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**To adhere or not to adhere: Rates and reasons of medication adherence in hematological cancer patients**

**Running title:** Rates and reasons of medication adherence in hematological cancer patients

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## **Abstract**

To conduct a comprehensive review to examine among hematological cancer patients: (1) rates of adherence to self-administered cancer treatments; and (2) factors impacting on their adherence. Fifty two eligible publications were identified. The majority focused on Chronic Myeloid Leukaemia (CML) (n=40) and Acute Lymphoid Leukaemia (ALL) (n=11) patients. Adherence rates varied and depended on the definition and measures used. Patient understanding about their disease and treatment, and forgetting to take their medication impacted on patients' level of adherence; while the use of reminders reduced forgetfulness. There is a lack of valid and reliable information relating to medication adherence of hematological cancer patients. Based on the limited data available we provide a profile of CML and ALL patients at potential risk of medication non-adherence, as well as a proposed checklist that can be used by health care providers in assessing and supporting patients in adhering to their medication.

**Key words:** Hemato-oncology; Adherence; Compliance; Medication; Hematological cancer

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## 1. INTRODUCTION

There has been an increase in use of patient-administered treatments in oncology.[1] A patient's ability to adhere to the requirements of their medication regime is central to the successful delivery of self-administered anti-cancer treatments. Medication adherence is defined as the extent to which patients take their prescribed medications as recommended by their health care provider.[2] Optimal adherence is recognised as a patient taking their medication exactly as prescribed, at the exact time, dosage and for the recommended length of time.[3] Adherence affects disease relapse,[4] treatment effectiveness and treatment response.[5-12] Non-adherence has been found to be associated with increased health care utilisation including increased physician visits, higher rates of hospitalisation and longer average length of time spent in hospital,[3, 7, 13] as well as higher medical service costs.[13, 14] Medication adherence is related to disease type[15] and disease related factors.[7] The degree of adherence and the factors affecting adherence need to be assessed and addressed at a disease specific level.

Hematological cancers are increasingly being treated with self-administered medications,[16] many of which are long and complex treatment regimens.[16, 17] Strategies to improve medication adherence for patients with hematological cancers is critical given evidence that there is a negative association between medication non-adherence and lower perceived disease severity.[18] Second, medication adherence

has been found to decrease with long term medication use,[7] which may be problematic for many hematological cancers that require long-term treatment.

Medication adherence is a multi-factorial problem [7, 19, 20] influenced by numerous patient, treatment, disease, health system and social factors.[7, 19-21] Optimising adherence in long-term chronic conditions is likely to require complex, multi-component intervention strategies,[22] which target the main barriers affecting adherence.[21] To appropriately address medication adherence in hematological cancer patients it is necessary to both understand the true extent of non-adherence for this population, as well as identify the factors that impact on adherence. While several literature reviews have assessed medication adherence among specific sub-groups of hematological cancer patients,[3, 7, 23] no systematic reviews have examined medication adherence across all hematological cancers. Such a review would provide vital information about how future research and clinical practice may improve medication adherence for hematological cancer patients.

### 1.1 Aims:

To identify among hematological cancer patients:

- (1) Rates of adherence to self-administered cancer treatments; and
- (2) Factors impacting on adherence to self-administered cancer treatments.

## 2. METHODS

### 2.1 Literature search

The electronic databases Medline, PsychInfo, EMBASE and the Cochrane Library of Critical Reviews were searched. Searches were limited to publications published in English, between 2002 and 2012. The reference lists of all included publications were manually searched to identify any additional eligible publications.

### 2.2 Search strategy

A combination of keywords and subject headings were used. Terms relating to hematological cancers were combined with adherence related terms using the 'AND' Boolean operator. Each search strategy was tailored to the specifications of the individual database. A list of the search terms used is provided in Table 1.

### 2.3 Inclusion criteria

Publications were eligible for inclusion if the full-text publication could be accessed, and it reported rates of medication adherence or factors associated with, or impacting on, medication adherence in hematological cancer patients treated with self-administered cancer treatments. Both qualitative and quantitative studies were included. Studies that included heterogeneous samples of cancer patients were included if the sample consisted of at least 80% of hematological cancer patients. Conference abstracts were included if data relating to medication adherence could be extracted.

