.4.2 (Wickham, 2016).

Results

Characteristics of the study population

The study included a total of 182 participants with gout, with an age range of 19 to 89 years. The majority of participants were of NZ European ethnicity (56%), male (93%), had comorbidities (67%), did not have tophi (75%), and had an average 14.5 years of education. A significant proportion of the participants had experienced their first gout flare at an average age of 45 and were diagnosed with gout for an average of 11 years (Table 1).

Table 1. *Characteristics of the study population at 12 months following the initiation of allopurinol*

Variable	n (%)	Variable	n (%)
Gender		Comorbidities status	
Male	169 (92.8)	Absent	59 (32.4)
Female	13 (7.2)	Present	123 (67.6)
Ethnicity		Number of comorbidities (mean, 95% CI)	2.05 (1.70-2.41)
NZ European	102 (56.3)	Type of Comorbidities	
Māori	21 (11.5)	High blood pressure	81 (44.5)
Pacifica	19 (10.4)	High cholesterol or lipids	65 (35.7)
Asian	20 (10.9)	Kidney problem	60 (32.9)
Other	20 (10.9)	Chronic kidney disease	53 (29.1)
Number of tophi (mean, 95%CI)	1.01 (0.35-1.67)	Heart problems	37 (20.3)
0	138 (75.8)	Arrythmia	20 (10.9)
1	20 (10.9)	Heart attack	13 (7.14)
2	10 (5.4)	Type 2 diabetes	12 (6.5)
> 2	14 (7.9)	Angina	10 (5.4)
Serum urate level (mean, 95% CI)	0.31 (0.30-0.32)	Stroke	6 (3.2)
<0.36mmol/L or 6mg/dL	143 (78.6)	Heart failure	5 (2.7)
≥0.36mmol/L or 6mg/dL	39 (21.4)	Peripheral vascular disease	3 (1.6)
Age in years (mean, 95% CI)	56.89 (54.66-59.12)	Cardiomyopathy	1 (0.5)
Age of first gout flare in years (mean, 95% CI)	45.61 (43.27-47.95)	Duration of gout in years (mean, 95% CI)	11.31 (9.84-12.79)
Education in year (mean, 95% CI)	14.60 (14.15-15.05)		

Note. Values are the number and percentage unless otherwise indicated.

Association between INAS scores and adherence

The first aim of the study was to explore the correlation between overall INAS scores and INAS subscales and adherence measures including serum urate and number of missed dose(s) within a month among people with gout taking allopurinol. The results indicated that higher scores in INAS *Testing Treatment* were associated with higher levels of SU (r = 0.17, *P* = .025). We also found that INAS *Testing Treatment*, INAS *Medicine Sensitivity* and the overall INAS scores were correlated to the number of missed does(s) within a month; with respondents who scored higher at these scales reporting a greater number of missed allopurinol doses (Table 2).

Association between clinical and demographic features and adherence

Next, we explored the associations between demographic and clinical features and SU levels, as well as number of missed dose(s) within a month. The data showed that age was significantly correlated with levels of SU, indicating that younger patients were more likely to have higher levels of SU (r = -0.24, *P* <.001). We found no effects of gender [t (14.36) = 0.16, *P* =.869] or ethnicity [F (3,159)= 0.89, *P* = .444] on the levels of SU. No relationship was found between number of missed dose(s) within a month and clinical or demographic factors (Table 2). We also found no effects of gender [t (157) = 0.91, *P* = .360] or ethnicity [F (3,155)= 1.76, *P* = .157] on the number of missed doses.

Table 2. *Pearson's r for relationships between study variables and outcome measures at 12 months following the initiation of allopurinol*

Variable	Serum urate	*P*	Missed dose(s)	*P*
INAS – Total	0.01	.877	0.18	**.024**
INAS – Resisting Illness	-0.02	.739	0.12	.111
INAS – Testing Treatment	0.17	**.025**	0.36	**<.001**
INAS – Drug Specific Concerns	-0.04	.590	0.10	.208
INAS – Medicine Sensitivity	0.07	.332	0.16	**.040**
Number of tophi	0.01	.998	-0.01	.887
Number of comorbidities	-0.11	.137	-0.06	.385
Duration of gout in years	-0.12	.121	-0.14	.078
Age	-0.27	**<.001**	-0.13	.095
Years of education	0.10	.177	-0.02	.726

Note. Bold indicates significance at p< .05 level. INAS: Intentional Non-Adherence Scale.

Exploring factors modifying the association between INAS scores and adherence

Another aim of the study was to explore how clinical and demographic features might modify the relationship between the overall INAS scores and INAS subscales and medication adherence. Considering that age was the only factor found to be correlated to SU levels (Table 2), we examined the association between INAS *Testing Treatment* scores and SU levels in relation to age, as shown in Figure 7. Using the median age of 59 as the cut-off point, we found that younger patients with higher SU levels were more likely to score higher in INAS *Testing Treatment* (r = 0.25, *P* = .022). However, no significant correlations between INAS Testing Treatment scores and levels of SU were found among older participants (r = 0.08, P = .486). A Fisher's r-to-z transformation was conducted to compare the strength of these correlations. The findings indicated that the relationship between SU levels and INAS Testing Treatment scores differed significantly between younger and older patients (z = 1.96, P = .048).

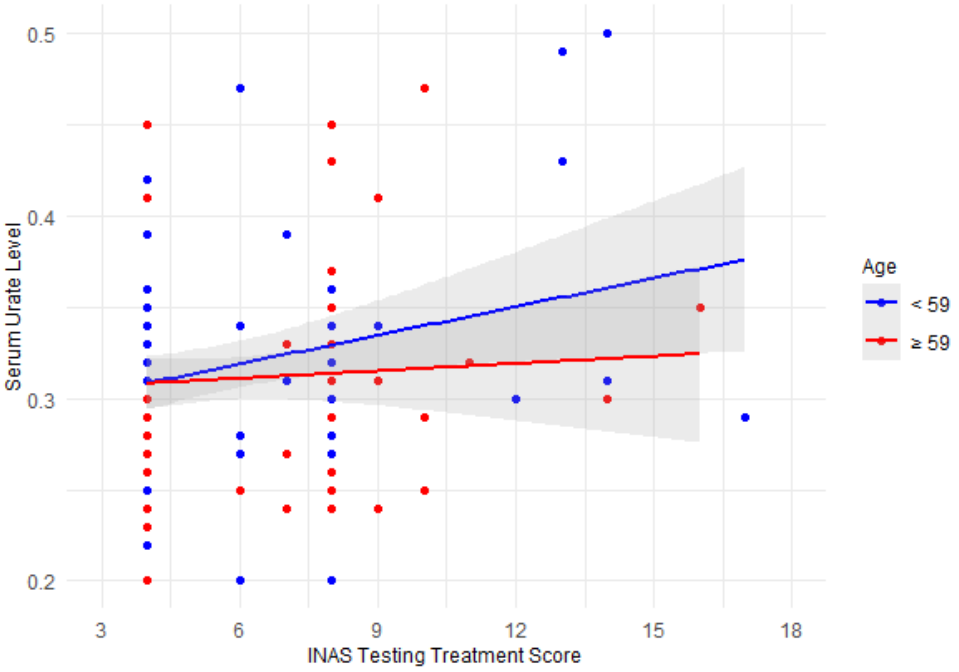

Figure 7. *Relationship between INAS Testing Treatment scores and serum urate levels by Age at 12 months following the initiation of allopurinol; INAS: Intentional Non-Adherence Scale.*

Exploring factors influencing adherence

Next, we looked at the factors contributing to allopurinol adherence measured by SU levels and number of missed dosed(s) withing a month, using a multiple linear regression analysis with the enter method. The results indicated that the total INAS scores, the INAS *Testing Treatment* scores and age remained significantly associated with the SU levels, while controlling for other factors (F (4,155) = 4.59, *P* <.001, R^2 $_{Adjusted}$ = 0.10; Table 3).

Table 3. *Multiple linear regression results for factors contributing to variations in serum urate levels at 12 months following the initiation of allopurinol*

Variable	*B*	*SE*	*β*	*95% CI Lower*	*95% CI Upper*	*P*
INAS – Total	0.002	0.001	0.377	0.000	0.004	**.028**
INAS – Testing Treatment	0.005	0.002	0.250	0.001	0.010	**.029**
INAS – Medicine Sensitivity	0.005	0.003	0.244	-0.001	0.010	.090
Age	-0.001	0.000	-0.255	-0.002	0.000	**.001**

Note. Bold indicates significance at p< .05 level. INAS: Intentional Non-Adherence Scale.

We also found that the INAS *Testing Treatment* scores remained significantly associated with the number of missed dose(s) within a month, while controlling for other factors (F (3,152) = 4.74, *P* <.001, R^2 $_{Adjusted}$ = 0.08; Table 4).

Table 4. *Multiple linear regression results for factors contributing to variations in number of missed dose(s) within a month at 12 months following the initiation of allopurinol*

Variable	*B*	*SE*	*β*	*95% CI Lower*	*95% CI Upper*	*P*
INAS – Total	0.012	0.017	0.116	-0.045	0.022	.495
INAS – Testing Treatment	0.147	0.050	0.344	0.049	0.245	**.004**
INAS – Medicine Sensitivity	0.018	0.050	0.049	-0.082	0.117	.727

Note. Bold indicates significance at p< .05 level. INAS: Intentional Non-Adherence Scale.

Differences between participants with and without serum urate at target

We also looked at the differences on overall INAS scores and INAS subscales according to SU at target. We found that respondents who did not achieve target SU levels had significantly higher INAS *Testing Treatment* scores. These respondents were younger compared to those who achieved target SU (Table 5).

Table 5. *Difference between outcome measures for respondents with and without serum urate at target at 12 months following the initiation of allopurinol*

Variable	SU at target (n = 143)	SU above target (n = 39)	*t (df)*	*P*
INAS – Total	32.14 (30.35-33.92)	32.88 (26.82-38.93)	-1.06 (21.89)	.297
INAS – Resisting Illness	10.55 (9.83-11.27)	10.56 (7.97-13.16)	-1.03 (23.11)	.313
INAS – Testing Treatment	5.47 (5.07-5.87)	6.69 (4.95-8.42)	-2.43 (160)	**.016**
INAS – Drug Specific Concerns	8.96 (8.37-9.54)	8.31 (6.95-9.67)	-0.12 (24.30)	.904
INAS – Medicine Sensitivity	7.16 (6.66-7.66)	7.31 (5.70-8.93)	-1.20 (23.30)	.239
Number of tophi	0.94 (0.12-1.76)	1.06 (0.21-2.33)	0.22 (52.80)	.822
Number of comorbidities	2.24 (1.84-2.63)	1.44 (0.09-2.79)	0.74 (22.40)	.463
Duration of gout in years	11.37 (9.73-13.02)	11.10 (7.64-14.56)	0.70 (27.50)	.486
Age	59.42 (57.14-61.70)	50.63 (40.96-60.29)	2.32 (161)	**.022**
Years of education	14.72 (14.20-15.25)	14.50 (13.54-15.46)	-0.38 (25.58)	.704

Note. Bold indicates significance at p< .05 level. INAS: Intentional Non-Adherence Scale. SU: Serum urate.

Discussion

This study on people with gout taking allopurinol aimed to assess the concurrent validity of the Intentional Non-Adherence Scale (INAS) for measuring medication adherence. We found higher INAS *Testing Treatment* scores were correlated with higher SU levels, particularly among younger patients, signifying a propensity for intentional nonadherence in this demographic. Furthermore, individuals failing to achieve target SU levels exhibited significantly higher INAS *Testing Treatment* scores and were younger. The research also highlighted that higher overall INAS scores, along with higher scores in INAS *Testing Treatment* and INAS *Medicine Sensitivity*, correspond to a greater frequency of missed allopurinol doses within a month. The INAS *Testing Treatment* scores remained associated with the number of missed doses after controlling for other factors. The total INAS scores and INAS *Testing Treatment* scores, in conjunction with age, were also found to remain associated with variations in SU levels after controlling for other factors, emphasising the potential utility of INAS as a valid tool for identifying intentional nonadherence to allopurinol.

The results demonstrate the importance of age in moderating the relationship between INAS *Testing Treatment* scores and adherence to allopurinol. Consistent with previous studies, we found that younger age groups were more likely to test ULT limits and see if they can get away with less or no treatment (Emad et al., 2022). This age-related trend can be attributed to the perception of gout as predominantly affecting older men (Kleinstäuber et al., 2020; Ragab et al., 2017), contributing to a sense of uncertainty regarding the diagnosis and the necessity of allopurinol among younger people with gout (Petrie et al., 2018).

Our results provide some indications to clinicians about how INAS scores may be used for people with gout in order to improve adherence to allopurinol. Firstly, the data from this study suggests that INAS can serve as a reliable and valid tool for screening individuals at a heightened risk of nonadherence to allopurinol. These findings present a potential for INAS to enable healthcare providers addressing adherence challenges in gout management, and to alert them to individuals who may struggle with adherence to allopurinol. Secondly, the INAS allows for designing and developing more tailored interventions. For instance, patients with higher INAS *Testing Treatment* scores may benefit from education on the importance of continuous allopurinol intake in controlling gout symptoms, regardless of their age, while those with high INAS *Medicine Sensitivity* scores may require alternative treatment options with fewer perceived side effects. This tailored approach can

lead to more effective adherence interventions and improved patient outcomes. Finally, the INAS may have the potential to aid in monitoring adherence behaviours over time, which could be explored in future studies. This could enable clinicians to assess the impact of interventions and adapt strategies as needed for long-term treatment success.

Despite its contributions, the study has several limitations that should be considered. Firstly, the administration of colchicine and allopurinol in one study arm of the original study may have influenced INAS scores and the frequency of missed doses due to varying experiences with allopurinol. In addition, providing information about allopurinol at the study's outset could have shaped participants' perceptions and rationalisations of medication adherence, potentially impacting their INAS scores and missed dose frequency. Moreover, geographical differences, as patients were recruited from different cities in the original study, may have contributed to variations in adherence behaviour due to contextual factors or access to healthcare resources.

Additionally, the cross-sectional design restricts the ability to assess INAS predictive capabilities. Future research could benefit from longitudinal studies to provide a deeper understanding of the dynamics of intentional nonadherence over time. Moreover, the reliance on self-reported missing dose(s) data may introduce bias. Participants may under-report or over-report nonadherence due to social desirability or memory recall issues. To mitigate this limitation, future studies could incorporate objective measures of adherence, such as electronic pill bottle monitors, to provide a more accurate assessment.

Furthermore, the study's findings may be specific to the population studied, namely individuals with gout taking allopurinol, and may not generalise to other medical conditions or medications. Moreover, that the average serum urate of our sample was well controlled, which may further limit the generalisability of the findings. In addition, the educational background of our study participants tended to be relatively high. Hence, our findings might not be fully applicable to individuals with lower levels of education. To ensure the broader relevance of our results, it could be beneficial to replicate the study with a more diverse and nonadherent group of patients. The complexity of medication adherence was another limitation. While the INAS effectively captures psychological reasons behind intentional nonadherence, a comprehensive assessment of medication adherence should consider a broader range of determinants, including socioeconomic status and healthcare system-related factors.

In conclusion, this study has shed light on the potential of the INAS as an effective tool for assessing adherence to allopurinol. The INAS's ability to identify intentional nonadherence, highlights its utility for developing targeted intervention and tailored adherence strategies. The results of this study have advanced our understanding of medication adherence assessment in gout management.

Chapter Four

Exploring Motives of Intentional Nonadherence in Gout

Preface

As discussed in Chapter Two, most existing research primarily focuses on general patterns of adherence, without giving sufficient attention to intentional nonadherence. While several theories pinpoint patient-related factors including medication beliefs as primary reasons for nonadherence (e.g., necessity beliefs, concerns about the medication), a critical gap remains—no study has undertaken a comprehensive exploration of what drives intentional nonadherence in gout.

Exploring the fundamental reasons behind intentional nonadherence in gout holds considerable importance, offering numerous advantages. Through a better understanding of what drives intentional nonadherence, tailored interventions that address the underlying factors affecting each patient's medication adherence are made possible. This approach goes beyond generic treatment plans, offering personalised strategies that can potentially improve allopurinol adherence, resulting in better health outcomes and slower gout progression.

Furthermore, understanding these underlying reasons fosters enhanced communication between healthcare providers and patients. As healthcare providers are able to see why patients may intentionally stop taking their prescribed medications, they can engage in more constructive dialogues, offering information and guidance that may challenge unhelpful beliefs and misconceptions about treatment. Moreover, identifying people at higher risk of nonadherence and targeting their reasons behind this behaviour has the potential to mitigate the financial burdens associated with nonadherence and reduce the need for additional medical treatment.

Therefore, the following manuscript aims to determine what drives intentional nonadherence in people with gout who are taking allopurinol (Emad et al., 2022). We selected the Intentional Nonadherence Assessment Scale (INAS) as our primary tool for exploring the reasons behind nonadherence for several reasons. Chapter Three indicated that the INAS is a validated tool for assessing medication adherence. This scale also offers a multifaceted approach to exploring nonadherence motivations, allowing us to explore a range of beliefs, and perceptions influencing patients' decisions to deliberately deviate from their medication regimens. Analysis of the findings will enable us to answer the question: why do patients not take allopurinol?

Abstract

Objective. The objectives of this study were to examine the reasons patients give for non-adherence to allopurinol and examine differences in intentional non-adherence for patients with and without serum urate at treatment target. **Methods.** Sixty-nine men with gout attending rheumatology clinics, all prescribed allopurinol for at least six months, completed the Intentional Non-Adherence Scale (INAS). Differences in the types of intentional non-adherence were analysed between patients who did and did not achieve the treatment target serum urate (SU) levels (<0.36mmol/L, 6mg/dL). **Results.** The most frequently endorsed reason for not taking their urate lowering medication was because participants wanted to lead a normal life (23%) or think of themselves as a healthy person again (20%). Patients also reported not taking allopurinol as a way of testing if they really needed it (22%). Participants with SU above target endorsed significantly more INAS items as reasons for not taking their medicine, had more medicine-related concerns and were more likely to give testing treatment as a reason for non-adherence. Participants who were younger, single and non-NZ European also endorsed more reasons for not taking their allopurinol. **Conclusion.** The major reasons behind the patient's decision not to take allopurinol relate to the desire to lead a normal life and the strategy of testing the treatment to see if they could reduce the dose without getting symptoms. These results provide some potentially modifiable targets for adherence interventions and some recommendations to clinicians about how to reframe ULT for patients in order to improve adherence.

Introduction

Gout is a chronic disease of monosodium urate crystal deposition. Urate-lowering therapy (ULT) is indicated for patients with recurrent gout flares, joint damage due to gout, and tophaceous gout (FitzGerald et al., 2020). Allopurinol is recommended as first-line ULT, and is the most widely used treatment, accounting for >90% of all ULT used in the US (Kim et al., 2021). The benefits of ULT are realised with long-term, continuous therapy to maintain the serum urate (SU) below 0.36mmol/L (6mg/dL). However, adherence rates for ULT are very low (Scheepers et al., 2018a) even in comparison to other chronic illnesses (Briesacher et al., 2008). Typically, adherence steadily declines in patients continuing treatment after their initial prescription and less than half of patients take allopurinol as prescribed at 12 months (De Vera et al., 2014; Scheepers et al., 2018a). The low rates of adherence to ULT have led to a call to better understand patient-related factors that lead to intentional nonadherence to gout therapy (Perez-Ruiz & Desideri, 2018).

Early research in medication adherence largely focussed on unintentional factors, such as forgetting or uncertainty about the treatment regimen (Ley, 1982). Interventions based on this approach, including many apps, have concentrated on reminders, but because most non-adherence is intentional (Barber et al., 2004; Mukhtar et al., 2014), these often have little effect on improving adherence (Choudhry et al., 2017). Intentional nonadherence describes the process by which patients decide not to take their medication based on specific perceptions about their condition or treatment. Intentional non-adherence is a new area in adherence research and a new measure, the Intentional Non-Adherence Scale (INAS), has recently been developed as a way of ascertaining patients' reasons for nonadherence behaviour (Weinman et al., 2018).

Currently there is a lack of research on what beliefs and perceptions drive people with gout to not adhere to ULT. It is frequently assumed that nonadherence is driven by side effects (Perez-Ruiz & Desideri, 2018). Patients are often asked about medication side effects and clinicians often target these beliefs to improve adherence, however, there are a wide range of reasons that could influence non-adherence. A better understanding of the drivers of intentional nonadherence with ULT may allow the development of interventions designed to change these beliefs in order to improve adherence behaviour.