## 2.4 Exclusion criteria

Adherence to medications to treat non-cancer related conditions were excluded. Unique populations of hematological cancer patients, such as children diagnosed with Down Syndrome, were excluded as such populations are likely to have specific adherence issues. Patients with non-malignant hematological disorders or non-hematological cancers were excluded. Clinical trials and intervention studies were excluded given the tightly controlled conditions of such studies are known to influence adherence rates.[24] Case studies, commentaries, letters to the editor, books, protocol publications and review publications were excluded.

## 2.5 Publication analysis

One reviewer identified and removed all duplicate publications. The titles of all publications were assessed for eligibility by one reviewer. The abstracts of remaining publications were then reviewed by the same reviewer. As a measure of quality assurance a second reviewer assessed 20% of all publication titles and abstracts. All full-text publications were then independently reviewed by two reviewers to assess eligibility. All discrepancies were discussed and resolved. Data from all eligible publications were analysed and extracted independently by two reviewers.

## 2.6 Data coding and extraction

Only outcome data relating to medication adherence by hematological cancer patients were extracted and analysed. The information extracted from each publication included: author name, journal, year of publication, country where the study was conducted, patient age group, sample size, response rate, study design, disease type, participant

sex, treatment type, definition of adherence used, measurement of adherence used, method used to calculate adherence rates, characteristics and factors associated with adherence rates and reasons for adherence/non-adherence and conclusions.

Meta-analysis was not performed due to wide variation in methodologies, patient populations, definitions of medication adherence and methods used to assess medication adherence.

## 2.7 Methodological quality

The methodological quality of observational quantitative studies was assessed using an adapted version of the seven-point quality checklist developed by Barely et al.[25]

Studies which reported five or more of the six 'yes/no' quality indicators of this scale were classified as being of adequate methodological quality.[25] The Critical Appraisal Skills Programme (CASP) checklist[26] was used to assess the methodological quality of qualitative studies. Qualitative studies reporting at least seven out of the 10 quality indicators were classified as being of acceptable quality.[25]

# 3. RESULTS

## 3.1 Publication screening

Figure 1 outlines the publication screening process. A total of 1,402 publications were initially identified from database searches. Following removal of duplicate publications, 1,215 titles, 813 abstracts and 219 full-text publications were screened for eligibility. Hand searching of the reference lists identified an additional 116 abstracts and 25 full

text publications for eligibility screening. The main reasons for exclusion of full-text publications included: non-databased publications such as reviews, letters to the editors, commentaries, case studies and editorials; articles that were not focused on patient's medication adherence; and articles not focused on hematological cancers (see Figure 1). A total of 52 publications representing 45 studies were identified as eligible and included in this review.

### 3.2 Characteristics of included studies

Of the 52 included publications, 45 reported on quantitative outcomes, five reported qualitative outcomes and two a mix of quantitative and qualitative outcomes. The majority of publications focused on medication adherence in patients diagnosed with Chronic Myeloid Leukaemia (CML) (n=40)[5, 6, 8-11, 13, 14, 27-58] and Acute Lymphoblastic Leukaemia (ALL) (n=11)[4, 59-68], with only one study including a heterogeneous sample of hematological cancers [69]. The majority of publications assessed patients' adherence to Imatinib only treatment (n=28; 54%)[5, 6, 8-11, 13, 14, 27, 29, 30, 32, 34-37, 41-43, 46-48, 50-53, 55, 57], followed by assessing adherence to a variety of Tyrosine Kinase Inhibitors[28, 31, 33, 38-40, 44, 45, 49, 54, 56, 58]. The number of patients included in each study ranged from 19[11] to 2,145 [57] with a mean number of 292 patients. There was wide variation in the methods used to assess medication adherence, ranging from patient self-report (n=17; 33%)[5, 6, 9, 10, 31, 34, 37, 44, 45, 51, 60, 61, 64-68], claims data (n = 12; 23%)[13, 14, 32, 36, 38, 39, 41, 49, 50, 54-56], Medication Event Monitoring Systems (MEMS) (n=7; 13%) [4, 8, 29, 42, 43, 47, 59]; chart review (n=6; 12%)[11, 40, 44, 61, 65, 68] and pill counts (n = 4; 7.7%)[5, 30, 48, 51]. A quarter of the included publications employed multiple methods to

measure adherence rates (n=13; 25%)[5, 6, 11, 30, 37, 40, 44, 51, 59, 61, 65, 66, 68]. In two studies it was not clear what methods were used to measure adherence[28, 70].