This study had 3 aims designed to improve our current understanding of intentional non-adherence in patients with gout who take allopurinol. First, we utilised the INAS to find out what

reasons patients with gout give for not taking allopurinol. Second, we investigated the differences in the types of intentional nonadherence between those with and without SU at treatment target (<0.36mmol/L, 6mg/dL). SU is an important biomarker of gout disease and an acceptable objective measure of adherence (Dalbeth et al., 2017). Last, we explored the relationships between intentional nonadherence and demographic factors in patients with gout.

Method

Participants

This was a cross-sectional study of 69 men with gout. The participants were recruited from rheumatology clinics between September 2019 and March 2020. Inclusion criteria were: (1) age ≥ 18 years; (2) a rheumatologist-confirmed diagnosis of gout; (3) allopurinol prescription ≥ 6 months; and (4) English-speaking. The New Zealand Health and Disability Ethics Committee approved this study (ref. HDEC19/CEN/148) and all patients provided written informed consent. Participants completed demographic and clinical data form and study questionnaires. SU result was obtained through medical record review.

Measurements

Intentional Non-Adherence Scale (INAS). This 22-item scale assesses the potential reasons behind intentional non-adherence behaviour (Weinman et al., 2018). The scale is prefaced with the following instructions: “People have different experiences when taking medication and use their medications in ways that suit them. Sometimes people forget or decide not to take their medication for various reasons. We are interested in your personal views and experiences of your prescribed medication regime and the way you use your medications. Listed below are some of the reasons why people sometimes stop taking their medications. We would like to know how often each of the following statements is true for you in the past 6 months”. The scale asks patients whether they have not taken their medicine due to a list of 22 reasons scored on a 5-point Likert scale from strongly agree (5) to strongly disagree (1). The INAS comprises 4 subscales: (1) Resisting Illness, which links the decision not to take treatment with not wanting to be reminded of one's illness and the desire to feel normal and healthy (e.g., “Because it reminds me I have an illness”); (2) Testing Treatment, which assesses the individual’s reasons for not taking treatment based on the person's attempts to see if they can get away with taking less or no treatment at all (e.g., “To see if I really need it”); (3) Drug-Specific Concerns, such as the side effects and becoming dependent on the medicine (e.g.,

“Because I don’t like the side effects”); and (4) General Sensitivity to Medicines, which consist of a set of beliefs about how they are personally affected by medicine and need to control the medicine intake to minimize harm (e.g., “To give my body a rest from the medicine” and “I don’t like medicines accumulating in my body”). All items and the subscales are shown in Figure 8. Scores on the total Intentional Non-Adherence Scale range from 22 to 110 with higher scores indicating more motives for intentional nonadherence behaviour. Each of these subscales shows acceptable internal consistency with Cronbach’s alpha ranging from 0.91-0.93 in the current sample and the INAS total was 0.95.

Statistical Analysis

All statistical analyses were performed using SPSS version 25.0 (IBM Crop.). Medians with ranges and percentages were used to describe the clinical characteristics of participants. As the INAS scores were not normally distributed, Mann-Whitney U tests were conducted to investigate differences in INAS scores for participants categorised as adherent versus non-adherent on the basis of being at SU target. Spearman's correlations were also used to describe the associations between variables. All tests were 2-tailed and a significance level of .05 was used to determine significance for all analyses.

Results

Characteristics of the study population

A total of 69 men with gout with an average age of 63.5 years were included in the study. Most patients were NZ European (66%), married (67%) with university education (67%). On average, the participants had been taking allopurinol for eight years (Table 6). Using the SU level criterion for treatment adherence, 46 patients were classified as adherent and 23 as nonadherent.

Table 6. *Characteristics of the study population*

Patients' Characteristics	n	%	Patients' Characteristics	n	%
Age (mean ± SD years)	63.5 ± 14.2		Marital Status		
Gender			Single	5	7.2
Male	69	100	Divorced/Widow	6	8.6
Female	0	0	Permanently separated	5	7.2
Level of Education			Married	46	66.6
Primary School	2	2.9	In a de facto relationship	7	10.1
Secondary School	21	30.4	Employment Status		
Tertiary	35	50.7	Full-time	20	28.9
Post-graduate	11	15.9	Part-time	4	5.7
Ethnicity			Retired	24	34.8
NZ European	45	65.5	Self-employed	15	21.7
Māori	3	4.3	Student	2	2.8
Pacific	9	13.4	Beneficiary	4	5.7
Chinese	4	5.8	Allopurinol treatment duration		
Other	8	11.5	(mean ± SD years)	7.6 ± 5.3	

Note. Values are the number and percentage unless otherwise indicated.

Reasons behind non-adherence

To look at the main reasons gout participants gave for not taking their medicine, we ranked each INAS item by the percentage of patients agreeing (agree, strongly agree) with each statement, and these are shown in Figure 9. The graph indicates that the top 4 reasons why patients with gout do not take their allopurinol are made of 2 *Resisting Illness* items including “because I want to lead a normal life again” (23%) and “because I want to think of myself as a healthy person again” (20%), and 2 *Testing Treatment* items including “to see if I really need it” (22%) and “to see if I can do without it” (22%). The next 3 items were *Drug-Specific Concerns*: “because I don’t like the side effects” (17%), “because I am worried about becoming dependent on my medicine” (16%) and “because I think the drug might become less effective over time” (16%). The *Medicine Sensitivity* items formed most of the middle-ranked items such as “because the medicine is harsh on my body” (13%). Other drug-specific concerns made up the less endorsed items, such as “because I think I am on too high dose” (6%) and “because I don’t think the treatment is worth it” (1%).

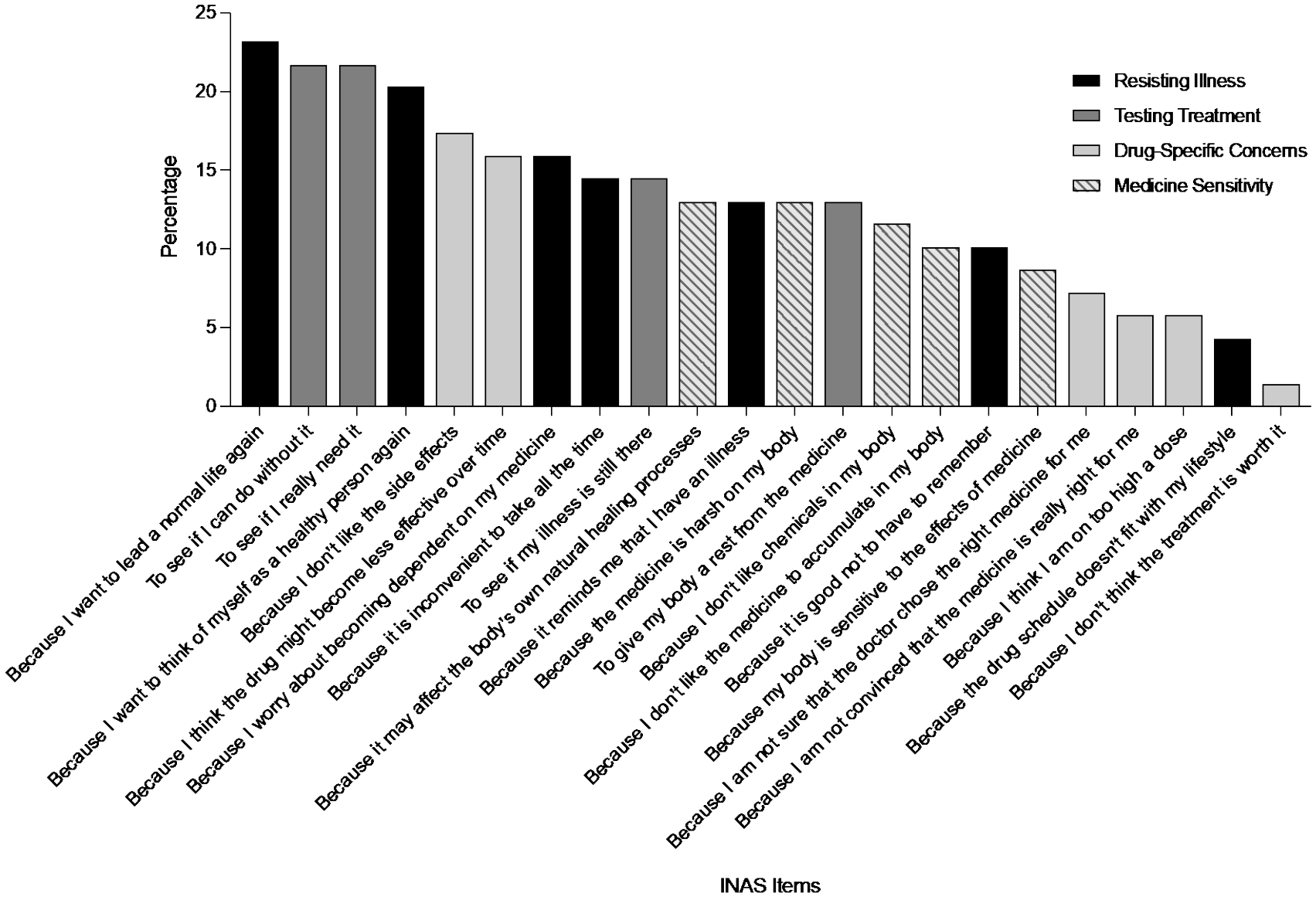

Figure 8. *Percentage of respondents agreeing or strongly agreeing with INAS items about why they did not take their allopurinol. INAS: Intentional Non-Adherence Scale.*

Differences between participants with and without serum urate at target

Next, we looked at the differences on overall INAS scores and INAS subscales according to SU target. We found that, as expected, respondents who did not achieve target SU had significantly higher total INAS scores, as well as significantly higher INAS *Testing Treatment* and INAS *Drug-Specific Concerns* scores (Table 7).

Table 7. *INAS total and INAS subscales' scores for those with and without serum urate at target (<0.36mmol/L, 6mg/dL)*

Variable	SU at target (n = 46)	SU above target (n = 23)	*U*	*P*
INAS – Total	44 (29-49)	48 (43-69)	358	**.03**
INAS – Resisting Illness	14 (10-15)	16 (13-21)	394	.08
INAS – Testing Treatment	8 (4-9)	10 (8-12)	364	**.03**
INAS – Drug Specific Concerns	12 (8-12)	14 (11-17)	353	**.02**
INAS – Medicine Sensitivity	10 (7-11)	10 (9-15)	384	.06

Note. Bold indicates significance at p< .05 level. INAS: Intentional Non-Adherence Scale. SU: Serum urate.

Associations between INAS scores and demographic features

The third aim was to explore any demographic differences in terms of INAS scores. The data showed that age was significantly correlated with the INAS *Testing Treatment* subscale, indicating that younger patients were more likely to test their treatment and see if they can get away with taking less or no treatment (r_s = -0.27, *P* =.02). However, there were no significant correlations between age and the INAS total score (r_s = -0.20, *P* =.10) or the other INAS subscales. There were also no significant correlations between time on allopurinol and the total INAS score or any of the INAS subscales. NZ Europeans had significantly lower total INAS scores and all four subscale scores than non-NZ European ethnicities. We found that single participants had significantly higher total INAS scores, and INAS *Testing Treatment* subscale scores compared to those reporting other relationship status (Table 8). Education or employment status showed no effects for the total INAS score or INAS subscales.

Table 8. *Differences between INAS total and INAS subscales in demographic subsamples*

Variable	NZ European (n = 45)	Other Ethnicities (n = 24)	*U*	*P*	In Relationship (n = 53)	Single (n = 16)	*U*	*P*
INAS – Total	44 (40-47)	54 (42-67)	362	**.02**	44 (43-48)	58 (43-71)	280	**.04**
INAS – Resisting Illness	14 (11-14)	17 (13-22)	374	**.03**	14 (13-14)	18 (13-22)	395	.06
INAS – Testing Treatment	8 (7-8)	12 (7-13)	357	**.02**	8 (6-9)	12 (9-15)	326	**.004**
INAS – Drug Specific Concerns	12 (9-12)	14 (11-18)	374	**.03**	12 (10-12)	14.00 (10-17)	322	.14
INAS – Medicine Sensitivity	10 (9-10)	12 (9-15)	375	**.04**	10 (9-11)	12.00 (9-15)	321	.14

Note. Bold indicates significance at p< .05 level. INAS: Intentional Nonadherence.

Discussion

The INAS allowed us to investigate in more detail the reasons from the patients' perspective that lie behind not taking their urate lowering medication. Looking at the items with the highest level of endorsement suggests that the major reasons behind the decision not to take allopurinol relate to wanting to lead a normal life and patients wishing to think of themselves as healthy again. Another important motivation is the strategy of testing treatment. Here, nonadherence represents a deliberate effort to see if the patient can get away with taking less or none of their allopurinol medication without their painful symptoms returning. Two drug-specific concerns, side effects and the belief that allopurinol might become less effective over time, were the next frequently endorsed items. As expected, the INAS scores differed significantly between those who did and did not achieve target SU, with those not at target endorsing more INAS items. Those not at target also scored significantly higher in INAS *Testing Treatment* and INAS *Drug-Specific Concerns* subscales. The INAS scores were also higher patients who were younger, of non-NZ European ethnicities, and not in a current relationship.

The results demonstrate the importance of the patients' view of their illness and treatment in the long-term management of gout (Serlachius et al., 2017; Dalbeth et al., 2011). Intentional nonadherence generally decreased with age and the strategy of testing treatment was more common in younger age groups, where the disease diagnosis may not fit comfortably with the common illness model of gout being typically that of older men. Development of gout later in life is more normative and has been shown to be less stigmatising at an older age (Kleinstäuber et al., 2020). This mismatch between illness perception and treatment can make the patient feel uncertain about the diagnosis and taking long-term urate lowering treatment (Petrie et al., 2018). Previous studies in other illnesses show that illness beliefs can be modifiable by targeted interventions, and this can lead to improved illness outcomes (Petrie & Weinman, 2012; Petrie et al., 2012; Petrie et al., 2002).

Our results provide some indications to clinicians about how ULT may be framed for patients in order to improve adherence. The data from this study suggest that framing ULT as a way of correcting an unhealthy imbalance that will allow a return to normal activity and lifestyle may be a useful strategy when initiating treatment. Further, an early discussion about the drawbacks of testing treatment by reducing medication or the problem of basing medication-taking on symptoms rather than SU level may also be helpful. Additionally, when patients have doubts about effectiveness and

worries about their prescribed medication, they may become nonadherent when the perceived risk of taking medication outweighs its perceived benefits over time (Singh, 2014). Therefore, it may be beneficial to correct the concern that allopurinol will become less effective over time.

The study has a number of strengths including the use of a new measure that allowed a closer examination of the reasons behind patients' non-adherence with allopurinol and the use of an objective marker of adherence. Whereas previous work on nonadherence has concentrated on demographic and clinical factors associated with it (Scheepers et al., 2018a; Briesacher et al., 2008; De Vera et al., 2014; Scheepers et al., 2018b), the current study focus is on psychological factors that could be potentially modifiable in an intervention. However, the study sample size was modest and consisted only of men who were recruited from a hospital clinic; these may limit generalisability and should be considered when interpreting findings. While there is a strong relationship between allopurinol adherence and achieving target SU levels, it should be acknowledged that there may be reasons for low levels other than nonadherence, such as inadequate dosage (Stamp et al., 2014). Although self-report, pill counts, and interviews typically provide other measures of nonadherence in gout (Rashid et al., 2015), SU level does have the advantage of assessing a widely recommended clinical outcome.

The patients in the study were also more adherent than the nonadherence rates identified in previous research (Scheepers et al., 2018a; Briesacher et al., 2008; De Vera et al., 2014; Scheepers et al., 2018b). This may be due to nonadherent patients being less likely to participate in such research or a Hawthorne effect in reaction to participation in the study. Nonadherent patients may include both patients who do not fill a prescription and those who collect allopurinol but do not take it regularly. It should also be noted that SU levels not reaching target could be due to inadequate dosing as well as patient nonadherence (Yin et al., 2018). This possibility should be addressed in future research with the INAS. It would be also valuable to examine the relationship between intentional nonadherence and other clinical data, such as comorbidities, the presence of tophi, and the prescription of other medications.

In conclusion, our study highlights a potentially effective new approach to decrease ULT nonadherence, which is a prevalent problem for long-term management of gout. Examining the motivations that patients provide for not taking their medication has identified some potential targets for interventions in patients with gout who are finding it difficult to adhere to ULT. These include

reframing the treatment as a way of returning to feeling normal again and identifying for patients the potential difficulties of using symptoms as a way of testing the dose of ULT (Doherty et al., 2018). Further research is needed to turn these insights into workable and scalable interventions that could provide improvements in reducing nonadherence.

Chapter Five

Evaluating Patient Online Gout Resources on Adherence

Preface

In the era of abundant digital information, patients increasingly turn to online educational resources to better understand their medical conditions and treatment options (Bussey & Sillence, 2019). As discussed in Chapter Two, patients who take an active role in their healthcare tend to seek more information about their prescribed medications and their illness. Recognising the importance of online educational resources in facilitating decision-making processes, we conducted a content analysis to explore how adherence to urate lowering medications, including allopurinol, are discussed in online gout resources.

The significance of this analysis becomes apparent when we consider several factors. First, patients' engagement with online health information is at an all-time high, with many actively seeking knowledge to make informed decisions about their healthcare (Sun et al., 2022). Second, online educational resources vary widely in terms of quality, accuracy, and depth of information. Some websites offer comprehensive insights into medication adherence, while others provide only surface-level guidance (Thapa et al., 2021).

Moreover, tailored provision of information emerges as a critical determinant of improved patient outcomes in disease management. Patients significantly benefit when they receive information tailored to address their specific needs and concerns (Ramsubeik et al., 2018). This section aims to provide a clearer overview of what information is available to individuals with gout, shedding light on the current state of online educational resources about adherence, pinpointing gaps, and areas for improvement.

To date, the exploration of this topic has been relatively limited, leaving a significant gap in our understanding of how online gout educational resources address medication adherence. The following manuscript describes an evaluation of online gout educational resources in six English-speaking countries, aiming to understand how medication adherence is addressed. This study assesses the readability of adherence materials and quantifies how much text is dedicated to medication adherence. Through a cross-country content analysis, this study investigates the frequency of adherence discussions and the specific motives of nonadherence to urate lowering

medications addressed in online gout educational resources (Emad et al., 2023b). To analyse the content found in these resources regarding the targeted reasons for nonadherence, the Intentional Non-Adherence Scale (INAS) was used as a guiding framework for the coding process, as discussed in Chapter Four. This allowed the study to systematically examine and categorise the information available in these resources, providing a structured approach to current analysis. This study also examines the information available to help patients adhere to their gout medication. The following manuscript describes the results from this study.

The aim of this work is to identify gaps in existing online gout educational resources on medication adherence. The findings have the potential to benefit healthcare providers, content creators, and individuals with gout, underscoring the importance of addressing intentional nonadherence and developing strategies that target the main motives behind this behaviour. This research takes a significant step toward bridging the knowledge-action gap, facilitating more effective support for those navigating the complexities of gout management.

Abstract

Objective. This study aimed to investigate how medication adherence is addressed in online gout educational resources in six countries. We investigated how often adherence was referred to, the strategies suggested to improve patient adherence, and the types of nonadherence that were targeted. We also examined the readability of the adherence material. **Methods.** A content analysis was conducted on 151 online gout resources from medical and health organisations in six English-speaking countries. Two reviewers coded the content of the websites into categories (kappa 0.80). The analysis involved coding the resources for reasons for nonadherence, and adherence-promoting strategies. Flesch-Kincaid Reading Ease scores and word count were also computed. **Results.** Out of 151 websites examined, 77 websites discussed medication adherence (51%), with intentional nonadherence being more prevalent than unintentional nonadherence. 67 websites targeted different types of nonadherence, included drug-specific concerns (50%), misconceptions of gout curability and the necessity of medication (16%), forgetfulness (16%), and other practical challenges (5%). Strategies to promote adherence were found in one-third of the websites, with medication education being the most prevalent strategy (17%), followed by healthcare provider engagement (13%) and memory aid strategies (6%). On average, about 11% of the words (89.27, *SD* = 76.35) in the entire document were focused on adherence. Difficult reading comprehension was found in one-fifth of adherence-related websites. **Conclusion.** Findings reveal limited medication adherence coverage and narrow strategies in online gout educational resources. Improved adherence portrayal is needed for effective gout management through comprehensive strategies and clear, understandable information.

Introduction

Low adherence to urate lowering therapy (ULT) represents a major clinical issue in the management of gout. Recent systematic reviews have shown that continuation rates for ULT are low (Scheepers et al., 2018) with a steady number of patients discontinuing treatment after their initial prescription and less than half of people with gout still taking their urate-lowering medication regimen at 12 months (Yin et al., 2018; De Vera et al., 2014).

Nonadherence can be classified into two categories: unintentional and intentional. Intentional nonadherence describes the process by which patients decide not to take their medication based on specific beliefs and perceptions about their condition or treatment (Weinman et al., 2018). For instance, some people with gout may choose not to adhere to their medication regimen out of concerns about experiencing adverse side effects. On the other hand, unintentional nonadherence is not a deliberate act of omission, but rather an unplanned behaviour, such as forgetting to take the medication, challenges in obtaining medication refills, or encountering logistical barriers like travel or disrupted routines (Elliot, 2009).

Intentional nonadherence poses a significant challenge in effectively managing gout, as it hinders the optimal utilisation of urate-lowering therapy and undermines its potential benefits. Recent studies have identified four main reasons behind intentional nonadherence to ULT. The first is r*esisting illness*, which is the desire to feel healthy and maintain a sense of normalcy, and not to be reminded of the fact that the patient has gout. Secondly, *testing treatment*, which is the patient testing the limits of treatment by taking the least amount possible to avoid gout attacks, Thirdly, *drug-related concerns*, these include worries about the side effects from the medication, concern that the ULT will lose effectiveness over time, and anxiety about developing drug dependency. Fourthly, *medicine sensitivity* which refers to the patient feeling highly sensitive to the effects of ULT (Emad et al., 2022).

Recent studies have emphasised the significance of online health information seeking as a potential factor that can impact adherence to prescribed medications (Lim et al., 2022). The way in which people with gout consume online health information can shape their beliefs surrounding their condition and medication use (Jordan et al., 2019), ultimately impacting their behaviour and level of adherence to prescribed medications (Spragg et al., 2023). Previous studies show that the majority of patients with gout tend to seek online health information about their condition and medications (Li et al., 2022; Rai et al., 2018). However, the readability and comprehensibility of online gout educational

resources have remained fairly understudied. Readability, which encompasses factors such as sentence structure and vocabulary, plays an important role in patient understanding and engagement (Oktay et al., 2021). Poor readability can create barriers to patients' ability to comprehend and follow the recommended adherence strategies (Jimenez-Liñan et al., 2017).

To date, while limited studies have explored the topic, a comprehensive examination of how adherence is framed and discussed in online gout educational resources remains lacking. Our study aimed to fill this gap by investigating how medication adherence is addressed in online gout educational resources, including how often it is mentioned, the types of nonadherence that are targeted, the strategies used to promote adherence and the readability of the provided information. The findings may help identify the gaps in online patient education around adherence behaviour, and provide a clearer picture of what is needed to help patients adhere to their ULT.

Method

Data sources

The resources were identified using a Google search in an "incognito window" to avoid personalization of search results based on the computer's browsing history. The keywords "gout", "gout arthritis", "gout treatment", "gout medication", "pills for gout", "gout drugs", "allopurinol", "febuxostat", "probenecid", and "benzbromarone" were used to perform a separate search for each of the Google domains using the Google advanced search tool. The first 50 search outcomes in each country were reviewed to identify resources from medical and health organisations and collated for further analysis.

Selection of websites

Information from patient resources for gout was analysed from medical and health organisations, including the World Health Organisation (WHO), the Food and Drug Administration (FDA), health governing agencies [including Ministry of Health and Primary Health Organisations (PHOs)], health and disability non-profit non-governmental organisations (NGOs), National Institutes of Health, health organisations funded by or affiliated to health governing agencies, medical and pharmacological associations, hospitals, universities, and academic institutions.

Inclusion and exclusion criteria

All included resources provided information on gout and adherence to urate lowering medications, aimed at people with gout and the public, dated from 2018 onwards, and were accessible online in six

English-speaking countries encompassing Australia, Canada, Ireland, New Zealand, South Africa, the United States, and the United Kingdom. These countries were selected based on previous research that assessed texts in educational materials about gout (Krasnoryadtseva et al., 2020).

Resources were excluded from the content analysis if they only consisted as published articles, e-books, book chapters, interviews, or reports, or needed to be downloaded as doc, docx and pdf document. Other types of resources excluded included PowerPoint slides aimed at health professionals and those that included no information about gout or medication adherence for gout (e.g., provided insurance advice for patients). Material that required a paid subscription or creating an account or did not come from a medical/health organisation were also excluded.

Content analysis

A sample of websites was initially reviewed by two reviewers (YE, CD), and nine categories were agreed upon. Both reviewers (YE and CD) then coded the content of all websites into intentional nonadherence categories. Kappa (SE) was calculated to assess the level of agreement between the two reviewers, and the calculated value was 0.80 (0.03), indicating substantial agreement between the reviewers regarding their assessments of the materials based on the established codes for promoting adherence strategies and the targeted reasons for nonadherence. A total of 151 cases were included in the analysis, and the observed agreement between the reviewers in their assessments of the adherence promotion strategies and nonadherence reasons was 0.93. Any discrepancies in coding were resolved through review by a third author (KP). The analysis involved calculating the frequency and percentage of reasons for nonadherence and the strategies employed to promote adherence within the categories. To facilitate organisation and interpretation of the data, relevant nonadherence categories were further divided into subcategories.

Website material was initially categorised by two reviewers into intentional and unintentional adherence. Unintentional adherence material addressed reasons, such as forgetfulness or physical inaccessibility, while intentional material focused on nonadherence reasons identified in previous studies, such as drug-specific concerns or medication-taking causing disruption of normal life. The reviewers then coded the content of all websites into nine nonadherence categories, including perceived disruption of normal life (e.g. if you do not keep your serum urate under control, you may not be able to do something as simple as accompany your kids to the school bus stop or walk your dog), inconvenience with medication administration (e.g. not easy to take med all the time),

misconception of gout curability and medication necessity (e.g. gout cannot be cured, you need to take your medication lifelong; you need to take your medication everyday), perceived lack of need when feeling well or without active symptoms/attacks (e.g. you need to keep taking allopurinol even when you have no active symptoms or no gout attacks), delayed efficacy awareness (e.g. it will take a while to see the benefits of your medication; Allopurinol takes 2 to 3 months to become fully effective), flare-driven nonadherence (e.g. experiencing flare-ups after initiating allopurinol), side effects, nonadherence due to concern about being on the wrong dose, and concerns about medication dependency.

A Flesch-Kincaid Reading Ease score was calculated for the adherence-related text using a web-based readability measurement tool at https://readability-score.com. This score indicates what level of education is typically needed to comprehend a piece of writing. In addition, we quantified the word count of the adherence-related content, using Notepad.

Ethical statement

Ethical approval was not required for this study, as it involved the analysis of publicly available data, in accordance with the policy of the University of Auckland Human Participants Ethics Committee. The content used in this research was obtained from the public domain, and therefore, individual consent or consent from websites was not obtained.

Results

The analysis of online gout resources involved an initial search that yielded a total of 270 websites. After excluding irrelevant or duplicate websites, 151 websites met the inclusion criteria and were included in the analysis.

Frequency and types of nonadherence

Our first objective was to explore how often medication adherence was discussed in online gout resources. Among the 151 websites, we found 77 websites mentioned adherence to urate-lowering medication (50.9%). 67 websites (44.3%) specifically targeted different types of nonadherence and examined the potential reasons associated with this behaviour.

Out of the 151 websites, intentional nonadherence was reported in 66 sites (43.7%), while unintentional nonadherence was mentioned in 30 sites (19.8%).

Targeted reasons for nonadherence

Next, we conducted an analysis of 67 websites focusing on adherence to urate lowering medications to explore the specific reasons targeted when discussing nonadherence. The identified reasons were then categorised into four main categories. Firstly, Drug-Specific Concerns emerged as the primary contributing factor, encompassing half of the identified reasons. This category included nonadherence due to experiencing flare-ups after initiating treatment, medication delayed effectiveness, side effects, concerns about being on the wrong dose, and anxiety about developing drug dependency. Secondly, misconceptions of gout curability and medication necessity were identified in 24 websites (15.8%). This category encompassed perceived lack of need when feeling well or without active symptoms/attacks and misconception of gout curability. Thirdly, forgetfulness was targeted as a reason for nonadherence in 24 websites (15.8%). Lastly, other factors were targeted in 7 websites accounting for 4.6% of the identified reasons, including difficulties accessing medication, perceived disruption of normal life, and inconvenience with medication administration. All of the figures are out of 151 (Table 9).

Table 9. *Proportion of targeted reasons for nonadherence used among websites included in the study (n = 151)*

Targeted reasons for nonadherence	*n (%)*
Drug-Specific Concerns	76 (50.33)
Flare-driven nonadherence (e.g., you may experience flare-ups after initiating allopurinol)	41 (27.15)
Delayed efficacy awareness (e.g., it will take a while to see the benefits of your medication; Allopurinol takes 2 to 3 months to become fully effective)	19 (12.58)
Side effects	10 (6.62)
Nonadherence due to concern about being on the wrong dose	5 (3.31)
Concerns about medication dependency	1 (0.66)
Misconception of gout curability and medication necessity	24 (15.89)
Perceived lack of need when feeling well or without active symptoms/attacks (e.g., you need to keep taking allopurinol even when you have no active symptoms or no gout attacks)	17 (11.25)
Misconception of gout curability (e.g., gout cannot be cured, you need to take your medication lifelong)	7 (4.63)
Forgetfulness	24 (15.89)
Other	7 (4.63)
Inconvenience with medication administration (e.g., it is not easy to take medicine all the time)	4 (2.64)
Perceived disruption of normal life (e.g., if you do not keep your serum urate under control, you may not be able to do something as simple as accompany your kids to the school bus stop or walk your dog)	2 (1.32)
Difficulty accessing medication	1 (0.66)

Note. The percentages reflect the proportion of websites targeting each reason individually, but not collectively. Since some websites targeted multiple reasons, the sum of percentages may exceed 100%.

Adherence-promoting strategies

We also identified and categorised strategies utilised in the online gout resources to facilitate adherence. A comprehensive analysis was conducted on the 45 websites that discussed one or more adherence-promoting strategies. Through this analysis, we identified and categorised the following strategies. Firstly, providing medication education was prominently featured in the analysed websites, accounting for almost two thirds of the strategies (60% or 27). The most prevalent medication education strategy involved explaining the mechanism of action and highlighting the benefits of the prescribed medication, constituting 53% of the identified approaches (or 24 websites). Strategies emphasising the consequences of medication nonadherence, such as joint damage and kidney stones, were also featured, accounting for almost 7% of the identified approaches (or 3 websites). Secondly, healthcare provider engagement was emphasised by 42% of the analysed websites (or 19 websites), such as advice to contact healthcare providers for support and guidance on medication adherence. Thirdly, memory aid strategies were found to be employed by approximately one fifth of the analysed websites (or 9 websites). These strategies included establishing a daily medication routine, providing recommendations for optimal medication administration, enhancing medication accessibility and visibility (4% or 2), utilising reminders or alarms, and using a pill box. Lastly, additional strategies to promote adherence included getting regular blood checks, making a treatment or emergency plan, reading medication label instructions, contacting available patient helplines, and following instructions by healthcare providers. All of the figures are out of 45 (Table 10).

Table 10. *Proportion of strategies used among websites included in the study (n = 151)*

Adherence-promoting strategies	*n (%)*
Providing Medication Education	27 (17.88)
Educational emphasis on medication nonadherence symptom consequences	3 (1.98)
Explaining medication mechanism of action and benefit	24 (15.89)
Healthcare provider engagement	
Contacting the healthcare provider	19 (12.58)
Memory Aid Strategies	9 (5.96)
Using a pill box	1 (0.66)
Reminder/Alarm utilisation	2 (1.32)
Improving medication accessibility	2 (1.32)
Optimal medication administration	4 (2.64)
Establishing a daily medication routine	11 (7.28)
Other	8 (5.29)
Contacting Healthline	1 (0.66)
Following given instructions	1 (0.66)
Reading medication label instructions	2 (1.32)
Making a treatment or emergency plan	2 (1.32)
Regular blood check	4 (2.64)

Note. The percentages reflect the proportion of websites that employed each strategy individually, but not collectively. Since some websites utilised multiple strategies, the sum of percentages may exceed 100%.

Content readability

Lastly, we conducted an assessment of content readability and word count for adherence-related information in online gout resources. Our findings revealed wide variations in the readability and comprehensiveness of the content, as evaluated using the Flesch-Kincaid Reading Ease scores. The analysis showed that the majority of content in adherence text fell within the "very easy" to "moderately easy" range (79.2% or 61 websites). However, approximately one fifth of sections (or 16 websites) were categorised as "difficult", “moderately difficult”, and "very difficult" (Figure 9). This suggests that certain website content may pose challenges for readers, potentially hindering their understanding and engagement with the information. All the figures are out of 77.

In addition to the Flesch-Kincaid Reading Ease scores, the average word count across the analysed sections was 89.27 (*SD* = 76.35; *Range* = 401-11), constituting approximately 11.1% of the mean word count of the evaluated content (*M* (*SD*) = 804 (392.6); *Range* = 2140-156). This indicates that the sections are relatively concise, presenting a moderate amount of information.

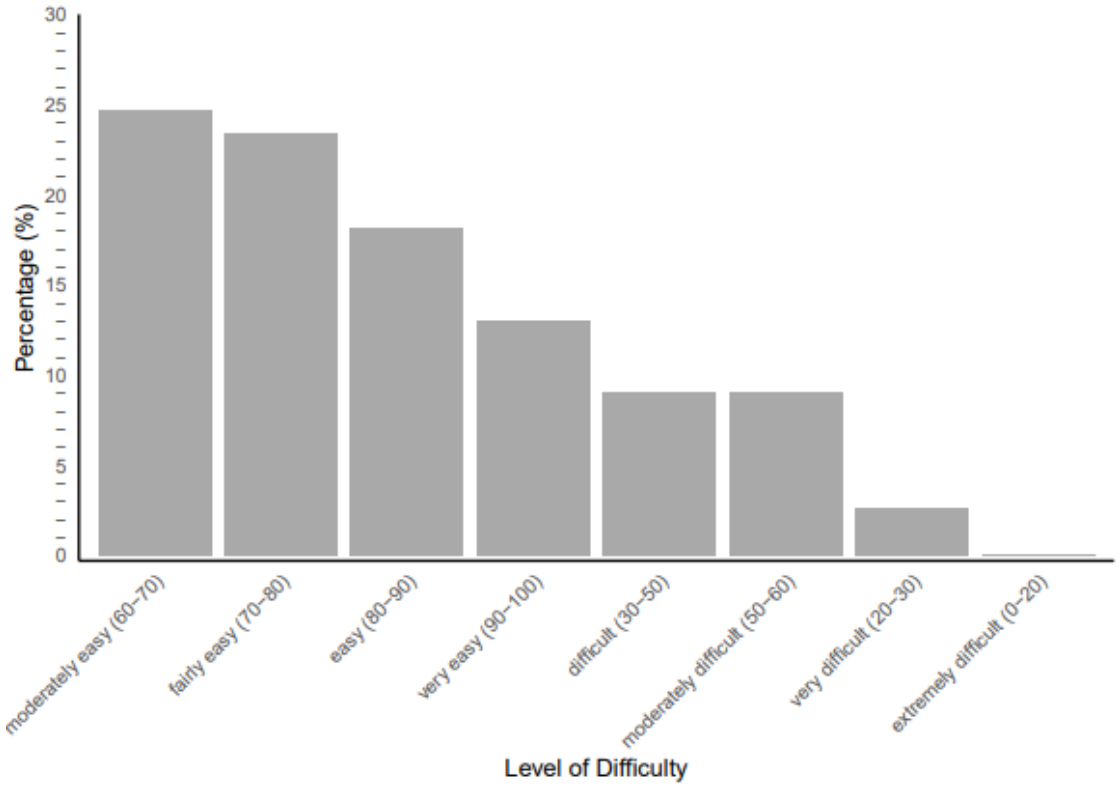

Figure 9. *Flesch-Kincaid Reading Ease scoring for websites included in the study (n = 151).*

Discussion

To our knowledge, this study represents the first comprehensive analysis of online gout educational resources with a specific focus on nonadherence to urate lowering medications. Contrary to the existing literature emphasising the pivotal role of adherence in optimising gout management (Perez-Ruiz & Desideri, 2018), our study found that only half of the websites mentioned medication adherence, highlighting a significant gap in online educational resources for patients. Even when mentioned, only a limited attention was given to adherence as proportion of word count in this study indicated. Our analysis further revealed that online gout educational resources predominantly targeted intentional nonadherence, with less attention given to unintentional barriers. This focus signifies a growing recognition of intentional nonadherence as a major cause of non-adherent behaviour in gout, as it is in other chronic illnesses (Emad et al., 2022).

In this study, we examined the focus of online material about gout nonadherence. Aligning with research about the causes of nonadherence (Kvarnström et al., 2021; Robinson & Schumacher, 2013), drug-specific concerns emerged as a prominent category of the material for patients, encompassing a significant proportion of identified factors. Within this category, experiencing flare-ups after initiating medication and perceiving delayed efficacy were commonly discussed, recognising that patients may modify or discontinue their medication during flares, possibly perceiving it as ineffective (Aung et al., 2017; Becker et al., 2005).

The necessity of ongoing medication even in the absence of symptoms was another important focus in websites discussing nonadherence. These findings are in line with previous studies, emphasising the importance of patient education on the chronic nature of gout and the importance of consistent adherence to prevent future attacks and long-term complications (Fields & Batterman, 2018). By fostering a comprehensive understanding of gout as a chronic condition and elucidating the benefits of sustained medication use, websites can foster informed decision making among patients and promote a long-term commitment to therapy (Te Kampe et al., 2022; Ofanoa et al., 2023).

The analysis of websites also highlighted important gaps in online patient resources on adherence to urate-lowering medication. Previous work has identified that many patients do not adhere to urate lowering medication out of a desire to feel healthy and maintain a sense of normalcy (Emad et al., 2022). Framing ULT as a way of maintaining normal functioning and activity without the

interruption of gout attacks may be an important way to address these patient concerns. Another important reason for patient nonadherence is a deliberate strategy to test their treatment and see if they can get away with less or no treatment. This aspect is rarely addressed in the current material on nonadherence to gout medications and could be a focus of increased attention.

Unintentional factors could also receive more consideration in website material. Studies suggest forgetfulness is a challenge faced by many people with gout in adhering to medication regimens (Spragg et al., 2023; Rai et al., 2018). However, our analysis reveals that memory aid strategies were only discussed in roughly one-fifth of websites despite their demonstrated effectiveness in promoting medication adherence (Hargis & Caste, 2018). Other strategies such the use of visible location of the medication, coordinating medicine-taking with the patient's daily routine and the development of "if-then" plans and utilising social support could be usefully incorporated into the website materials to address common unintentional causes of nonadherence (Molloy & O'Carroll, 2017; Gellad et al., 2009; Osterberg & Blaschke, 2005).

This study also aimed at examining the content readability of online gout resources to provide primarily insights into the accessibility and comprehensiveness of the information presented. Our data revealed a range of readability levels, about a fifth of websites containing material that was classified as "difficult" or "very difficult." This indicates that some parts of the online resources may pose comprehension challenges for readers, hindering their engagement and understanding of the information (Jimenez-Liñan et al., 2017).

Several limitations of the research should be acknowledged. Firstly, our analysis was restricted to English-speaking countries and so may not be generalisable to patient websites presented in other languages. Secondly, there are currently no guidelines for what types of material on nonadherence should be covered in patient websites, which perhaps explains some of the variability in material. Given the large numbers of patients that access material about their illness and medications online, this should be the focus of future work. Thirdly while the study looked at how easy the website material was to read; readability scores alone cannot serve as an indicator of the quality or comprehensiveness of the information provided. Finally, our analysis primarily focused on the type of information available on the websites, without assessing the accuracy or scientific rigour of the content.