Thirty three percent (n=15)[4, 8, 13, 14, 32, 37, 39, 41, 46, 50, 54, 56, 64, 66, 67] of the publications describing quantitative outcomes and six of the seven [35, 55, 60, 62-64] publications employing qualitative methods were classified as demonstrating acceptable levels of methodological quality. Of the publications reporting on quantitative outcomes, the most poorly addressed methodological quality indicators were 'being free from conflict of interest' (n=35) [5, 8, 11, 13, 14, 27, 29-34, 36, 38-52, 54-57, 65, 66, 68] and 'appropriate control for bias' (n=27) [4, 6, 9-11, 27-31, 33, 36, 38, 40, 42-45, 47, 51, 52, 59-61, 65, 68, 69]. Of the publications reporting qualitative outcomes, the most poorly addressed quality indicators were an 'adequate description of the relationship between the participants and the researchers' (n=5) [35, 40, 55, 60, 64] and 'taking into consideration ethical issues' (n=3).[40, 55, 64]

Although the original aim of this review was to assess medication adherence in all hematological cancer patients, as almost all eligible publications focused on either CML or ALL the majority of the results of this review are devoted to publications assessing adherence in these two disease groups. Due to the wide variation in disease and treatment characteristics of CML and ALL patients, the results for each of these disease groups are presented separately.

### 3.3 Adherence rates

#### **CML**

Thirty four publications reported prevalence rates of medication adherence in CML patients (Table 2). Nineteen focused on adult patients [5, 6, 8-10, 28, 31, 32, 34, 42-48, 50, 52, 56]; one on adults, adolescents and children[37]; one included a mix of age groups[13] and 13 were unclear [11, 14, 28-30, 36, 38-41, 49, 54, 55].

As shown in Table 2, the measures and definitions of medication adherence varied between studies. Some studies reported adherence as a percentage rate[5, 6, 8, 29, 30, 32, 36, 40, 42-44, 47, 48], others reported a mean adherence rate [5, 8-10, 28-30, 32, 36, 42, 43, 47], some reported the score from an adherence measure [5, 13, 38, 39, 46, 50, 52, 54, 55], while others classified patients into categories of adherence, such as low, medium and high levels of adherence[11, 13, 14, 28, 31, 32, 34, 37, 40, 41, 45, 46, 50, 52, 55]. Such variation prohibits the ability to combine data and adequately estimate the rate of medication adherence in CML patients. However, most studies report a level of non-adherent behaviour in a proportion of patients. Of those studies providing data on the number of patients who were fully or 100% adherent [14, 28, 34, 40, 45, 55], very few patients meet this criteria, with rates ranging from 20%[28] to 53%[40]. Alternately, when mean adherence rates were provided, patients level of adherence ranged from 76% [36] to 98% [6, 8, 29, 30, 43, 47].

### ***ALL***

Nine publications reported prevalence rates of medication adherence in ALL patients (Table 3). Six focused on children[4, 59-61, 65, 68]; one on children, adolescents and adults[64]; one on adolescents[66]; and one on parents of children with ALL[67]. Again,

measures and definitions of medication adherence varied between studies (Table 3). However, similar to the CML publications most studies reported non-adherent behaviour in a substantial minority of patients (Table 3). For instance, the percentage of patients reporting some level of non-adherent behaviour (e.g. missing, stopping or changing their medication dose) ranged from 6%[44] to 35%[66].