In conclusion, this study presented a comprehensive content analysis of online gout educational resources, with a specific emphasis on intentional nonadherence to urate lowering medications. The study showed that around half of websites providing patient information on gout did not cover adherence or provide any strategies to help patients keep to their medication regimen. The findings also identified the need to include more content that addresses common patients' beliefs and perceptions related to their urate lowering medication, which often drives intentional nonadherence behaviour. Websites could also be improved with greater attention to unintentional factors such as forgetting and through improving readability to help patients with lower health literacy.

Chapter Six

Targeting Intentional Nonadherence Motives using Smartphone Notifications

Preface

As discussed in Chapter Two, various interventions have been developed to improve medication adherence, ranging from educational approaches to behavioural strategies. However, despite the diversity of these interventions, a notable gap exists in our knowledge regarding the use of technology to enhance adherence to urate lowering medications, specifically allopurinol, in individuals with gout.

In Chapter Four, we investigated the key reasons behind intentional nonadherence to allopurinol in people with gout. Understanding these motives offers a more comprehensive view of the relationship between medication beliefs and actual medication-taking behaviour. It suggests that targeting these motives with tailored interventions could be effective in improving medication adherence (Van Lierde et al., 2022).

Mobile Health (mHealth) encompasses the utilisation of mobile phones and other wireless technology in medical care (WHO, 2011). The smartphone stands out as the most prevalent and appealing device in mHealth with more than 83% of the global population owning a smartphone (Taylor, 2023). mHealth apps provide a novel and convenient avenue for delivering personalised and tailored interventions (Lee, 2016). Recent years have seen the emergence of smartphone-based interventions as a promising strategy to enhance medication adherence, with previous studies demonstrating their potential in promoting behaviour change and improving treatment outcomes (Peng et al., 2020; Xiong et al., 2018; Petrie et al., 2012). However, empirical evidence is crucial to determine whether smartphone notifications can indeed enhance medication adherence and health outcomes in people with gout.

To date, no study has explored the potential of smartphone notifications in addressing the main motives behind intentional nonadherence to urate lowering medications, specifically allopurinol. To address this gap, the following manuscript describes a feasibility study to evaluate the practicality of using smartphone notifications to improve medication adherence in people with gout. This study aimed not only to assess the feasibility of this intervention but also to investigate its potential in improving medication adherence among individuals managing gout with allopurinol. This study also

used the Technology Acceptance Model (AlQudah et al., 2021) to assess the acceptability of this intervention (Emad et al., in press).

Presented work in the following manuscript aimed to evaluate the effectiveness of smartphone notifications in addressing common reasons for medication non-adherence among individuals with gout. Specifically, tailored smartphone notifications were implemented to assess their acceptability and impact on improving medication adherence.

Abstract

Objective. This feasibility study aimed to assess the acceptability of smartphone notifications to modify gout patients' beliefs about their medications. We evaluated the feasibility and acceptability of the intervention using the Technology Acceptance Model. We explored adherence rate differences and outcomes between the intervention and control groups. **Methods.** 52 gout patients prescribed allopurinol were randomly assigned to the active control (n = 24) or intervention group (n = 28). Over 3 months, both groups used a study application on their smartphones. The control group received notifications about general health advice, while the intervention group received tailored notifications targeting nonadherence. The feasibility and acceptability of the smartphone application was measured through semi-structured interviews. Adherence rate was assessed through serum urate levels and missed doses at three distinct time points: baseline, 3 months (post-intervention), and 6 months (follow-up). **Results.** The intervention demonstrated high feasibility with strong participant retention and compliance. The participants expressed high levels of satisfaction with the application's user-friendliness and content, highlighting its acceptability. Both groups showed a significant reduction in missed doses over time, but no significant differences in serum urate levels were found between the groups. Patients who received adherence-targeted notifications reported finding it more convenient to take allopurinol (P = .001) and expressed higher overall treatment satisfaction throughout the study (P = .033). **Conclusion.** Smartphone-based interventions that target motives of intentional nonadherence have the potential to be an effective and scalable approach to supporting medication adherence in gout patients. Further research is needed with larger samples to refine the components of the intervention and explore its optimal implementation.

Introduction

Intentional nonadherence, which involves the conscious decision of patients to not follow their prescribed medication regimen, poses a critical challenge in the management of chronic conditions (Huyard et al., 2017). Intentional nonadherence extends across the three stages of adherence: initiation and implementation (period of persistence), followed by discontinuation (period of non-persistence) (De Geest et al., 2018; Spragg et al., 2023). Understanding the complex nature of intentional nonadherence is crucial for developing effective interventions. In this regard, Weinman et al. (2018) introduced the Intentional Non-Adherence Scale (INAS), a valuable tool that provides a comprehensive framework for measuring intentional nonadherence and gaining insights into patients' decision-making processes (Weinman et al., 2018).

Gout management is particularly affected by intentional nonadherence to urate-lowering therapy (ULT), leading to significant limitations in the therapy's effectiveness (Toprover & Pillinger, 2021). Intentional non-adherence not only compromises patients' health and quality of life but also underscores the need to address and modify patients' beliefs and perceptions regarding medication (Kong et al., 2019). Emad et al. (2022) conducted a study utilising the Intentional Non-Adherence Scale (INAS) and identified four key factors contributing to intentional nonadherence in ULT for gout. These factors include (1) the desire to avoid reminders of the condition and resist the illness to maintain a sense of normalcy (2) the inclination to test the limits of treatment effectiveness in terms of using as little medication as possible (3) concerns regarding medication, such as potential side effects and the risk of dependency, and (4) the perceived sensitivity to medication affecting the body's natural healing processes. These findings shed light on the multifaceted nature of intentional nonadherence and its impact on gout management, particularly in the implementation phase, where individuals' perceptions of medication necessity and concerns play an important role in influencing adherence (Spragg et al., 2023).

In recent years, smartphone-based interventions have emerged as a promising strategy to tackle medication nonadherence, with previous studies demonstrating their potential in promoting behaviour change and enhancing treatment outcomes (Peng et al., 2020; Xiong et al., 2018; Petrie et al., 2012). However, there is a dearth of research specifically focusing on intentional nonadherence among people with gout and the effectiveness of smartphone interventions in addressing this issue. While some studies have explored the use of smartphone reminders to enhance adherence, few have

investigated the potential of targeted messages that directly address patients' beliefs and perceptions regarding their medications (Sinnappah et al., 2022).

Therefore, the main objective of this study was to assess the clinical and technical feasibility of using smartphone notifications as an intervention to modify patients' beliefs and perceptions toward their medications in gout management. More specifically, we examined the feasibility of collecting outcome measures such as adherence rates using serum urate levels, and questionnaire responses from people with gout. We also evaluated the acceptability of this smartphone-based intervention to the people with gout using the Technology Acceptance Model (TAM), a widely adopted theoretical framework analysing perceptions of the intervention's usefulness and ease of use, influencing behavioural intention and technology adoption (AlQudah et al., 2021). Furthermore, we sought to explore any potential differences in adherence rates and other outcome measures between the experimental group that received the targeted smartphone notifications addressing determinants of intentional nonadherence and the active control group that received some general health advice via smartphone notifications at three different time points (baseline, post-intervention, and 6-month follow-up). In addition, we conducted a longitudinal assessment to evaluate how these notifications influenced the outcome measures within each study group over time.

Method

Participants

This was a randomised controlled feasibility study of 52 patients with gout. The participants were recruited from rheumatology clinics between December 2021 and April 2022. Inclusion criteria were (1) aged 18 or over; (2) a rheumatologist-confirmed diagnosis of gout; (3) prescribed allopurinol; (4) owner of a smartphone; and (5) English-speaking. The New Zealand Health and Disability Ethics Committee approved this study (ref. AH23037) and all patients provided written informed consent.

Sample size

The sample size was in line with recommendations for determining the sample size for a randomised feasibility study (Viechtbauer et al., 2015). For the current trial to have the 80% power to detect a 10% change from baseline with two-sided alpha of 0.05 and standardised effect size to be small (0.1), a feasibility trial with a sample size of 22 patients per treatment arm (1:1) was recommended. We estimated the dropout rate to be 15% (according to recent studies) (Bunphong & Narongroeknawin, 2018), and therefore included 28 participants in each arm. Four of the participants who were allocated

to the control group withdrew from the study, hence, we finished analysing data for 52 participants (24 and 28 in the intervention group and the control group, respectively).

Randomisation and allocation

We used a simple randomisation technique by creating a computer-generated list, which was performed by an independent research assistant not involved in recruitment, assessment, or delivering the intervention and who had no prior knowledge of the participants, to allocate participants into the intervention or control arm.

Intervention procedure

Participants were randomly allocated to either the intervention group or the active control group. The intervention group received smartphone notifications that targeted intentional nonadherence determinants highlighted in previous studies. For example, Emad et al. (2022) indicated that nonadherent patients often associate discontinuation of allopurinol with the desire to resume a "normal" life. In order to address this issue, the notification "By taking allopurinol on a regular basis, you can keep doing what matters to you" was included as part of the smartphone intervention in the current study. This targeted message aimed to encourage adherence by highlighting the connection between regular medication use and the ability to maintain a meaningful and fulfilling lifestyle. The active control group received general health advice via smartphone notifications, which included advice on the importance of regular exercise, the impact of good sleep on physical and mental performance, stress management techniques, and the benefits of staying hydrated. All participants received 130 one-way notifications - which means participants were not expected or asked to respond to notifications they received for 3 months. Instead of a constant frequency, participants received 2 notifications per day for the first 8 weeks, followed by 1 notification per day for the next 2 weeks, 3 notifications per week in week 11, and 1 notification per week in week 12. To receive the notifications, both groups were required to download a smartphone application and received brief training on how to read, save, or delete notifications.

Outcome measures were assessed at baseline, after the intervention (3 months from baseline) and then again at 6 months from the baseline to investigate the effects of notification intervention over time. To obtain a better understanding of the potential barriers and facilitators at the service delivery and individual level to the uptake of this programme, participants from both groups attended a semi-structured interview either in person or online (Figure 10).

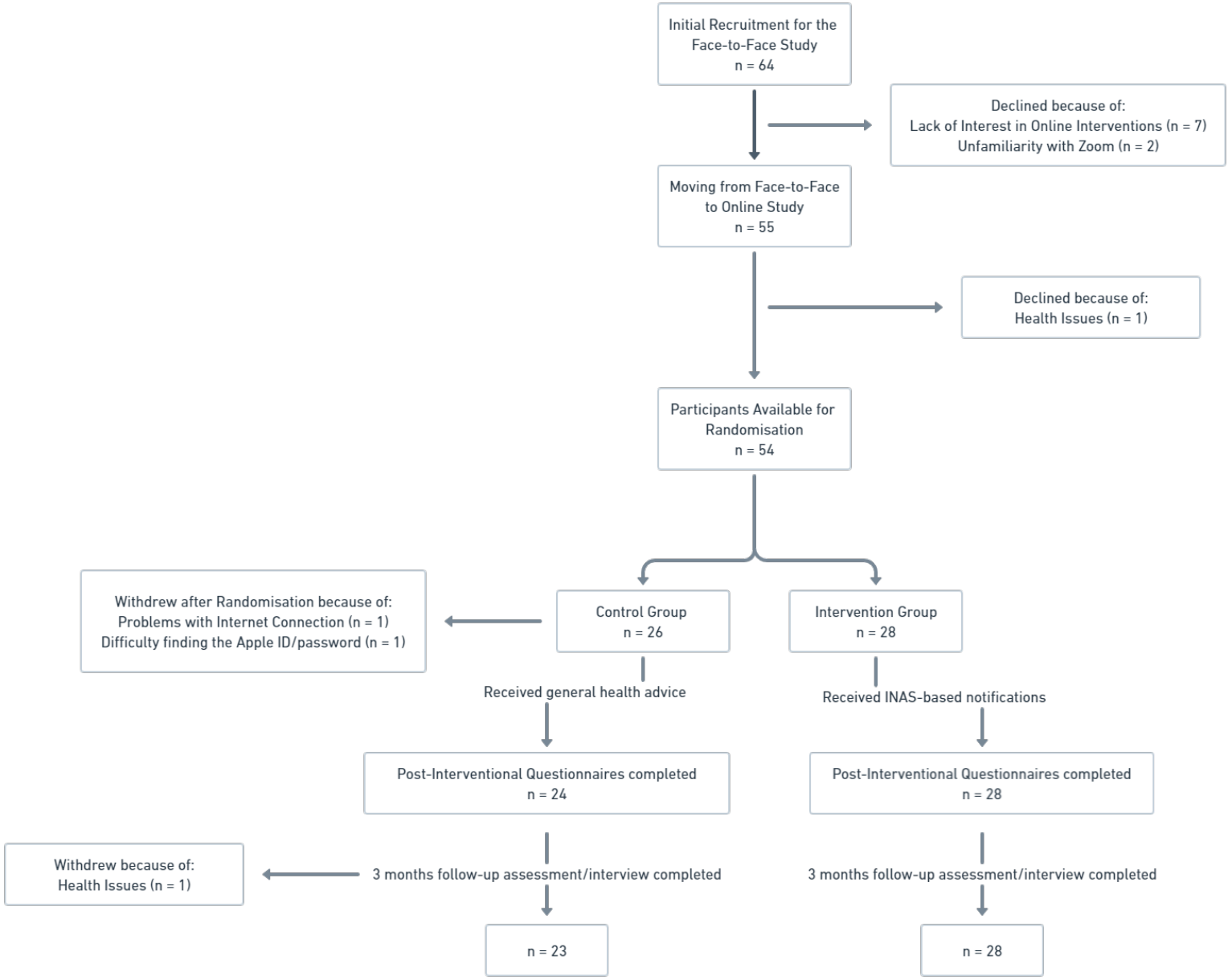

Figure 10. *Recruitment and participation flowchart.*

Data collection

After obtaining written informed consent, participants actively utilised the study application to complete demographic and study-related questionnaires. Serum urate results were obtained through a review of patients' medical records.

Measurements

Feasibility of the intervention. To evaluate technical feasibility, the study collected any technical problems associated with the healthcare innovation. Patients directly reported some of these issues, while others were identified by the researcher during the project. In addition, questionnaire responses were collected through the smartphone application, and any encountered technical issues during the submission of answers were identified and addressed.

Clinical feasibility was evaluated through issues encountered during the assessment of outcome measures, including adherence rates using serum urate levels. Adherence rates were determined by evaluating serum urate levels retrieved from participants' medical records, thus obviating the necessity for frequent blood tests. This information allowed us to identify potential challenges or limitations in implementing the innovation in a clinical setting.

Acceptability of the intervention. To investigate patient satisfaction with the app, all participants were asked to rate their overall experience with the application including willingness to continue with the app, ease of use, understandability, usefulness, tone, language, timing, and frequency of notifications, on a scale of 0-10, with 0 being the least favourable score and 10 being the most favourable score.

Analysis of study groups

Adherence. Rate of adherence to allopurinol was assessed by measuring serum urate levels and the patient-reported number of missed doses at baseline, post intervention (3 months from baseline) and again at 6 months from baseline, focusing on the implementation phase of adherence.

Psychological Factors. Patients completed the Treatment Satisfaction Questionnaire for Medication (TSQM) (Atkinson et al., 2004), a 14-item scale that utilises a rating scale ranging from 1 to 7 and the Intentional Non-Adherence Scale (INAS, 4), consisting of 22 items scored on a scale from 0 to 5. These questionnaires were completed at baseline, post intervention (3 months from baseline) and again at 6 months from baseline.

Comparative assessment of study groups

To evaluate the effects of smartphone notifications, we conducted a comparative analysis of outcome measures between the interventional group and the control group at baseline, post intervention (3 months from baseline) and again at 6 months from baseline.

Longitudinal assessment of study groups

To evaluate the effects of smartphone notifications over time, we conducted a longitudinal analysis of outcome measures for each study group at baseline, post intervention (3 months from baseline) and again at 6 months from baseline. These assessments were designed to capture any potential improvements in medication adherence within the intervention group which might be attributed to the INAS-based notifications, as well as within the control group, where health advice could potentially serve as a reminder.

Statistical analysis

The statistical analysis was conducted using SPSS version 25.0 (IBM Crop.). Descriptive statistics including medians with ranges and percentages were used to summarize the clinical characteristics of the study participants. As the outcome measures were not normally distributed, non-parametric tests were employed. Mann-Whitney U tests were conducted to examine differences in adherence and psychological factors between the experimental and control groups. In addition, a non-parametric Friedman test was conducted for longitudinal analysis of any differences in outcome measures over time, followed by a post-hoc analysis using a Wilcoxon signed-rank test with a Bonferroni correction for multiple comparisons.

In this study, we primarily employed nonparametric statistical methods for data analysis to account for the skewed distribution of several variables. However, for the variable 'missed dose within a month,' which exhibited a consistent median value of 0 across all time points, we opted to report the mean along with 95% Confidence Intervals (CI). This decision was made due to the unique distribution of this variable, where most observations had zero values, making it unsuitable for traditional nonparametric tests. The use of the mean and 95% CI allows for better representation of central tendency and provides a more informative summary of this specific variable.

In addition, due to the repeated measures nature of the 'missed dose' variable collected at multiple time points, we applied a general linear model with a repeated measures design and t-tests to assess changes over time and between groups. These statistical approaches were chosen to

account for within-subject dependencies and evaluate differences in 'missed dose' between groups while considering the temporal aspect of the data.

All statistical tests were two-tailed, and data outliers were excluded from the analysis. A significance level of .05 was used to determine statistical significance for all analyses. For data visualisation and creating scatterplots, we utilised the R programming language version 4.3.1 (R Core Team, 2021) and the ggplot2 package version 3.4.2 (Wickham, 2016).

Results

Characteristics of the study population

A total of 52 patients with gout with an average age of 63.6 years were included in the study. Most patients were male (98.8%), NZ European (71.2%), married (57.7%) with university education (71.2%). On average, the participants had been taking allopurinol for eight years (Table 11). Among all, 24 of the patients were randomly allocated to the control group to receive some general health advice and the rest (n = 28) were allocated to the intervention group to receive the INAS-based notifications.

Table 11. *Characteristics of the study population*

Participants' Characteristics	n	%	Participants' Characteristics	n	%
Age (mean ± SD years)	63.6 ± 14.4		Marital Status		
Gender			Single	2	3.8
Male	51	98.8	Divorced/Widow	10	19.2
Female	1	1.2	Permanently separated	3	5.8
Level of Education			Married	30	57.7
Primary School	2	3.8	In a de facto relationship	4	7.7
Secondary School	13	25.0	Other	3	5.8
Tertiary	24	46.2	Employment Status		
Post-graduate	13	25.0	Full-time	20	38.5
Ethnicity			Part-time	4	7.7
NZ European	37	71.2	Retired	17	32.7
Māori	4	7.7	Self-employed	7	13.5
Pacific	2	3.8	Beneficiary	2	2.8
Chinese	4	7.7	Other	2	3.8
Other	5	9.6	Allopurinol treatment duration (mean ± SD)	7.7 ± 8.17	

Note. Values are the number and percentage unless otherwise indicated.

Feasibility of the intervention

Regarding technical feasibility, the study encountered a total of five technical issues. Two participants from the control group experienced unstable internet access and were unable to install the application, leading to their withdrawal from the study before it commenced. The research team promptly resolved the issues faced by two other participants, enabling them to install the application successfully. Additionally, one participant reported difficulties submitting their questionnaire responses through the application, but this was also resolved by the research team.

In terms of clinical feasibility, the present study used participants' medical records to collect serum urate levels, obviating the need for regular blood tests. However, a substantial proportion of baseline data (23%) dated back more than six months and a considerable number of participants had no recorded serum urate levels at the end of the programme (48%) and at the 3-month follow-up (57%).

Acceptability of the intervention

Overall participants showed high engagement and commitment to the research study, with a 0% attrition rate once enrolled. Nearly half of the patients (49%) expressed willingness to continue using the application after completion of the study, and a majority (80%) said they would recommend it to others. Participants rated their experiences with the application on a scale of 0 to 10, where 0 represented the worst and 10 represented the best. The results indicated that the application received high ratings for ease of use, with all participants giving it a score of 10 out of 10. Content understandability received a high rating, with a median score of 10 out of 10, indicating that nearly all participants (98%) found the content of the notifications easy to comprehend. The perceived usefulness of the application was moderately positive, as indicated by a median rating of 6 out of 10 (IQR = 5-7). Regarding the language and tone of the notifications, while three participants (6%) preferred more scientific terms, the majority found the language to be simple and relatable, and all participants found the tone to be appropriate and non-offensive. In terms of notification preferences, some participants (25%) expressed a desire for flexibility in timing, while the majority (86%) preferred less frequent notifications, such as once or twice fortnightly.

Comparison of intervention effects on nonadherence between study groups

To look at the potential effects of smartphone notifications on nonadherence rate, we compared the level of serum urate and number of missed doses (within a month) between the control group and the

intervention group at three time-points (baseline, post-intervention, and 3-month follow-up). There were no significant differences between the study groups in terms of serum urate levels and the number of missed doses at each time point, suggesting that smartphone notifications did not have a significant effect on nonadherence rate (Table 12).

Table 12. *Differences between the intervention group and the control group in terms of serum urate levels and number of missed doses at baseline, post-interventional condition, and follow-up condition*

Variables	Baseline Median (95% CI)		Post-interventional condition Median (95% CI)		Follow-up condition Median (95% CI)	
	Control group (n = 24)	Intervention group (n = 27)	Control group (n = 16)	Intervention group (n = 22)	Control group (n = 15)	Intervention group (n = 17)
Serum urate level	0.26 (0.23-0.45)	0.36 (0.32-0.53)	0.28 (0.25-0.37)	0.32 (0.25-0.43)	0.28 (0.23-0.35)	0.31 (0.29-0.41)
	U = 288.0, P = .496		U = 175.5, P = .988		U = 97.0, P = .248	
	Baseline Mean (95% CI)		Post-interventional condition Mean (95% CI)		Follow-up condition Mean (95% CI)	
	Control group (n = 24)	Intervention group (n = 28)	Control group (n = 24)	Intervention group (n = 28)	Control group (n = 24)	Intervention group (n = 28)
Missed doses in a month	1.12 (0.15-2.09)	1.63 (0.32-2.93)	0.66 (0.04-1.29)	0.48 (0.59-1.06)	1.00 (0.12-1.87)	1.19 (0.11-2.25)
	t (35.08)= -1.19, P = .241		t (31.89)= -0.74, P = .464		t (34.93)= -0.95, P = .345	

Note. Bold indicates significance at p< .05 level.

Comparison of intervention effects on psychological factors

Next, we investigated the potential effects of smartphone notifications on treatment satisfaction and treatment satisfaction subscales, as well as INAS scores and INAS subscales. We compared these psychological factors between the control and intervention groups at three time-points (baseline, post-intervention, and follow-up). There were no significant differences between the study groups regarding these variables at any of the time points, indicating that the smartphone notifications did not have a significant effect on the measured psychological factors (Table 13).

Table 13. *Differences between the intervention group and the control group in terms of psychological factors contributing to nonadherence at baseline, post-interventional condition, and follow-up condition*

Variables	Baseline		Post-interventional condition		Follow-up condition	
	Control group	Intervention group	Control group	Intervention group	Control group	Intervention group
INAS – Total	44 (22-65)	38 (25.7-58)	44 (32.4-62.8)	32 (22-46.8)	47 (33.3-65)	35.5 (22.7-62)
	U = 310.5, P = .636		U = 261.0, P = .161		U = 269.5, P = .626	
INAS – Resisting Illness	14 (7-23)	14 (7-21)	17 (7-22.6)	12 (7-17.6)	17 (12.1-21.2)	13.5 (7.5-20)
	U = 305.0, P = .564		U = 268.0, P = .202		U = 293.0, P = .577	
INAS – Testing Treatment	8 (4-12)	6 (4-13.6)	8 (4-16)	4.5 (4-10.6)	8 (5.3-10)	9 (4-14.5)
	U = 329.0, P = .894		U = 272.5, P = .224		U = 319.0, P = .954	
INAS – Drug Specific Concerns	11 (6-16)	7 (6-16.6)	13 (6-17)	6 (6-14.2)	14 (6-16)	11 (6-16.618.2)
	U = 330.5, P = .918		U = 259.5, P = .144		U = 297.5, P = .630	
INAS – Medicine Sensitivity	10 (5-14)	6 (5-14)	11 (5-17)	5.5 (5-13.6)	11 (5-14)	9.5 (5-14.2)
	U = 291.5, P = .391		U = 256.0, P = .128		U = 285.5, P = .478	
TSQM – Total	23 (16-52.4)	23.5 (15.2-39.6)	19 (16.7-43.2)	22.5 (15-32.8)	16 (14-24)	20 (16.2-30.8)
	U = 302.0, P = .530		U = 295.0, P = .449		U = 292.0, P = .567	
TSQM – Side Effects	5 (5-17)	9 (5-10.9)	5 (5-9)	5 (5-12.7)	5 (5-8)	5 (5-11.2)
	U = 284.5, P = .315		U = 297.0, P = .440		U = 261.0, P = .196	
TSQM – Effectiveness	6 (3-9.2)	4.5 (3-8.4)	4 (3-8)	5.5 (3-9)	4 (3-6)	6 (3.2-8)
	U = 312.0, P = .649		U = 303.5, P = .537		U = 287.5, P = .503	
TSQM – Convenience	3 (3-6)	6 (3-7.6)	3 (3-6)	4 (3-6.3)	3 (3-3)	3 (3-5)
	U = 300.0, P = .475		U = 329.0, P = .889		U = 316.5, P = .903	
TSQM – Global Satisfaction	6 (3-12)	6 (3-6)	6 (3-8)	4.5 (3.5-6)	3 (3-8)	5 (3-9)
	U = 288.5, P = .373		U = 288.0, P = .365		U = 310.5, P = .820	

Note. Bold indicates significance at p< .05 level. INAS: Intentional Non-Adherence Scale. TSQM: Treatment Satisfaction Questionnaire for Medication.

Effects of notifications in the intervention group

The third aim of the study was to investigate the potential effects of INAS-based notifications on nonadherence and other psychological factors over time. A non-parametric Friedman test was employed to examine differences among repeated measures. When applicable, a post-hoc analysis was conducted using the Wilcoxon signed-rank test, with a Bonferroni correction applied to account for multiple comparisons. The results indicated that there were no significant effects of the intervention on the level of serum urate over time [X^2 (2) = 5.29, *P* = .071]. This tentatively suggests that the INAS-based notifications did not have a significant impact on nonadherence as measured by serum urate levels over the course of the study.

However, we found a significant effect of the intervention on the number of missed doses within a month [F (2,52) = 4.22, *P* = .026, ηp^2 = 0.25]. Subsequent post hoc tests using the Bonferroni correction indicated that this was the result of participants being more likely to take allopurinol as prescribed after receiving the smartphone notifications compared to the baseline (*P* = .019). There was also a significant difference between post-interventional condition and follow-up condition (*P* = .045). No difference was found between baseline and follow-up condition (*P* = .062; Figure 11).

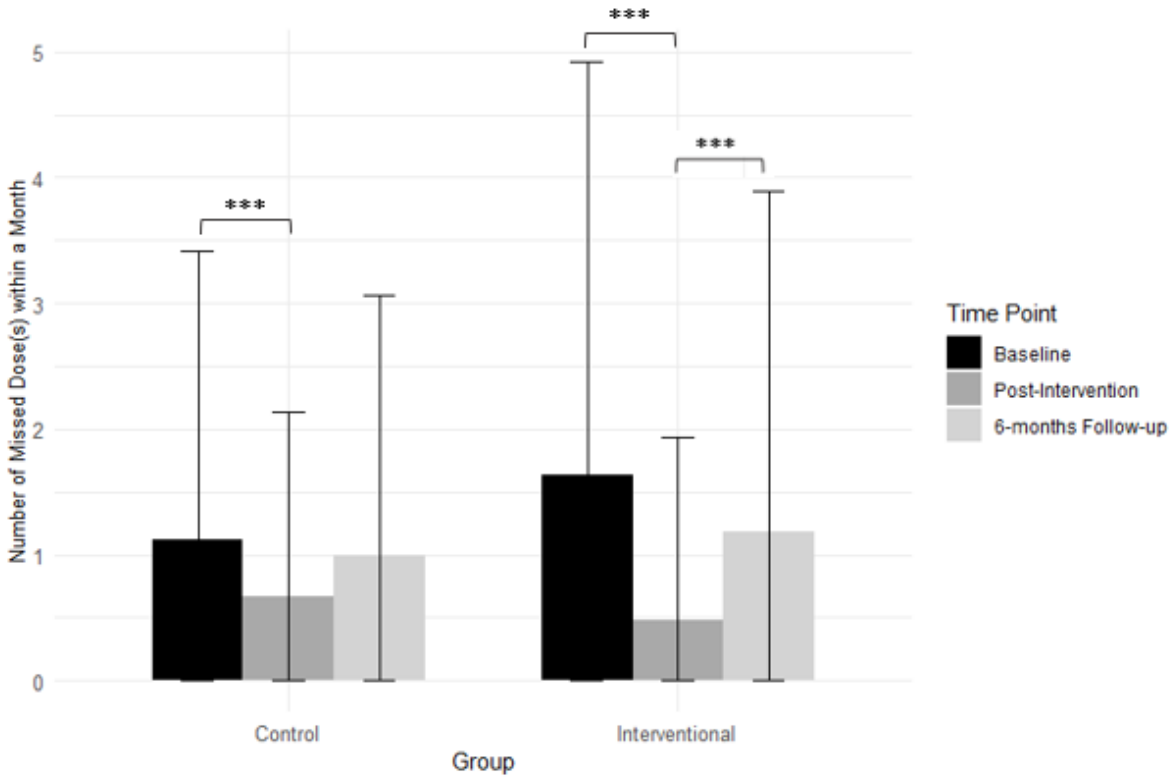

Figure 11. *Average number of missed dose(s) within a month for study groups in different time-points.*

In terms of other psychological factors, we found no significant effects of the intervention on INAS scores [X^2 (2) = 1.14, *P* = .566], as well as INAS subscales (Table 14). However, there was a significant effect of the INAS-based smartphone notifications on the extent to which participants considered treatment administration more convenient [X^2 (2) = 14.25, *P* = .001, *W* = 0.25]. This was the result of allopurinol intake being more likely to be considered convenient three months after receiving the intervention compared to the baseline (*P* = .009). There was no significant difference between baseline and post-interventional condition (*P* = .071) as well as post-interventional condition and follow-up condition (*P* = .423).

There was also a significant effect of the INAS-based smartphone notifications on the extent to which participants were more satisfied with taking allopurinol [X^2 (2) = 6.80, *P* = .033, *W* = 0.12]. This was the result of participants being more likely to be satisfied with how allopurinol works three months after receiving the intervention compared to the baseline (*P* = .019). There was no significant difference between baseline and post-interventional condition (*P* = 0.142) as well as post-interventional condition and follow-up condition (*P* = .385).

Table 14. *Results of the Friedman test for differences in serum urate level, number of missed doses, and other psychological factors across time among the study groups*

	Control group				Intervention group			
Variables	Chi-Square	df	P	W	Chi-Square	df	P	W
Serum urate level	3.67	2	.159	0.13	5.29	2	.071	0.16
INAS – Total	1.36	2	.506	0.03	1.14	2	.566	0.02
INAS – Resisting Illness	0.22	2	.893	0.00	5.34	2	.069	0.09
INAS – Testing Treatment	2.31	2	.315	0.05	2.03	2	.362	0.03
INAS – Drug Specific Concerns	0.76	2	.683	0.01	4.88	2	.087	0.08
INAS – Medicine Sensitivity	1.70	2	.426	0.03	1.67	2	.432	0.03
TSQM – Total	0.02	2	.987	0.00	6.80	2	**.033**	0.12
TSQM – Side Effects	1.20	2	.549	0.02	1.82	2	.402	0.03
TSQM – Effectiveness	0.45	2	.796	0.01	0.74	2	.689	0.01
TSQM – Convenience	0.05	2	.973	0.00	14.25	2	**.001**	0.25
TSQM – Global Satisfaction	1.76	2	.414	0.03	3.46	2	.177	0.06

Note. Chi square values reported in the table are derived from the Friedman test. Bold indicates significance at p< .05 level. INAS: Intentional Non-Adherence Scale. TSQM: Treatment Satisfaction Questionnaire for Medication.

Effects of notifications in the control group

To explore the potential impact of general health advice on nonadherence and psychological factors over time, we conducted a non-parametric Friedman test to compare control group data at three distinct time-points, baseline, post-intervention, and 3-month follow-up, followed by a post-hoc analysis using the Wilcoxon signed-rank test with a Bonferroni correction for multiple comparisons. In terms of nonadherence rate, there were no significant effects of general health advice on the level of serum urate over time [X^2 (2) = 3.67, *P* = .159]. However, there was a significant effect of the general health advice on the number of doses missed within a month [F (2,52) = 3.28, *P* = .051, ηp^2 = 0.20]. Subsequent post hoc tests using the Bonferroni correction indicated that this was the result of participants being more likely to take allopurinol as prescribed after receiving the smartphone notifications compared to the baseline (*P* = .043). There was no significant difference between baseline and follow-up condition (*P* = .172) as well as post-interventional condition and follow-up condition (*P* = .797; see Figure 12).

With respect to other psychological factors, we found no significant effects of receiving general health advice neither on treatment satisfaction scores and the relevant subscales, nor INAS scores and the relevant subscales (see Table 14).

Discussion

This was the first study to explore the feasibility and acceptability of utilising smartphone notifications as an intervention to modify patients' beliefs and perceptions towards their medications in gout management. Regarding technical feasibility, the study encountered some minor issues related to installation of the application. However, these technical challenges were quickly resolved, highlighting the importance of providing good technical support during the implementation of smartphone-based interventions. Ensuring stable internet connectivity and user-friendly app interfaces is also crucial in enhancing the overall feasibility of smartphone-based interventions.

Despite the successful resolution of technical challenges, the reliance on medical records for collecting serum urate levels has limitations. A notable proportion of baseline data was outdated, and a significant number of participants lacked recorded serum urate levels at various time points, particularly at the six-month follow-up. This resulted in missing data and variability in the timing of measurements. To enhance the feasibility of collecting serum urate levels in future studies, alternative methods such as real-time remote monitoring or the use of wearable devices could be explored.

These approaches may offer more accurate and timely data collection, mitigating the risk of missing information and providing a more comprehensive assessment of serum urate levels throughout the study duration.

The intervention was well-received by the participants, with high levels of actual use, positive attitudes toward using the app and a perception of ease of use. The absence of any drop-out among the participants is noteworthy and suggests that the intervention was not burdensome or inconvenient. Moreover, nearly half of the participants indicated their willingness to continue using the app after the study ended, indicating a high level of user engagement. The majority of the participants said they would recommend the app to other patients on allopurinol therapy, further underscoring the positive attitudes toward the intervention. The feedback regarding language and tone of the notifications were generally positive, with most participants finding the language simple and relatable, and the tone appropriate. However, a small number of participants preferred more scientific language, indicating that the intervention could benefit from customization options to cater for individual preferences.

The present study also allowed us to investigate differences in adherence rates and other outcome measures between the experimental group that received the targeted smartphone notifications addressing determinants of intentional nonadherence and the control group that received some general health advice over time. Our findings showed positive effects of INAS-based notifications on medication adherence and treatment satisfaction with allopurinol in people with gout. Notably, our results demonstrated a considerable decrease in the number of missed doses among patients who received these tailored notifications.

The effectiveness of tailored notifications in addressing the underlying reasons for intentional nonadherence is consistent with previous research (Fahrni et al., 2022; Emad et al., 2022; Ramsubeik et al., 2018). Our study expands upon this knowledge by demonstrating a significant positive impact on patients' beliefs and perceptions towards their medication through tailored notifications. By effectively acknowledging and addressing factors associated with intentional nonadherence, such as resistance to illness, maintenance of normalcy, testing treatment limits, concerns about medication, and sensitivity to medication effects, our intervention seemed to provide a useful perspective for patients on ULT. Reframing medication as a means to restore normal health and life might have motivated patients to adhere to their prescribed medication.

In addition, our study revealed that patients who received INAS-based notifications felt it was more convenient taking allopurinol and expressed greater overall treatment satisfaction. These findings align with previous research that has examined the effects of tailored interventions on treatment satisfaction. Spragg et al. (2023) found that reassuring information that highlights the necessity and long-term effectiveness of allopurinol can increase treatment satisfaction and improve adherence in people with gout. Therefore, educational strategies that address the key reasons for intentional nonadherence have the potential to improve treatment satisfaction and medication adherence with allopurinol by engaging patients in gout management (Sinnappah et al., 2022). These strategies may also help patients understand the potential challenges associated with using symptom-based approaches to test the efficacy of urate-lowering treatment, leading to enhanced treatment satisfaction.

Looking at the findings, receiving general health advice can have a positive impact on medication adherence among people with gout by reducing the number of missed doses. This is consistent with previous research indicating that medication reminders can help prevent missed doses (Bunphong & Narongroeknawin, 2018; Dong et al., 2018; Zhao et al., 2019). While our study did not involve sending specific medication reminders, patients were informed of general health advice through both email and the app. It is possible that simply receiving a notification can serve as a reminder and help decrease the frequency of skipped doses. These results can convey the importance of unintentional nonadherence, which is the failure to take medication due to factors such as forgetfulness, as a common reason for nonadherence (Perez-Ruiz F & Desideri, 2018). It is worth noting that a considerable proportion of the control group had serum urate levels at baseline that were well-controlled and below the therapeutic target for ULT. This baseline characteristic may have influenced the findings related to medication adherence in the control group, as individuals with well-controlled gout may have different perceptions and behaviours toward their medication compared to those with uncontrolled gout. This discrepancy in baseline characteristics is an important consideration when interpreting the results and may indicate the need for further investigation into the specific factors influencing adherence in such populations.

The study had several limitations, including the small sample size and the short duration of the study, which may not have been sufficient to capture the full impact of the intervention. Furthermore, given that the study sample exclusively comprised patients who had been taking

allopurinol for an average of eight years, it is possible that the findings may not fully reflect the experiences of individuals who are newly prescribed allopurinol or who differ from the study population in other ways. In addition, many of the sample who enrolled in the study did not report any missed doses indicating that there was no room for improvement in adherence for those individuals.

Moreover, the observed high baseline adherence in our study population may not be representative of the broader population of patients with gout, potentially limiting the generalisability of our findings. This could be attributed to unrepresentative sample characteristics, as our participants had a history of active participation in previous gout-related projects, resulting in heightened awareness of medication adherence. Although we required a rheumatologist-confirmed diagnosis of gout as the primary eligibility criterion, we did not specifically consider the severity or activity level of gout in our participants at the outset of the study as an inclusion criterion.

While we collected adherence data through patient-reported missed doses, it is important to acknowledge that this method can be prone to recall bias and may not provide a comprehensive view of medication adherence. Future work in this area would greatly benefit from more objective methods of measuring adherence, such as pill count and electronic pill bottle monitoring.

Furthermore, our study underscored the need for more reliable methods of measuring serum urate levels, as the collection of data from patients' medical records proved to be inconsistent. Serum urate levels were not systematically assessed at predefined intervals in this study, which constrained our ability to comprehensively evaluate the intervention's impact on serum urate levels and treatment goals. While the initial findings appear encouraging, it is important to acknowledge the significant amount of missing data in the serum urate analysis. This data gap may have limited the statistical power of our study to detect meaningful differences, necessitating a cautious interpretation of the results.

Another limitation to consider is the relatively high level of education observed among our study participants. Hence, the generalisability of our findings to individuals with lower educational attainment may be limited. Thus, it may be necessary to replicate the study with a more diverse and nonadherent patient sample to assess the generalisability of the results. In addition, smartphone interventions rely on access to technology and mobile data, which could pose challenges for individuals with limited financial resources or those residing in rural areas with restricted connectivity. These disparities raise concerns about the equitable distribution and accessibility of such

interventions. Future research and implementation strategies should take these equity issues into account, ensuring that the benefits of smartphone-based interventions are accessible to a broader population. Alternative approaches or support systems may be necessary to assist individuals facing technology-related barriers.

In conclusion, the findings of this study suggest that the smartphone-based intervention holds great potential as a patient-centred approach to enhance adherence to allopurinol among people with gout. Despite limitations, this study provides preliminary evidence for the feasibility and potential effectiveness of such interventions. The high levels of patient acceptability and the minor technical issues encountered indicate that the intervention is feasible and easily implementable in clinical settings. Moreover, the incorporation of educational strategies and tailored notifications addressing key motivators for nonadherence showed positive outcomes. These interventions may be particularly valuable for patients with limited access to traditional healthcare services, given their cost-effectiveness and accessibility.