### **Mixed samples of hematological cancer survivors**

One study assessed factors influencing a heterogeneous sample of 24 hematological cancer patients adherence to oral imatinib and thalidomide treatment[69]. Results from the self-report Morisky Medication Adherence survey indicated that all patients surveyed reported high (67%) to moderate (33%) adherence[69]. Increasing age and higher levels of patient satisfaction with hospital services and higher levels of support from patients support networks were significantly related to patient medication adherence[69].

### **3.4 Factors impacting on adherence**

A variety of patient, social, disease, treatment and health system factors were found to impact on medication adherence rates in CML and ALL patients. However, for a number of the factors identified there was inconsistent evidence as to the level and/or direction of the association with medication adherence in CML and ALL patients. For the purposes of this review the factors identified have been summarised into two groups: (1) factors identified as impacting on adherence rates; and (2) factors for which there is inconsistent evidence of impact on adherence.

### 3.4.1 Factors identified as impacting on CML patients medication adherence

Table 4 lists the factors identified from quantitative studies as being statistically significantly associated with CML patients' adherence rates. A comprehensive summary of factors identified from both qualitative and quantitative studies are discussed below.

#### *Patient characteristics*

The three broad patient characteristics that were found to impact on hematological cancer patient's medication adherence were: (i) forgetfulness, (ii) patient education, knowledge and understanding, and (iii) patients' physical and emotional feelings.

Forgetting to take the medication as prescribed was a common reason for patient non-adherence. In two studies CML patients[35, 55] described using reminders to prompt their medication taking behaviour. Reminders included the use of pill dosage boxes,[35] building medication adherence into their daily routine (e.g. taking the medication with a meal),[35] storing the medication in a visual and commonly used area[35] and the use of clear and monitored treatment schedules (e.g. use of reminder charts or calendars).[35]

CML patient's education, knowledge and understanding were all found to influence medication adherence behaviour. Patients with a secondary or higher level of education[5] reported higher levels of adherence compared to those with a lower level of education. Patients who reported inadequate medical knowledge[55] were more likely to be non-adherent. While those who reported better knowledge of the impact of non-adherence on their disease and treatment[5, 27] were more likely to be adherent. Furthermore, patients who were blasé about their treatment[55] as well as those who

had a tendency to become complacent after long periods of disease control[55] were less likely to adhere to their prescribed medications.

Patient's physical and emotional feelings also impacted on adherence. Higher levels of perceived functional status[5] (i.e. patients perceptions about how they perform usual activities[71]) and quality of life as measured by the SF-8 Health Survey were found to be associated with higher levels of medication non-adherence;[5] while higher levels of patient perceived self-efficacy in relation to long-term medication behaviour as measured by the Long-Term Medication Behaviour Self-Efficacy scale, was found to be associated with better medication adherence.[5] Reducing the impact that the drug had on the patient's life was identified in one qualitative study as a reason patients did not adhere.[55]

#### *Disease and treatment characteristics*

Time since diagnosis was found to be associated with CML patient's level of medication adherence in two publications (Table 4).[5, 27] Patients who were further from diagnosis had higher rates of medication non-adherence.[5, 27] Although, in one of these studies this association was only significant in the multivariate analysis and not at the univariate analysis stage.[5] Similarly, longer time between diagnosis and the medication prescription being filled was associated with higher rates of non-adherence.[50] Higher rates of treatment side effects,[8] was associated with higher rates of non-adherence. Two studies found that patients often reduced, stopped or altered their medication

without medical advice in an attempt to avoid treatment side-effects and to make them feel more physically well.[35] [44]

Patients who reported higher cancer related complexity[32] had higher rates of medication non-adherence while patients with more cancer related complications also reported lower levels of medication adherence.[36] Although, one study found only a weak correlation between patient-reported symptoms and their bothersomeness and patient adherence behaviour; and the same study also found no statistically significant association with these variables and patient adherence behaviour.[5] Participation in a clinical trial[28, 33] was identified in two publications as being associated with greater treatment adherence. Taking medication independent of meals was associated with higher rates of non-adherence.[8]

#### *Social characteristics*

Patient's social characteristics such as living arrangements and social support were associated with CML patient's level of medication adherence. Patients living alone,[5, 27] had higher levels of non-adherence, while higher levels of social support[34] were associated with higher adherence. Economic factors such as low socioeconomic status and higher percentage of co-payment of treatment[50] were associated with non-adherence.

#### *Health care characteristics*

The type of health care services accessed by CML patients was found to be associated with their level of medication adherence. Patients who made use of individual counselling about medication adherence,[40] or attended an institution which had established protocols on managing patient adherence[40] had higher adherence rates to their prescribed medication regime. A number of health care provider characteristics were also associated with patient's level of adherence. A higher number of health care providers' years of professional experience,[5] higher number of active patients seen in the last year,[5] median duration of first visit with a newly diagnosed patient[5], practicing in a University or teaching hospital and holding a specialisation in hematology[5] were all associated with greater medication adherence. While shorter median duration of follow-up visits was associated with increased non-adherence[5].

Physician and patient communication was identified as affecting patients' level of adherence.[35, 55] Miscommunication between patients and physicians,[55] patients who were unable to access prompt medical guidance[55] and patients who felt they were reassured by their physicians that their non-adherence would not have a detrimental effect on their treatment response,[35, 55] reported higher levels of medication non-adherence.

### 3.4.2 Factors inconsistently identified as impacting on CML patient's adherence rates

#### *Patient characteristics*

There were inconsistent findings as to whether younger or older age was related to higher levels of adherence, with three studies identifying older age as being associated with non-adherence,[5, 27, 51] two studies identifying adherence as being associated

with increasing age,[36, 69] and two studies finding younger age to be related to non-adherence.[8, 50] Sex was not consistently found to be associated with medication adherence rates. In two studies females reported higher rates of medication non-adherence[32] or lower levels of adherence;[36] while one study identified male as being related to higher rates of medication non-adherence.[5]

#### *Disease and treatment characteristics*

In six studies [5, 8, 13, 29, 32, 50] higher dosage or an increase in medication dosage was found to be associated with higher levels of non-adherence. Similarly one study found a lower dose of medication to be associated with medication adherence;[56] while one study reported that a starting dosage of  $\leq 400$ mg of imatinib was related to non-adherence.[50]

Four studies found longer use of treatment to be associated with higher levels of non-adherence.[5, 27, 28, 51] Although, in one of these studies this association was only significant in the multivariate analysis and not the univariate analysis.[5] In contrast, another study identified a shorter exposure time to treatment to be associated with non-adherence.[50]

Medication type was associated with non-adherence[28, 39, 49, 54] with two studies reporting lower adherence in patients treated with dasatinib compared to those treated with nilotinib.[39, 54] Nilotinib use was further found to be related to higher rates of medication adherence compared to imatinib and dasatinib use.[28] Comparatively,

Oliveria et al[49] found patients treated with nilotinib reported poorer rates of adherence compared to dasatinib users.

Adherence to cancer medications was also found to decrease with an increase in the number of medications (cancer and non-cancer medications) patients were required to take.[5, 36] Similarly, a higher concomitant of prescriptions was found to be related to patient medication non-adherence.[50] In comparison, Efficace et al found a higher concomitant of drug burden was related to higher rates of medication adherence.[34]

### 3.4.3 Factors identified as impacting on ALL patients medication adherence

Table 5 lists the factors identified from quantitative studies as being significantly related to ALL patients' adherence rates. A comprehensive summary of factors identified from both qualitative and quantitative studies are discussed below.

#### *Patient characteristics*

Older age was found to be associated with non-adherence in ALL patients.[4, 59, 64]

Race was identified as being associated with non-adherence in two publications.[4, 59]

In both studies Hispanics were found to report higher levels of non-adherence compared to Caucasians.[4, 59] In one study Asian and African American patients were found to report higher rates of medication non-adherence compared to Caucasians.[59]