Chapter Seven

Discussion

Overview

The thesis presents empirical work investigating intentional nonadherence to urate lowering medications among people with gout. Continuous adherence to urate lowering medications is of great importance in gout management. However, a substantial portion of the gout population faces difficulties in adhering to their prescribed drug regimens, which can result in compromised treatment outcomes and avoidable health-related challenges.

Theoretical work suggests that targeting patient's beliefs and perceptions towards their medications can empower them to make more informed decisions, while also enhancing their motivation to adhere by providing an insight into otherwise general and one-size-fits-all health advice. The limited existing evidence on the use of tailored information in gout management highlights significant gaps in our understanding of how to address the determinants of nonadherence as an intervention technique. First, we need a better understanding of what drives nonadherence to urate lowering medication in people with gout and how we can screen this behaviour. Second, we yet need to understand to which extent the main motives of nonadherence are addressed in online gout educational resources, given their crucial role in shaping medication beliefs. Finally, there is a need for substantial evidence regarding the feasibility and acceptability of utilising tailored technology-based interventions to address the common motives for nonadherence to urate lowering medications. Using technology to modify medication belief and perceptions could be an effective approach for improving medication adherence in gout. The few existing technology-based interventions in the context of gout suggest a positive effect on how people with gout view their urate lowering medications and adhere to them, although more research is needed to confirm these findings.

The thesis had several aims to address these limitations within the current literature. A more general aim of this thesis was to explore the Intentional Non-Adherence Scale (INAS) capabilities in assessing medication adherence and to broaden understanding of the main reasons behind intentional nonadherence in people with gout. This thesis also aimed to evaluate how online gout educational resources addressed medication adherence and analysed their content regarding targeted reasons for nonadherence and strategies for promoting medication adherence. The last aim

of this thesis was to provide an insight into whether using smartphone notifications to target common motives of intentional nonadherence could be a feasible and acceptable intervention technique for improving medication adherence in people with gout.

This final chapter consolidates the conclusions drawn from the work presented within this thesis. First, key findings of the four empirical studies are summarised. These findings are then incorporated into the existing literature on medication adherence in gout. The chapter also addresses the study limitations and discusses the strengths and clinical implications of the current research, followed by some directions for future research.

Summary of Study findings

Four studies were conducted in order to investigate the aims of this thesis. The first two studies investigated methodological and assessment strategies for understanding medication adherence in people with gout. Chapter Three reported the concurrent validity of the Intentional Non-Adherence Scale (INAS; Weinman et al., 2018) in assessing medication adherence. This manuscript details the use of this 22-item scale for assessing medication adherence measured by serum urate levels and number of missed dose(s) within people with gout taking allopurinol (Emad et al., 2023a). The findings indicated that higher scores on the INAS *Testing Treatment* subscale were associated with higher levels of serum urate (SU), specifically among younger patients, suggesting a greater tendency for testing allopurinol limits among younger individuals. In addition, patients who did not achieve their target SU levels were also younger and had higher scores on the INAS *Testing Treatment* subscale. The research also showed that higher INAS *Testing Treatment* and INAS *Medicine Sensitivity* subscales, were linked to a higher frequency of missed allopurinol doses. The INAS overall score demonstrated significant association with SU levels and the number of missed allopurinol dose(s) after controlling for other factors. Overall, scores on this scale suggested a promising avenue for assessing medication adherence in people with gout, and identifying people who are at heightened risk of intentional nonadherence.

The study in Chapter Four investigated what drives intentional nonadherence to allopurinol in people with gout (Emad et al., 2022). Looking at the INAS items with highest endorsement, this study found that the major reasons behind the decision not to take allopurinol relate to wanting to lead a normal life and regain a sense of overall health. Another important motivation was found to be the strategy of testing treatment, where the patient tests the limits of treatment to see if they can manage

by taking less or none of their allopurinol medication. The study also identified two drug-specific concerns, side effects and medication effectiveness over time, that contributed to intentional nonadherence. There were also significant differences in INAS overall scores between those with and without the SU at target (<0.36mmol/L or 6mg/dL). Patients whose serum urate level was not at target endorsed more INAS items and scored higher in INAS *Testing Treatment* and INAS *Drug-Specific Concerns* subscale. These results suggested some potentially modifiable targets for adherence interventions and some recommendations to clinicians and gout content makers about how to reframe ULT for patients in order to improve adherence.

The second part of the thesis presented two manuscripts, including a content analysis and a feasibility study. Chapter Five included a cross-country content analysis that explores how adherence to urate lowering medications is addressed in online gout educational resources (Emad et al., 2023b). This manuscript investigated how often adherence was referred to, the strategies used for enhancing medication adherence, and the motives of nonadherence that were targeted. This study also evaluated the word count and readability of the adherence material in online gout educational resources. The findings demonstrated a significant gap in online gout educational resources, with only half of the websites addressing medication adherence. Even when mentioned, only a limited attention was given to adherence as proportion of word count in this study indicated. This analysis further revealed that online gout educational resources predominantly targeted intentional nonadherence, with less attention directed towards unintentional barriers. Commonly discussed reasons for nonadherence included drug-specific concerns, misconceptions about gout curability and medication necessity, forgetfulness, and practical challenges. Strategies for promoting adherence were found on about one third of websites, with medication education being the most prevalent strategy, followed by healthcare provider engagement and memory aid strategies. This analysis also reported difficult comprehension in one-fifth of adherence materials. These findings suggested that online gout educational resources inadequately address ULT adherence and employ a limited range of strategies to enhance medication adherence. These findings also highlighted the need for an improved adherence portrayal in online gout educational resources, requiring provision of tailored, clear and comprehensible information.

Chapter Six reported the findings from a study investigating the feasibility and acceptability of using smartphone notifications as an intervention to modify patients' beliefs and perceptions towards

their medication in gout management (Emad et al., in press). This intervention aimed to target the main motives of intentional nonadherence to allopurinol to enhance medication adherence. Participants were randomly assigned to either the intervention group or the control group; with both groups using a study application on their smartphones to receive notifications over three months. The intervention group received tailored smartphone notifications aimed at addressing intentional nonadherence determinants highlighted in Chapter Four (Emad et al., 2022); while the control group received general health advice. For both groups, medication adherence was assessed at baseline, post-intervention (3 months), and 6 months later. This study evaluated the feasibility and acceptability of the intervention using the Technology Acceptance Model (TAM). The results reported high participant retention and compliance rate, demonstrating high feasibility of the intervention. Participants were also highly satisfied with the user-friendliness and content of the application, underscoring the high acceptability of the intervention. The findings showed a significant decline in the number of missed doses over time for both study groups. However, there were no significant variations in serum urate levels between the two groups. Participants who received nonadherence-targeted notifications reported finding it more convenient to take allopurinol and expressed higher overall treatment satisfaction throughout the study. These results indicate that the intervention has a potential to be an effective and scalable approach for enhancing medication adherence and changing maladaptive beliefs about allopurinol. The intervention also demonstrated that smartphone notifications appear to have an additive effect in improving satisfaction with allopurinol, compared to receiving general health information only.

Integration into the Broader Literature

This thesis makes three significant contributions to the current body of literature. First, it offers compelling evidence supporting the effectiveness of the Intentional Non-Adherence Scale (INAS) as a reliable and valid tool for assessing medication adherence to urate lowering medications. Second, it shed light on the main motives behind intentional nonadherence, providing insights to guide the development of tailored interventions in the future. Third, it shows how understanding the common reasons behind intentional nonadherence can be strategically applied in healthcare to enhance medication adherence among people with gout. In the following section, these contributions are considered and integrated into the existing literature.

The first major contribution of this work is increased evidence for the effectiveness of the INAS in assessing medication adherence among people with gout. The INAS stands as the sole existing tool designed to assess what drives intentional nonadherence among patients. The findings presented in Chapter Three of this thesis provide efficacy for using the INAS to assess adherence to allopurinol (Emad et al., 2023a). These findings are consistent with previous research, reaffirming the INAS's capacity to assess medication adherence (Sampaio et al., 2021; Weinman et al., 2018), and emphasising the importance of accurate assessment tools for identifying high-risk patients (Basu et al., 2019; Iragorri & Spackman, 2018). Taken together, this scale could be utilised in clinical practice as an effective screening tool to identify patients who are at heightened risk of nonadherence, allowing for timely interventions to prevent or mitigate adverse outcomes.

Importantly, the findings presented in Chapter Four of this thesis shed light on the main motives behind intentional nonadherence among people with gout taking allopurinol (Emad et al., 2022). This extension of the broader literature on medication adherence is of great importance as it provides a deeper understanding about the specific factors influencing intentional nonadherence in gout, moving away from general adherence considerations and a one-size-fits-all approach (Easthall & Barnett, 2017). By identifying distinct motivations, such as the desire to maintain a sense of normalcy and health or the willingness to test ULT limits, this research offers practical guidance to healthcare providers, underscoring the importance of developing strategies and interventions that address these motives to enhance medication adherence. Furthermore, these outcomes align with the Hierarchical Model for Medication Adherence (HMMA), emphasising the crucial role of patients' beliefs and perceptions in medication adherence (Unni & Bae, 2022). This contribution aligns with existing studies advocating for tailored approaches to improving medication adherence, emphasising that understanding and targeting determinants of nonadherence is a critical step in designing effective interventions and strategies (Zullig et al., 2019).

The second main contribution of the work presented is support for targeting nonadherence motives as an applicable technique to improve educational resources and to enhance clinical and health outcomes. In Chapters Five and Six, the analysis of gout educational resources (Emad et al., 2023b) and the utilisation of smartphone notifications as an intervention technique to address these motives are explored (Emad et al., in press). These studies align with previous preliminary evidence that targeted strategies and tailored interventions can improve medication adherence effectively

(Doherty et al., 2018; Petrie et al., 2012).

Importantly, the empirical work presented here can inform the design of tailored strategies aiming to enhance medication adherence in gout. Chapter Five includes the first study to analyse the content of the online gout educational resources to see how medication adherence has been addressed, taking into account the main motives for intentional nonadherence. This study found limited medication adherence coverage and narrow strategies in online gout educational resources (Emad et al., 2023b). This finding highlights the need for more comprehensive, patient-centered educational materials that target the main reasons for nonadherence, echoing a broader challenge of building health literacy affecting patient beliefs and perceptions toward their medication (HMMA, Unni & Bae, 2022). The thesis serves as a call to action, highlighting the importance of developing educational materials that comprehensively address the main reasons behind nonadherence, aligning with the broader literature's emphasis on the role of patient education and support in improving medication adherence (Neogi & Dalbeth, 2018; Fields & Batterman, 2018; Aung et al., 2017).

This thesis also addresses the gap between understanding the reasons behind nonadherence and implementing effective interventions. Chapter Six provided evidence for the feasibility, acceptability and potential effectiveness of utilising smartphone notifications as a tailored intervention technique to enhance medication adherence in people with gout, aligning with the growing interest in the application of mobile health (mHealth) solutions within healthcare interventions. Medication nonadherence remains a persistent challenge in modern healthcare (Kleinsinger, 2018; De Vera et al., 2014). Establishing interventions that can enhance medication adherence continues to be a central goal in health psychology research. While existing research emphasise the importance of providing targeted information to modify patient beliefs (Te Kampe et al., 2022; Petrie et al., 2012), the findings of this thesis contribute a novel perspective to the literature. The research demonstrates that targeting nonadherence motives through smartphone notifications holds significant potential as an effective, feasible and acceptable intervention strategy (Emad et al., in press). Furthermore, this thesis extends its contributions by providing evidence that mobile health applications (mHealth apps) can be applied to influence medication adherence as a belief-modifying technique. This aligns with earlier research highlighting the importance of introducing new gout management applications to enhance self-management of this chronic disease (Day et al., 2020; Nguyen et al., 2016). Overall, this thesis underscores the potential of technology-driven solutions in addressing complex healthcare

challenges including medication adherence.

Limitations of Study Findings

There are important limitations which should be acknowledged when interpreting these results. This section addresses general limitations applicable across the studies presented. First, the measurement of outcomes within the reported studies, including Intentional Non-Adherence Scale (INAS) scores, treatment satisfaction, and number of missed doses of prescribed medication, relies upon self-report, which can be susceptible to sources of bias. Most relevant to the current research would be social desirability or recall bias. Social desirability bias refers to when participants are inclined to provide responses that they believe are more socially acceptable or favourable (Wagner & Miller, 2004). For instance, when asked about their adherence to prescribed medications, participants might feel compelled to give responses that portray them in a positive light, even if their actual experiences or behaviours differ (Stirratt et al., 2015). However, it is important to note that, within the clinical setting, there are limited alternatives for measuring psychological constructs. Moreover, existing research has provided evidence suggesting that social desirability bias may not significantly influence evaluations in chronic disease management programmes (Nolte et al., 2013). Recall bias, on the other hand, pertains to variations in self-reporting responses concerning past experiences, including the number of medication doses a patient may have missed within a specific period (Savioni & Triberti, 2020). To mitigate the potential effects of recall bias, future work in this area would greatly benefit from more objective methods of measuring adherence, such as pill count and electronic pill bottle monitoring.

Second, this thesis measured medication adherence using serum urate levels which were obtained through medical records review, resulting in unavoidable missing data which necessitates a cautious interpretation of the results. In Chapter Six, relying on medical records for detecting serum urate levels was found to be inconsistent and not fully feasible, which diminished the statistical power to detect significant differences between the study groups (Emad et al., in press). This limitation could be avoided by requesting independent blood tests at predefined intervals as part of study participation instead of relying upon data collected from routine care. However, asking participants to have a blood test during the study could potentially heighten their awareness of monitoring, resulting in behaviour changes due to the Hawthorne effect (Berkhout et al., 2022). These changes might then conflate with the effects of the intervention and complicate the process of result interpretation.

The cross-sectional design of the study in Chapter Three limited the ability to evaluate the predictive capabilities of the Intentional Non-Adherence Scale (INAS) regarding medication adherence. One limitation of this design is that it captures data at a single time point, preventing the assessment of how INAS scores relate to future adherence behaviour or health outcomes over an extended period. To overcome this limitation, future research could employ a longitudinal study, following participants over time to better assess the INAS's predictive capabilities in relation to subsequent adherence behaviour and health outcomes.

The study in Chapter Five also was limited to English-speaking countries, which may not generalise to online gout educational resources in other languages (Emad et al., 2023b). In addition, there are currently no guidelines for developing the content of adherence materials on educational gout resources, leading to variability in the information provided. Furthermore, while readability scores were assessed in this thesis, they alone cannot indicate the overall quality or comprehensiveness of the information. The content analysis in Chapter Five primarily focused on the type of information available on the websites. While the findings provided applicable insights into adherence material provided in educational gout resources, future research should consider evaluating the accuracy and scientific rigour of website content.

Another limitation is that the research presented here comprised patients who had been taking allopurinol for at least six months. Hence, it is possible that the findings may not fully reflect the experiences of individuals who are newly prescribed allopurinol or who differ from the study population in other ways. Another limitation to consider is the relatively high level of education observed among the participants, limiting the generalisability of the findings to individuals with lower levels of education. The study population in Chapter Six was also comprised of participants with both high baseline adherence and a history of active participation in previous gout-related projects. This may have led to increased awareness of medication adherence, potentially limiting the applicability of the findings to a broader population. Thus, studies with a more diverse patient sample are needed to assess the generalisability of the results.

Finally, although the feasibility study presented in Chapter Six provided preliminary evidence for positive changes in adherence outcomes, we are yet to conduct a larger scale, randomized controlled trial (RCT) to assess the intervention's effectiveness and establish its broader impact on medication adherence and clinical outcomes. Furthermore, it is important to acknowledge that

mHealth apps and using smartphone notifications rely on access to technology and mobile data, which may pose challenges for individuals with limited resources or residing in areas with poor connectivity. Equity issues related to accessibility should be considered in future research and implementation strategies. Perhaps providing subsidies or community-based access centres for those with limited financial resources or restricted connectivity could be a more effective and inclusive solution. Alternative approaches or support systems may be necessary to assist individuals facing technology-related barriers. In summary, while this study offers valuable insights, these limitations provide avenues for future research to further enhance our understanding of intentional nonadherence and its management.

Strengths and Clinical Implications

Despite the limitations highlighted above, there are considerable strengths of the research included within this thesis. First, the thesis used a newly introduced measure that allowed assessing medication adherence in people with gout through a closer examination of the reasons behind patients' nonadherence with allopurinol. Moreover, the quantitative studies presented in this thesis used levels of serum urate as an objective marker of medication adherence in people with gout. This approach eliminates the influence of bias that often comes with self-reported information and provides a clearer picture of effects upon medication adherence and clinical outcomes. Second, the thesis consistently adopts a patient-centred approach, focusing on understanding and addressing the specific determinants of intentional nonadherence to urate lowering medications. This approach reflects a growing recognition of the importance of tailored interventions in healthcare.

Moreover, this thesis includes a comprehensive content analysis on online gout educational resources to assess how adherence to urate lowering medications is addressed, with a specific focus on targeted reasons for nonadherence (Emad et al., 2023b). This study highlights the limitations in existing resources and emphasises the need for more tailored and patient-centred adherence materials. By pinpointing the gaps, the thesis contributes to a better understanding of the shortcomings in current online gout educational resources, providing guidance for improving patient education materials.

This thesis also includes the first feasibility study to assess the potential effectiveness of nonadherence-targeted smartphone notifications on adherence with allopurinol among people with gout (Emad et al., in press). Feasibility studies are the most useful to investigate acceptability of an

intervention among study population and to inform practical problems while implementing the intervention in a large scale. By uncovering logistical challenges, recruitment difficulties, resource constraints, or unforeseen barriers, feasibility studies help researchers fine-tune their strategies for the larger study. In addition, these studies serve as a testing ground for research procedures and data collection methods, ensuring their appropriateness and effectiveness (Bowen et al., 2009).

The feasibility study presented in this thesis also includes an active control group in its design (Emad et al., in press). Although previous work has used an active control group (e.g., Petrie et al., 2012), this study compared the information tailored toward patients' main motives for intentional nonadherence to an alternative form of intervention (general health advice). The active control group in the study described in Chapter Six matched the intervention in amount of contact, length of intervention, and frequency of notifications provided. Including an active control group helped account for non-specific effects such as attention and their use as reminders, which can sometimes overshadow the actual impact of intervention contents (Donovan et al., 2009). This design allowed for a more comprehensive understanding of the distinct, additive elements of general health advice in the study.

Lastly, another strength of the research presented in this thesis is the use of technology. The utilisation of e-health information is growing as a prevalent practice among patients (Sobon, 2022). Hence, technology-based interventions have the potential to be scaled up and reach a broader audience (Coleshill et al., 2019). The utilisation of online resources in Chapter Five and smartphone notifications in Chapter Six reflects the real-world context in which patients often seek information and support for their health conditions using technology. This approach aligns with the way many patients access information in today's digital age, enhancing the relevance and applicability of the research to contemporary healthcare practices.

There are clear clinical implications of the research studies described within this thesis. First, the presented findings suggest that the INAS can serve as an effective tool for screening individuals who may struggle with adherence to urate lowering medications, allowing for early-enough interventions to prevent nonadherence and achieve better clinical outcomes. The INAS also allows healthcare providers to track changes in adherence behaviours over time and develop more tailored interventions in clinical context. Second, the research included within this thesis suggests that clinicians can improve adherence to urate lowering medications by framing it as a means to restore a

normal life and emphasising the importance of continuous medication intake. Early discussions about medication-related concerns and the drawbacks of skipping medication doses or relying on symptoms rather than urate levels can also be beneficial. This understanding can be extended to the development of educational gout resources. To enhance medication adherence, content creators need to target common beliefs and perceptions related to urate lowering medication, which often drives intentional nonadherence behaviour. In addition, they may need to pay greater attention to unintentional factors such as forgetfulness, as well as to improve the readability of the provided content to help patients with lower health literacy.

The successful feasibility and acceptability of targeted smartphone notifications in this research suggest that healthcare providers from various clinical backgrounds, not limited to health psychologists, could efficiently deliver these notifications to patients. Given the increasing utilisation of mobile technology in healthcare (Sharma et al., 2022), integrating such interventions into standard care appears applicable without significant excessive resources or time commitments. Moreover, clinicians could explore this application's potential as supplementary educational material to enhance patient engagement and provide personalised support.

Future Directions

The research presented in this thesis contributes to a growing body of literature that explores medication adherence among people with gout. The results provide support for continued investigation into the INAS assessment capabilities, as there are remaining limitations yet to be understood. Future work should investigate the associations between INAS scores and medication adherence using longitudinal studies. As highlighted above, this would expand upon the research presented in this thesis by investigating whether these associations are modified by concepts discussed within the medication adherence literature, such as patient-provider communications, prescribed medication dosages, and risk perception. It would also provide an opportunity to predict medication adherence more effectively over time.

Another consideration for future work would be to investigate medication adherence portrayal among online gout educational resources in multiple languages. The study described in Chapter Four demonstrated limited adherence coverage and the narrow range of adherence-promoting strategies in educational gout resources in six English-speaking countries. However, we are yet to understand if the results would be different across different linguistic and cultural contexts. This allows researchers

to gain insights into how adherence content is presented to diverse patient populations, potentially exploring unique challenges and solutions in various populations. Although this research indicated that a significant portion of the adherence content was not comprehendible, future work should attempt to evaluate the accuracy, credibility, and scientific rigour of the information provided on the educational gout resources. Evaluating the quality of content in addition to readability would offer a more holistic understanding of the online patient resources available, ensuring that patients receive reliable and evidence-based information.

Evaluating the impact of patient education materials on actual patient behaviour and adherence outcomes is another important area of investigation. Future studies could include longitudinal research to assess whether exposure to specific types of educational content correlates with improved medication adherence over time. Such studies would provide applicable insights into the effectiveness of nonadherence-targeted education materials in influencing patient behaviour and health outcomes.

Another related consideration for future work could be the development of evidence-based guidelines as a framework for creating patient education materials related to medication adherence. Future studies could encompass both content recommendations, ensuring accuracy and relevance, and readability guidelines, ensuring that materials are accessible and understandable to patients. The development of such guidelines would promote consistency and quality in patient resources.

Future research should consider conducting larger and longer-term studies to evaluate the efficacy of nonadherence-targeted smartphone notifications on medication adherence in people with gout. The study described in Chapter Six demonstrated the feasibility and acceptability of this intervention. Hence, larger scale Randomised Control Trials (RCT) would provide sufficient statistical power and allow for a more robust examination of the intervention's actual effects. Additionally, longer-term studies would help capture the sustainability of any improvements in medication adherence over time. To enhance the generalisability of findings, future studies should aim to include a more diverse patient population. This could involve recruiting individuals who are newly prescribed urate lowering medications or who have varying durations of medication use. Including a broader range of patients would enable researchers to explore how adherence patterns differ among different patient groups.

Future studies should consider incorporating measures of gout severity and activity level at the baseline. This would allow researchers to assess whether the intervention's impact varies based on the severity of the condition. The research presented in Chapter Six measured medication adherence through serum urate levels and the number of missed doses as an outcome measure, which could introduce biases. Researchers should explore more reliable methods for measuring serum urate levels. This could involve implementing systematic and standardised approaches for collecting data on serum urate levels through regular blood tests or wearable devices throughout the study. Future work should also incorporate more objective methods of measuring medication adherence. For example, researchers could utilise pill counts or electronic pill bottle monitoring to avoid biases. Ensuring consistent and accurate measurement of this clinical outcome will strengthen the assessment of the intervention's impact on gout management.

A related consideration for future work is to replicate the research with a more diverse patient sample. This would involve including individuals with varying demographic and clinical features. Understanding how the intervention works across different demographic and adherence profiles can help tailor strategies for specific patient groups.

Given the disparities in technology access and connectivity, future research should explore alternative approaches to reach patients facing technology-related barriers. This could entail adapting the intervention delivery method to be less reliant on mobile data, for example, using text messages, or offering supplementary support to individuals facing technological resource limitations. Ensuring equitable access to interventions is essential for improving healthcare outcomes. These are just some examples of how future work could investigate the utility of the INAS and nonadherence-tailored interventions preventatively to improve gout management. The potential for enhancing medication adherence and gout management remains an exciting avenue for future research. By addressing the outlined research directions, future work can move toward more effective screening, more tailored interventions, better patient education, and equitable access to healthcare support, ultimately improving health outcomes among people with gout.

Conclusion

The benefits of gout management with urate lowering medications can be affected by many patient-related factors. Medication beliefs and perceptions result in nonadherence behaviour and problematic health outcomes. Methods which enable healthcare providers to identify patients at heightened risk of

nonadherence to urate lowering medications and understand the main motives behind this behaviour to produce changes in clinical outcomes deserve investigation through research. Although substantial theoretical support suggested the importance of medication adherence in gout management, limited empirical studies of intentional nonadherence had been conducted within the field of health psychology. In particular, there was a lack of understanding in the literature regarding why people with gout do not take their urate lowering medications and how these motives should be targeted in educational resources and tailored interventions.

The work presented within this thesis aimed to extend previous work and provide greater evidence for the utility of the Intentional Non-Adherence Scale (INAS) in assessing medication adherence. The studies presented here demonstrate that the INAS has significant capability in assessing medication adherence in people with gout. This scale was also used to deepen current understanding of determinants of nonadherence to urate lowering medications. The research within this thesis also explored how these determinants are reflected on online gout educational resources, shedding light on areas for potential improvement. The empirical work also provided insights regarding how feasible and acceptable it is to target determinants of nonadherence through smartphone notifications among people with gout taking urate lowering medications. The conclusions drawn from these studies provide significant contributions to the current literature and demonstrate a novel intervention strategy with high clinical applicability. While undoubtedly, further work is needed to understand the full scope of the applications for presented findings, evidence suggests that better understanding of medication adherence and incorporating nonadherence-targeted techniques into modern healthcare have the potential to enhance medication adherence and produce benefit in patient outcomes.

Appendices

Appendix A: The Intentional Non-Adherence Scale (INAS)

People have different experiences when taking medication and use their medications in ways which suit them. Sometimes people forget or decide not to take their medication for various reasons. We are interested in your personal views and experiences of your prescribed medication regime, specifically allopurinol and the way you use this medication. All the information you provide is confidential. There are no right or wrong answers to these questions – an answer is correct if it is true for you. We are most interested in your own opinion. Please choose the response that best fits with your circumstances. Listed below are some of the reasons why people sometimes stop taking their medications. We would like to know how often each of the following statements is true for you in the past six months. For each statement please tick (✓) one answer which best represents you.

To see if my illness is still there.				
1. Strongly disagree	2. Disagree	3. Neutral	4. Agree	5. Strongly agree
To see if I can do without it.				
1. Strongly disagree	2. Disagree	3. Neutral	4. Agree	5. Strongly agree
To see if I really need it.				
1. Strongly disagree	2. Disagree	3. Neutral	4. Agree	5. Strongly agree
Because I am not convinced that the medicine is really right for me.				
1. Strongly disagree	2. Disagree	3. Neutral	4. Agree	5. Strongly agree
Because I am not sure that the doctor chose the right medicine for me.				
1. Strongly disagree	2. Disagree	3. Neutral	4. Agree	5. Strongly agree
To give my body a rest from the medicine.				
1. Strongly disagree	2. Disagree	3. Neutral	4. Agree	5. Strongly agree
Because the medicine is harsh on my body.				
1. Strongly disagree	2. Disagree	3. Neutral	4. Agree	5. Strongly agree
Because I don't like the medicine to accumulate in my body.				
1. Strongly disagree	2. Disagree	3. Neutral	4. Agree	5. Strongly agree
Because my body is sensitive to the effects of medicine.				
1. Strongly disagree	2. Disagree	3. Neutral	4. Agree	5. Strongly agree

Because I don't like the side effects.				
1. Strongly disagree	2. Disagree	3. Neutral	4. Agree	5. Strongly agree
Because I don't like chemicals in my body.				
1. Strongly disagree	2. Disagree	3. Neutral	4. Agree	5. Strongly agree
Because it may affect the body's own natural healing processes.				
1. Strongly disagree	2. Disagree	3. Neutral	4. Agree	5. Strongly agree
Because I think I am on too high a dose.				
1. Strongly disagree	2. Disagree	3. Neutral	4. Agree	5. Strongly agree
Because I think the drug might become less effective over time.				
1. Strongly disagree	2. Disagree	3. Neutral	4. Agree	5. Strongly agree
Because I worry about becoming dependent on my medicine.				
1. Strongly disagree	2. Disagree	3. Neutral	4. Agree	5. Strongly agree
Because I want to think of myself as a healthy person again.				
1. Strongly disagree	2. Disagree	3. Neutral	4. Agree	5. Strongly agree
Because it reminds me that I have an illness.				
1. Strongly disagree	2. Disagree	3. Neutral	4. Agree	5. Strongly agree
Because I want to lead a normal life again.				
1. Strongly disagree	2. Disagree	3. Neutral	4. Agree	5. Strongly agree
Because it is good not to have to remember.				
1. Strongly disagree	2. Disagree	3. Neutral	4. Agree	5. Strongly agree
Because it is inconvenient to take all the time.				
1. Strongly disagree	2. Disagree	3. Neutral	4. Agree	5. Strongly agree
Because the drug schedule doesn't fit with my lifestyle.				
1. Strongly disagree	2. Disagree	3. Neutral	4. Agree	5. Strongly agree
Because I don't think the treatment is worth it.				
1. Strongly disagree	2. Disagree	3. Neutral	4. Agree	5. Strongly agree

Appendix B: The Treatment Satisfaction Questionnaire for Medication (TSQM)

We would like to ask you about the level of your satisfaction with your medication. For the following questions, please circle the number that best corresponds to your views. There are no right or wrong answers. We are interested in your personal views.

How satisfied or dissatisfied are you with the ability of the medication to prevent or treat your condition?						
1 Extremely satisfied	2	3	4	5	6	7 Extremely dissatisfied
How satisfied or dissatisfied are you with the way the medication relieves your symptoms?						
1 Extremely satisfied	2	3	4	5	6	7 Extremely dissatisfied
How satisfied or dissatisfied are you with the amount of time it takes the medication to start working?						
1 Extremely satisfied	2	3	4	5	6	7 Extremely dissatisfied
As a result of taking this medication, do you currently experience any side effects at all?						
1 No side effects at all	2	3	4	5	6	7 Extreme side effects
How bothersome are the side effects of the medication you take to treat your condition?						
1 Not at all	2	3	4	5	6	7 Extremely bothersome
To what extent do the side effects interfere with your physical health and ability to function (i.e., strength, energy levels, etc.)?						
1 Not at all	2	3	4	5	6	7 Extremely Interfering
To what extent do the side effects interfere with your mental function (i.e., ability to think clearly, stay awake, etc.)?						
1 Not at all	2	3	4	5	6	7 Extremely Interfering

To what degree have medication side effects affected your overall satisfaction with the medication?						
1 Not at all	2	3	4	5	6	7 Extremely affected
How easy or difficult is it to use the medication in its current form?						
1 Extremely easy	2	3	4	5	6	7 Extremely difficult
How easy or difficult is it to plan when you will use the medication each time?						
1 Extremely easy	2	3	4	5	6	7 Extremely difficult
How convenient or inconvenient is it to take the medication as instructed?						
1 Extremely convenient	2	3	4	5	6	7 Extremely inconvenient
Overall, how confident are you that taking this medication is a good thing for you?						
1 Extremely confident	2	3	4	5	6	7 Extremely unconfident
How certain are you that the good things about your medication outweigh the bad things?						
1 Extremely certain	2	3	4	5	6	7 Extremely uncertain
Taking all things into account, how satisfied or dissatisfied are you with this medication?						
1 Extremely satisfied	2	3	4	5	6	7 Extremely dissatisfied

Appendix C: Intervention Evaluation Script for Study 4 (presented in Chapter Six)

Script for Intervention and Control Group
We are interested in understanding the optimal way to deliver our intervention. Your feedback will help us to shape our study and improve adherence among patients with gout. Please let us know about your thoughts on the following questions.
Please summarise the intervention that you received.
What did you like/dislike about the intervention?
What were the obstacles (e.g., freeze, crash, slow, Wi-Fi /data cost)?
Are you happy to still be using the application to receive the notifications?
Are you happy to recommend the application to other people with gout?
Was the application easy to use? Why or why not?
Did you find the information was easy to understand and easy to navigate? Can you give me an example?
What could the developers of the intervention have done to make you want to use it more?
What do you think about the frequency of the notifications?
What do you think about the timing of the notifications?
What do you think about the tone of the notifications?
To which extend did you find the content of the notifications understandable?
To which extend did you find the content of the notifications helpful?
If you could change anything about the content of the modules, what would it be and why?
Do you have any further comments?

Appendix D: Notification Bank for Study 4 (presented in Chapter Six)

Notifications for the Control Group: General Health Advice

- Drinking enough water can have numerous benefits for your health. To start with, you can set reminders to drink water during the day.
- You can reap numerous health benefits by drinking enough water. The first thing you can do is set up a reminder for when it's time to drink water.
- Researchers recommend drinking six to eight glasses of water every day. You can set a daily goal and reward yourself once your goal is achieved.
- It is recommended that you drink six to eight glasses of water each day. A daily goal can motivate you to reach it and you can reward yourself once it is met.
- You need to drink plenty of fluids to stop you getting dehydrated. Remember to keep a reusable water bottle with you.
- Make sure you drink plenty of fluids to avoid becoming dehydrated. It is always a good idea to keep your water bottle on you.
- Sunlight is a great source of vitamin D. Aim to get 10–30 minutes of midday sunlight, five times per week.
- The vitamin D in sunlight is very helpful for your health. Take advantage of midday sunlight for 10 to 30 minutes five times a week.
- Vitamin D supplements are a good alternative for people who are unable to get adequate sun exposure. If you need expert advice for nutrition information, don’t hesitate to make an appointment with a registered dietitian.
- People who do not get enough sun exposure may benefit from vitamin D supplements. Don't hesitate to see a registered dietitian for nutrition advice if you need it.
- Regular exercise may help reduce your risk of getting serious health conditions. You can put your exercise plans into your calendar like any other meeting and try not to get pulled off track.
- Your health is likely to improve if you exercise regularly. It's a good idea to schedule your workout sessions as you would at any other meeting, especially if you don't want to get side-tracked.
- Doing exercise is one of the best things you can do for your mental and physical health. Let’s set realistic goals for yourself and monitor your progress.
- Exercising is the number one thing you can do for your mental and physical health. Setting realistic goals and monitoring your progress will help you reach your goals.
- Your body loses its strength and stamina without regular activity. Let’s plan your workouts for the time of day when you’re most awake and energetic.
- A body without exercise loses strength and endurance. We suggest scheduling your workouts for the time of day when you're most alert and energetic.
- Regular physical activity can help your body to function properly. Does a goal of exercising for 30 minutes a day, 5 times a week sound good?

- You can maintain a healthy body by participating in regular physical activity. Aiming to exercise for 30 minutes a day, 5 times a week, sounds reasonable, doesn't it?
- Regular exercise improves your brain health. To make exercise a habit, you can give yourself immediate rewards when you successfully complete a workout.
- You can improve your brain health by exercising regularly. Giving yourself rewards for a successful workout is a great way to make exercise a habit.
- Exercise triggers your body to release proteins and other chemicals that improve the structure and function of your brain. You can consider exercise an important appointment with yourself and mark it on your daily agenda.
- Exercise improves the structure and function of your brain by triggering the release of proteins and other chemicals. Putting exercise on your daily agenda can help you see it as an important appointment with yourself.
- Exercise can help improve cognitive function. You can plan ahead of anything that might get in the way of exercise and remove obstacles.
- Improved cognitive function can be achieved through exercise. Any obstacles you might encounter during exercise can be planned ahead of time and removed.
- Physical activity stimulates various brain chemicals, making you feel happier, more relaxed and less anxious. To do it regularly, you can ask a friend or family member to check in on your progress.
- The various brain chemicals stimulated by physical activity improve your mood, make you feel relaxed, and less anxious. Having a friend or family member follow-up with you regularly is a great way to ensure your success.
- Regular physical activity can improve your muscle strength and boost your endurance. Announcing your goals to your social group (either online or in person) can help keep you on track.
- Strengthening your muscles and increasing your endurance is possible with regular physical activity. Maintaining motivation can be achieved by sharing your goals with your social circle.
- Exercise is a great way to boost your health but first, you need to choose your exercise carefully. If you hate the activity, you won't stick with it.
- The benefits of exercise are enormous, but the first step is choosing the right exercise. Getting into an activity that you hate won't keep you motivated.
- Exercise can build overall strength and endurance. To do it regularly, you can commit to another person, and hold yourself accountable.
- Strength and endurance can be improved through exercise. It is easier to sustain a regular workout routine if you hold yourself accountable.
- People who exercise regularly have a lower risk of developing chronic conditions. Aim to start from now and don’t leave it for later!
- Regular physical activity reduces the risk of chronic illnesses. Don't put off starting until later; start now!
- Research shows that physical activity can reduce your risk of mental health problems. Aim to

walk instead of drive, whenever you can.

- Physical activity has been shown to reduce mental health risks among adults. When possible, try to walk rather than drive.
- Exercise can boost self-esteem and mood. Setting a weekly goal and doing at least 10 minutes of physical activity at a time to reach that goal could be a good start.
- In addition to boosting self-esteem, exercise can improve mood. An ideal starting point could be to do at least 10 minutes of physical activity every day to reach a weekly goal.
- Regular physical activity can help with sleep quality. Aim to take the stairs instead of the escalator or elevator.
- It can improve the quality of your sleep if you engage in regular exercise. Instead of using escalators or elevators, consider taking the stairs.
- Regular physical activity can help with weight. Even a 10-minute walk at lunchtime would be beneficial.
- It is possible to lose weight by exercising regularly. It would be beneficial to walk for even 10 minutes at lunchtime.
- Weight loss or weight prevention can both be achieved through exercise. Walking children to school is a good idea.
- Regular exercise can help you control your weight. You can keep comfortable clothes and walking or running shoes in the car and at the office to be ready anytime!
- Maintaining a healthy weight can be achieved through regular exercise. Keeping comfortable clothes and the necessary walking or running shoes in your car and at work will keep you prepared at all times.
- Maintaining a healthy weight is important for health. Joining a weight management programme could be a good start!
- Keeping your weight in check is vital for good health. An effective way to lose weight could be joining a weight programme!
- Reaching and maintaining a healthy weight is important for overall health. Aim to monitor your weight by stepping on the scales once or twice a week.
- In order to maintain good health, it is crucial to maintain a healthy weight. Try to step on the scales once or twice a week to keep track of your weight.
- Managing your weight can lower the risk of chronic conditions. As eating breakfast may assist you with your weight maintenance goals, try not to skip your breakfast.
- The risk of chronic diseases can be reduced when you manage your weight. If you are trying to maintain a healthy weight, you may find eating breakfast beneficial.
- Research has proven that obesity has negative impacts on your health. You can always listen to your body ‘s physical cues to stop eating before you feel overly full.
- Obesity has been linked to negative health outcomes according to scientific research. Your body will tell you when to stop eating when it feels overfull so you can stop before you feel too full.
- Regular exercise can help your body manage insulin levels. There's no rule that says you have

to go to a gym or buy equipment; you can do a variety of activities you enjoy.

- Maintaining a healthy insulin level can be achieved with regular exercise. Fitness is not a one-size-fits-all thing; you can choose any activity that you enjoy.
- Exercise can improve your mood through releasing chemicals in your brain. To start with you can make exercise a priority and exercise first thing in the morning.
- The release of chemicals in your brain can boost your mood through exercise. If you begin exercising first thing in the morning, you can make exercise a priority.
- Regular exercise can help keep your thinking, learning, and judgment skills sharp as you age. Aim to exercise on your way home from work and do it even when you are too tired.
- Regular exercise keeps you sharp as you age in terms of your mental acuity, learning abilities, and judgment abilities. Even if you are too tired to exercise, aim to work out while you are on your way home from work.
- Regular exercise helps keep the bone density as you age. Aim to set a goal, log your activity and make a game of it.
- Maintaining bone density while aging requires regular exercise. Make a game of it by setting a goal, logging your activity, and making it enjoyable.
- Physical activity helps you to fall asleep faster and stay asleep longer. Walking for 10 minutes three times a day with a pedometer (or a dog) can help you sleep better at the end of the day!
- Sleeping better and staying asleep longer is easier when you've exercised. If you walk with a pedometer three times a day (or with your dog), you can sleep better at night!
- Studies show that physical activity can help you to live longer. Let’s decide on a goal and a reward, and work toward it.
- Exercise can prolong your life, according to studies. We can work toward a goal and a reward if we decide for one together.
- Exercise can reduce your chances of early dying. While choosing an exercise, consider what you like doing, and the environment you’d enjoy when being physically active.
- The chance of dying early can be reduced if you exercise. If you are thinking about doing a physical activity, consider what you enjoy and the environment you'd like.
- Drinking too much alcohol is linked to chronic diseases. Aim to skip a drink now and then and substitute with a non-alcoholic drink.
- Chronic diseases are linked to excessive drinking of alcohol. When possible, try to swap your alcoholic drinks for non-alcoholic beverages.
- Many health problems are strongly linked to drinking alcohol. You can keep track of how many drinks you are consuming and have a glass of water with your drink, and sip on that between sips of your drink.
- Drinking alcohol causes a variety of health problems. Keeping track of how many drinks you drink in a day and sipping on a glass of water between a sip of your drink is a good idea.
- Exercise can improve sleep quality. You can do it regularly by setting a time and sticking with that time.
- A good night's sleep can be improved by exercise. It's easy to do if you set a time and stick

with it.