Similar to CML patients, the feelings, beliefs and knowledge of ALL patients seemed to have a substantial effect on patient's level of adherence. For example, in one study children with ALL who had been counselled on the potential side effects of their medication felt better prepared to manage such side-effects[72] and as a result reported

higher levels of adherence to treatment. A desire to regain a sense of normalcy[63] and gain control of their lives[72] were other commonly identified factors affecting patients' level of medication adherence. For instance, in one qualitative study a number of patients saw their medication regime as a barrier to their normal life, which often impacted their engagement in adherent behaviour.[63] While patients who reported a perceived ability to incorporate their treatment into their normal routine, were reported to engage in better adherence-related behaviour.[63] Knowledge and understanding of the importance of the treatment in controlling ALL was identified as a critical factor in patient adherence.[62] In one study it was found that those who understood the important role their treatment played in potentially curing their disease exhibited and maintained more adherent behaviours compared to those who did not understand this connection.[62] The importance of patient understanding on their medication adherence is again emphasised in the Malabasa et al[63] study, which found that adolescent ALL patients who received positive feedback from their health care provider about their physical health (e.g. blood counts) after engaging in non-adherent behaviour, interpreted this feedback as positive reinforcement for being non-adherent. Finally, patients and parents who saw themselves as taking a central responsibility in medication administration engaged in more adherent behaviours.[62]

Forgetting to take medication as prescribed was also a common reason for non-adherence in ALL patients. In one study physicians were found to have poor detection of patient adherence particularly for those patients who reported repeated forgetfulness as the reason for their non-adherent behaviour.[64] The use of reminders by the

patients themselves[64] or by the parents of child patients,[60] and integrating the medication taking behaviour into the patients daily regime[62, 64] were found to be a useful way of overcoming forgetfulness. The types of reminders used by ALL and their parents, included: use of pill dosage boxes, reminder systems such as calendars[62, 64], drug reminder charts[60] and alarms[64].

#### *Disease and treatment factors*

Few studies identified disease or treatment related characteristics associated with ALL patients medication adherence. In one study the occurrence of hepatic side effects and disease relapse were significantly associated with lower medication adherence.[64]

#### *Social characteristics*

Patients with a fewer number of people residing at home[64] and single-parent families[4, 59] were identified as being associated with higher levels of non-adherent behaviour. Patients who felt supported[62] were more likely to administer their medication as prescribed. In one study, paediatric ALL patients reported parental monitoring and motivation as key supportive features to ensuring adherence to their medication.[63] While another study identified the close monitoring of adherence rates by parents as an important factor in patients receiving the medication as prescribed.[64]

#### 3.4.4 Factors inconsistently identified as impacting on ALL patient's adherence rates

Low socioeconomic status was found in one study to be associated with non-adherence[64]. Similarly, low household income (<\$50K vs. ≥50K per year) [59] was found to be statistically significantly associated with lower rates of adherence in ALL

patients. Comparatively, another study found that annual household income was not related to ALL medication adherence.[4]

## 4. DISCUSSION

Though this review aimed to assess medication adherence across all hematological cancers, the lack of research on other types of hematological cancers resulted in a comprehensive overview only of those factors that impact on CML and ALL patients' medication adherence.

For those CML studies that reported the percentage of patients who were fully adherent to their prescribed cancer medication, adherence rates were found to range from 20%[36] to 53%[40]. For ALL the percentage of patients reporting some level of non-adherent behaviour (e.g. missing, stopping or changing their medication dose) ranged from 6%[44] to 35%[66]. This is of concern as medication non-adherence negatively impacts on multiple health-related outcomes, including treatment effectiveness,[11-18] health care costs[19, 20] and health care utilisation.[9, 13, 19]. Consequently, health care providers should be aware of the possibility that some of their patients will not be taking their medication as prescribed, this is particularly important as health care providers have been found to overestimate their patients' level of adherence.[64]

### 4.1 Identifying patients at potential risk of medication non-adherence

Health care providers should be aware of, and provide additional support to patients at risk of non-adherence to self-administered medications. This may include individuals who live alone, with little social support, who have complex medication regimens, have

lower education and are experiencing greater physical impacts from their cancer and/or treatment.

#### 4.2 Recommendations on how to support patient's medication adherence

Careful attention to adherence initially and repeatedly at follow-up visits (whether they be with specialist, nurse or GP) is likely to assist in improving medication adherence for all patients; with additional time spent with the patient found to be related to adherence.[5]

Consistent with previous findings,[73] patients' level of social support was identified as an important factor influencing patient adherence for both CML and ALL patients[73] Interventions that involve patients' family members and significant others have had some effect in improving adherence to long-term treatment.[74]. Consequently, health care providers should be encouraged to involve members of the patients' social support network when addressing issues of medication adherence; while additional professional support may be needed by those patients with low levels of available support.