- Poor sleep can disrupt your appetite hormones. Aim to reduce blue light exposure in the evening by installing an app that blocks blue light on your smartphone. These are available for both iPhones and Android models.
- Your appetite hormones are disrupted when you don't get enough sleep. Utilizing an app that blocks blue light on your smartphone will help you reduce your exposure to blue light at night. Both iPhones and Androids can use these apps.
- Poor sleep can reduce your physical and mental performance. To start with, try not to consume caffeine late in the day.
- You can become mentally and physically less efficient if you do not get enough sleep. As a first step, try not to drink caffeine late at night.
- Poor sleep is one of the strongest individual risk factors for weight gain and obesity. Try to sleep and wake at consistent times and reduce irregular or long daytime naps.
- Individuals who do not get enough sleep are at higher risk of weight gain and obesity. It is a good idea to reduce irregular or long naps and sleep at consistent times.
- Being exposed to bright lights in the evening can disrupt your production of the sleep hormone melatonin. Aim to stop watching TV and turn off any bright lights two hours before heading to bed.
- Melatonin is a sleep hormone that is produced in response to bright light at night. Before you go to bed, try to stop watching TV and turn off bright lights at least two hours before bedtime.
- Sleep can be interrupted due to stress. Don’t forget to optimize your bedroom environment by setting the right temperature and eliminating external light and noise.
- In the case of stress, sleeping can be disrupted. By setting an appropriate temperature and reducing noise and external light, you can create the perfect sleeping environment.
- Managing stress can help you sleep better. Aim to learn and practice relaxation techniques for stress management.
- Your sleep can be improved by managing your stress. Practicing relaxation techniques will help you cope with stress.
- Managing stress can help you control your weight. Don't rely on alcohol, drugs or sweets to reduce stress, and try to find more efficient ways to manage your stress.
- Controlling your weight is possible if you manage your stress. Instead of looking for ways to reduce stress by drinking, smoking, or eating sweets, you can try to find more effective ways.
- Managing stress can boost your immune system. Physical touch and hugging a loved one can do a lot to relieve your stress.
- It's possible to boost your immunity by managing your stress. You can relieve stress a lot by touching and hugging your loved ones.
- Managing stress can improve your mood. Aim to try meditation, yoga, or tai-chi for stress management.
- A coping strategy can help you improve your mood. For stress management, you might want to try meditation, yoga, or tai-chi.

- By managing your stress, you can get along better with family and friends. Expanding your network and seeking out social support when stressed could be a good idea.
- You can become better friends and family members by managing your stress. When you are stressed, it might be a good idea to expand your network and seek out social support.
- Stress can cause weight gain in many ways. You can keep a stress diary for a few weeks to become more aware of the situations which cause you to become stressed.
- There are many ways that stress can contribute to weight gain. For a few weeks, you could keep a stress diary to gain a better understanding of the conditions that cause you stress.
- Stress messes with your appetite and sleep hormones. Avoiding, or at least reducing, your consumption of nicotine and any drinks containing caffeine and alcohol could be helpful.
- Stress throws off your body's hormones that control appetite and sleep. You might find it helpful to avoid or reduce your intake of nicotine and any alcohol and caffeine-containing drinks.
- Stress raises blood pressure, increasing your risk of cardiovascular diseases. You can reassess your To-Do Lists and reduce your workload, if needed.
- You are more likely to develop cardiovascular disease if you are stressed. Depending on your requirements, you can adjust your To-Do Lists and reduce your workload.
- Chronic stress can weaken your immune system. You can break down big problems into smaller parts, and take one step at a time, instead of trying to tackle everything at once.
- Your immune system can be compromised by chronic stress. When you attempt to tackle big problems all at once, you can break them down into smaller pieces and take them one at a time.
- Stress can reduce your productivity levels. Aim to learn problem-solving skills and decision-making techniques.
- Reduced productivity can be caused by stress. We can learn how to solve problems and make decisions.
- If your methods of coping with stress aren’t contributing to your greater emotional and physical health, it’s time to find healthier ones. Aim to develop a positive self-talk habit by practising it every day, everywhere!
- Changing your ways of coping with stress can help you achieve greater emotional and physical well-being. Practising positive self-talk every day, everywhere, will help you develop it.
- Coffee contains caffeine, which is a stimulant, so will increase your level of stress. Aim to try a decaf next time!
- The caffeine in coffee increases your level of stress, because this substance is a stimulant. The next time you go, try a decaf!
- Using alcohol to alleviate stress is not ultimately helpful. You can take a break to pet the dog, hug a loved one or do something to help someone else, when stressed.
- It is not necessarily helpful to use alcohol as a stress reliever. Whenever you're feeling stressed, you can pet the dog, hold hands with a loved one, or do something to help someone

else.

- Lack of sleep is a significant cause of stress. Each person needs six to eight hours of sleep.
- Stress is exacerbated by sleep deprivation. It is recommended that each person sleeps between six and eight hours per night.
- There are a wide range of techniques to manage stress so try a few and see what works best for you. You can seek treatment with a psychologist or other mental health professional trained in stress management.
- It can be helpful to try a few different techniques to manage stress to find what suits you best. An experienced psychologist or mental health professional trained to manage stress may be of help.
- Chronic stress can cause cardiovascular diseases. Try to check your blood pressure regularly.
- The effects of chronic stress on the heart are well known. Keeping an eye on your blood pressure is essential.
- Health issues such as insomnia and heart palpitations may result from excessive caffeine consumption. Having less than four cups of coffee per day is a safe and healthy way to enjoy coffee.
- The use of excessive caffeine may be associated with health problems. It is recommended to avoid high-sugar additives like sweetened creamer.
- Our daily water intake is often inadequate. However, our bodies depend on water to function properly.
- Were you aware that 60% of our body is water? It carries nutrients and oxygen around our bodies, helps keep our bodies hydrated and removes waste.
- During everyday activities, we lose water through urine, bowel movements, perspiration, and breathing. It can be helpful to have a water bottle on hand in order to replenish your water intake.
- Water intake per day should range between 2.7-3.7 liters. Let's drink some water before you put your phones down.
- Rest deprivation leads to eating more as a compensatory mechanism. There is usually some kind of junk food involved. When you get enough sleep, you won't need snacks to stay awake.
- We don't want to become prematurely aged by not getting enough sleep! Try to establish a healthy sleep hygiene.
- Exercise daily has been shown to have tremendous benefits for our health. For close distances, you can benefit from walking rather than taking a vehicle.
- Engaging in sports is a great way to exercise since they work out different muscles.
- The key to living a healthy life is to love yourself. A negatively distorted self-image inevitably affects one's mental health and outlook. Be kind to yourself!
- The key to a healthy life is having a positive mental attitude. There is no need to surround yourself with toxic people. If you feel a friend is being too critical or negative, let them go.

- Life cannot exist without oxygen. Taking breaths is necessary for life, but how well do you take breaths? Full breath is characterized by your lungs being fully inflated, your abdomen expanding and your shoulders moving very little. You can improve your breathing by having good posture.
- The long-term effects of second-hand smoking (breathing in the smoke of smokers) are similar to those of direct smoking. Where possible, avoid smokers.
- Many diseases take a long time to show any symptoms until it is too late. Getting regular checkups is of great importance.
- In addition to making you more desirable, good oral hygiene is also linked with better health. Make sure you brush your teeth twice a day.

Notifications for the Interventional Group: INAS-based Notifications

- Taking allopurinol on a regular basis can lead you to a normal life.
- Taking your allopurinol everyday will help you do what matters to you.
- Taking your allopurinol everyday will allow you to carry on with your normal life.
- Leading a normal life can be possible through taking allopurinol on a regular basis.
- Taking allopurinol prevents your gout from getting worse.
- Taking allopurinol helps you to carry on your everyday tasks such as driving.
- Taking allopurinol helps you with everyday physical functions.
- By taking your allopurinol every day, you can maintain your daily activities.
- Taking allopurinol can help to maintain your mobility.
- You can do all activities without pain by taking your allopurinol regularly.
- You can maintain your daily activities by taking your allopurinol every day.
- Taking your allopurinol every day allows you to continue to live your normal life.
- Daily use of allopurinol helps to keep your gout under control, so it doesn’t affect your normal life.
- You can live your normal life by taking your allopurinol every day.
- The best way to reduce the impact of gout on everyday tasks is to take your allopurinol every day.
- Regular, daily use of allopurinol will reduce the impact of gout on your normal life.
- Daily use of your allopurinol keeps your gout under control and reduces the effect of gout on your normal life.
- Taking allopurinol every day is the best way to prevent gout from interfering in your everyday physical functions.
- Taking your allopurinol every day is the best way to prevent gout from interfering in your normal life.
- Taking your allopurinol every day prevents your gout from getting in the way of living the life you want.
- Taking allopurinol every day reduces the impact of gout on your mobility.

- By taking your allopurinol every day, you can stop gout slowing you down.
- Taking allopurinol can stop gout getting in your way.
- Taking allopurinol every day allows you to do the things you want to do without your gout getting in the way.
- Taking your allopurinol every day allows you to do the things you want to do without your gout slowing you down.
- You can make a difference to your life by taking your allopurinol every day.
- Poorly controlled gout prevents you from doing normal things you want to do.
- Having high levels of urate can lead to acute gout attacks! But it doesn't have to!
- Managing a gout flare doesn't have to be difficult. The only thing you need is to take your allopurinol regularly.
- Allopurinol controls your gout by reducing the inflammation that causes gout. To manage your gout successfully, you need to take allopurinol every day.
- There is an absolute need for taking your allopurinol if you want to keep urate level low!
- Your gout needs allopurinol to be kept under control.
- Gout can progress into joint destruction! But not necessarily!
- If you stop taking allopurinol, your symptoms will come back.
- If you come off, painful gout will find you again.
- Allopurinol controls your gout by preventing your joints from swelling.
- Allopurinol controls your gout over the long term and prevents it from getting out of hand.
- Daily use of your allopurinol will keep your gout under control by reducing the level of urate in your body.
- Taking your allopurinol every day prevents you from having a symptom flare up.
- Taking your allopurinol every day protects you from gout symptoms.
- Studies show that when taken every day, your allopurinol is effective at keeping your gout under control.
- Taking your allopurinol every day is the best defense against uncontrolled gout.
- Daily use of your allopurinol can make a huge difference to the amount of gout you have.
- Skipping a few doses or stopping your allopurinol when you feel well will make your gout worse.
- Taking allopurinol every day allows you to control your gout.
- By taking your allopurinol every day, you are in control of your gout.
- You need to take your allopurinol every day and deal with your gout.
- A small amount of your allopurinol each day keeps the doctor away.
- Taking allopurinol every day is better for your health.
- Gout is a progressive illness which if not controlled can have serious consequences.
- Gout is a progressive illness which if not controlled can have life-long consequences.
- Taking allopurinol on a regular basis needs to be taken seriously, as gout is a progressive disease.

- Taking allopurinol everyday deals with your gout before you get symptoms.
- Your allopurinol deals with your gout so you don't get symptoms. Cutting off your allopurinol lets your symptoms come back!
- Gout can't be cured but it can be controlled by taking your allopurinol every day.
- The medicine you are taking builds up over time, so you need to take it every day, even when you are feeling well.
- Allopurinol should be taken every day – even on the days when you don't have symptoms.
- Your allopurinol should be taken every day – even on the days when you feel well.
- Don't let gout control you. Take your allopurinol every day to keep your gout under control.
- You can control your gout by taking your allopurinol regularly before it controls you.
- You can control your symptoms by setting up a routine to take your allopurinol regularly.
- You need to take your allopurinol on a regular basis to control your gout.
- If left untreated, gout can cause erosion and destruction of a joint.
- While gout cannot be cured, it can be controlled with treatment.
- To break up uric acid crystals you need to take your allopurinol regularly.
- Gout is caused by a condition known as hyperuricemia, where there is too much uric acid in the body. Research has shown that taking allopurinol on a regular basis can lower the level of urate and keep gout under control.
- When uric acid levels are high, crystals of it can accumulate in your joints. To avoid joint destruction, you need to take your allopurinol every day.
- Taking allopurinol daily is the best possible way to reduce uric acid to normal levels resulting in disappearance of urate crystals.
- The most effective way to decrease uric acid levels and eliminate urate crystals is to take allopurinol every day.
- The most common manifestation of gout is severe pain in a joint. To avoid this unbearable pain, you need to take allopurinol every day.
- Patients can never be cured of gout. It is a long-term disease that can be controlled by a combination of allopurinol to control the uric acid level.
- Considering that lowering the level of uric acid is key to treating gout, your medicine must be taken regularly.
- There is no cure for gout, but people can manage the condition with allopurinol.
- Gout is a life-lasting condition with no cure, only good management.
- Most people have their gout for life; however, they can control their gout by taking allopurinol regularly.
- Once you have gout, it is likely that it will stay with you for life. Without taking allopurinol regularly, gout never goes away.
- Gout is something that must be controlled by taking allopurinol over the long term.
- If you stop taking it, the medicine will leave your body and your symptoms may return.
- Quitting without consulting your doctor can be life-threatening.

- If you stop taking allopurinol, it causes the medicine to leave the body, and your symptoms could return.
- While many people are doomed to suffer from gout for life, they can control their condition by taking allopurinol every day.
- Taking allopurinol regularly is critical to treating gout because the purpose of your medicine is to lower the level of uric acid over time.
- You can control your gout and feel healthy by taking your allopurinol every day.
- Being healthy means keeping the level of biomarkers in a normal range. By taking your allopurinol every day, you can keep the level serum urate within a healthy range.
- By taking your allopurinol, your urate level will be kept in a healthy range.
- Taking allopurinol brings your body back to balance.
- Your allopurinol helps restore balance in your body.
- By taking your allopurinol every day, you can stop gout from affecting your health.
- Taking allopurinol each day keeps the doctor away.
- Taking allopurinol every day protects you from gout symptoms.
- Taking allopurinol prevents future deterioration and deformity.
- Uncontrolled gout can be life threatening but by taking allopurinol every day you can stay healthy and control problems before they start.
- Taking your allopurinol every day reduces the chance of having a gout attack.
- Taking allopurinol every day is the best way to keep gout out of your life.
- You can stay healthy by taking your allopurinol every day.
- The best way to reduce the impact of gout on your health is to take your allopurinol every day.
- If taken regularly, allopurinol can reduce the negative impact of gout on your health.
- Taking allopurinol every day reduces your gout symptoms and makes you feel healthy again.
- You can improve your health over time by taking allopurinol every day.
- You can reduce your risk of having a gout attack by taking allopurinol every day.
- You can reduce unnecessary doctor visits by taking allopurinol every day.
- You can reduce your gout symptoms by taking your allopurinol every day.
- You can reduce the feeling of stiffness by taking your allopurinol every day.
- You can reduce the feeling of extreme pain in your joints by taking your allopurinol every day.
- You can reduce your chances of joint inflammation by taking your allopurinol every day.
- You can reduce your chances of joint destruction by taking allopurinol every day.
- You can reduce your chances of swelling by taking your allopurinol every day.
- You can improve your joint mobility by taking allopurinol every day.
- Your allopurinol works over the long term to keep you healthy.
- Taking your allopurinol every day prevents gout symptoms.
- By taking your allopurinol, you can stop gout taking your health away.
- If you want to choose between bad and worse, which one would be your choice? Experiencing unbearable pain or dealing with side effects?

- By taking your allopurinol, you might have some minor side effects, however, your gout would be under control.
- Your doctor has chosen the right dose for you to avoid side effects as much as possible.
- Even safe painkillers might have some side effects, does it mean that you don’t take them when you are in pain?
- Although dealing with some side effects might be annoying, it is still worth it, as your pain will stay away.
- Despite the possibility of getting side effects, the benefits of allopurinol to your health may be worth it.
- Nearly all prescription drugs come with side effects, but it doesn’t mean that you will experience all of them.
- Allopurinol can carry side effects, but it is worth speaking to your doctor to evaluate the risk because of its preventive benefits.
- Most side effects are minor, and some are just an inconvenience, but not gout attacks! They are painful and should be taken seriously.
- Once you start taking your medicine, it is important to mention any unexpected symptoms to your doctor. Your doctor may be able to lower your dose, or try a different drug, if needed.
- Some side effects go away over time as your body gets used to a new drug, so it might be worth it to stick with your current plan for a little longer.
- There are a lot of factors that go into side effects, not just the allopurinol itself.
- You may be able to prevent some side effects by avoiding alcohol or certain foods, or by making other small changes to your diet or lifestyle.
- You may be able to tolerate some side effects, especially if they're temporary or if the pros outweigh the cons.
- Make sure to take allopurinol as prescribed to reduce your risk of side effects.
- It is important to take allopurinol correctly in order to get the most benefit from it and reduce your risk of side effects.
- If you avoid alcohol or certain foods, or if you make other small changes in your diet or lifestyle, you may be able to prevent some side effects.
- It is important to inform your doctor if you develop any unexpected symptoms while taking allopurinol. If your doctor deems it necessary, they can lower your dose or prescribe a different medicine.
- You might experience side effects when taking your allopurinol, but your gout would be controlled.
- You won't feel pain for as long as you take allopurinol, so despite some side effects being annoying, it still may be worth it.
- Although you might have to deal with some side effects, it's still worth it since it keeps the pain away.
- Allopurinol doesn’t work immediately but used regularly it will reduce the inflammation that

causes gout.

- Your allopurinol works best when taken every day.
- Allopurinol won’t become less effective over time.
- Research has shown that allopurinol doesn’t lose its effect when taken over the long term.
- Allopurinol must be taken regularly to be effective.
- It has been proven that allopurinol stays effective over time.
- Allopurinol works slowly. This means you may not notice any immediate changes after taking your allopurinol.
- You are taking a slow-acting medication, hence, taking allopurinol may not cause any immediate effects on you.
- Over time, allopurinol has been proven not to become less effective.
- Research has shown that allopurinol won’t become less effective over time.
- In studies, allopurinol does not become less effective with time.
- Although you might experience some gout-related symptoms, the effectiveness of allopurinol won’t lessen with passing time.
- Each time you take allopurinol, your body receives the same amount of allopurinol with the same level of effectiveness.
- Each time you take your allopurinol, it impacts your body the same way.
- The effectiveness of your allopurinol is dependent on its dosage rather than the duration of taking it.
- Different dosages of allopurinol have different impacts on body, however, the duration of taking allopurinol won’t affect its effectiveness.
- Taking allopurinol for long periods will not affect its effectiveness, regardless of the dosage.
- The same thing happens to your body each time you take allopurinol.
- Allopurinol is not addictive.
- Taking your allopurinol daily won’t make you dependent on it.
- The fact that you take your allopurinol daily will not turn you dependent.
- By taking your allopurinol on a regular basis, you won’t become dependent on it.
- By taking your prescription medicine regularly, you won't become dependent on it.
- Allopurinol is not an addictive medication.
- Allopurinol does not cause addiction.
- You can come off it anytime you want; however, by stopping taking allopurinol your gout could come back.
- Taking your allopurinol every day doesn’t mean that you may become dependent on it.
- You can stop taking your medicine without any withdrawal symptoms.
- Withdrawal symptoms of your medicine will not occur when you stop taking it.
- If you decide to come off it, you can! Allopurinol is not like Heroin.
- Unlike substances like Cocaine, allopurinol has no withdrawal symptoms.
- Allopurinol is not addictive and is safe to use every day.

- There’s a lot of research now showing that allopurinol is effective and very safe, even when taken over the long term.
- Allopurinol is safe to take every day.
- You won’t become dependent on allopurinol by taking it on a daily basis.
- Research has shown that allopurinol is not addictive.

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