Treatment and disease related side effects seem to be a particularly pertinent issue affecting medication adherence in cancer populations. In this review higher rates of treatment related side-effects [8], cancer-related complexity [32] and cancer-related complications [36] were found to be related to higher rates of medication non-adherence in CML patients. This finding is similar to studies conducted with other cancer populations, which have consistently identified higher rates of treatment side effects as related to medication non-adherence.[75, 76] While there was limited evidence of a

specific association between treatment related side effects and cancer-related complexity on medication adherence in ALL patients, this was most likely due to the small sample sizes of these studies and the lack of assessment of such factors. However, it must be noted that one study conducted in ALL patients did identify hepatic side effects and disease relapse as being related to lower rates of medication adherence,[64] which further highlights the importance of disease and treatment-related effects on medication adherence in these populations. Therefore, providing patients with additional support on how to cope with the physical consequences of their disease and treatment may assist in reducing medication non-adherence in such patients. For instance, in one of the studies identified ALL patients who underwent counselling on potential treatment side-effects felt better prepared to manage such side-effects when they occurred, which resulted in greater reporting of adherence by such patients.[72]

The level of understanding and knowledge that CML and ALL patients have regarding their disease and treatment also seems to be an important factor contributing to their medication adherence.[5, 27, 55, 62, 63, 72] A previous study of adherence in chronic disease patients has also found that patient beliefs about therapy had a stronger impact on patient adherence than other patient characteristics.[77] Providers should educate all patients regarding the link between medication adherence and disease control.

Providing counselling on the importance of the medication and written instructions about treatment administration have been effective in improving adherence to self-administered medications taken over a short term period.[22] It is important that such

education is appropriate for those with poor literacy and numeracy to avoid exacerbating health inequalities.

Forgetfulness was frequently identified as a common reasons for medication non-adherence in both CML and ALL patients.[40, 59, 64] Health care providers should encourage their patients to use the reminder strategies identified in this review as assisting hematological cancer patients to remember to take medication.

It is possible that factors identified in both CML and ALL populations as impacting on medication adherence could be used by health care providers to address medication adherence in all hematological cancer patients. Based on these findings we have developed a checklist that could be used as a quick guide tool to assist health care providers to quickly identify and appropriately address medication adherence in hematological cancer patients (see Appendix 1). Unlike other generic medication adherence checklists, such as the BSmart adherence checklist,[78, 79] the proposed checklist includes only concrete suggestions that are specific to hematological cancer patients. It is recommended that future methodologically rigorous intervention studies are undertaken to assess whether use of the checklist by health care providers improves medication adherence by hematological cancer patients. It is also suggested that the checklist is updated and further developed as more robust data on medication adherence in hematological cancer patients becomes available.

### 4.3 Limitations of studies included in the review

First, as a result of variation in the methods of the studies reviewed, it was not possible to provide an accurate and comprehensive estimation of the adherence rates.

Furthermore, a lack of consistency in the outcome assessed increased the difficulty in combining data from different studies and making definitive conclusions about what characteristics impact on medication adherence in these populations. For instance some studies assessed characteristics relating to increased adherence while others assessed characteristics associated with increased non-adherence. To overcome this limitation, studies should include several methods of measuring medication adherence to allow for cross-validation between the different methods and thus assist in reducing measurement error.[15, 80].

Second, ascertainment bias is a limitation of research in this area, with the majority of included publications assessing adherence in patients with CML who were prescribed self-administered imatinib treatment (n=28; 54%). There are a number of other hematological cancers, including Acute Myeloid Leukaemia, Multiple Myeloma and Non-Hodgkin's Lymphoma, that have self-administered treatments available, which are often different to those prescribed to treat CML and ALL.[16]

Finally, very few studies included a comprehensive assessment of characteristics possibly associated with medication adherence. For many studies it is likely that the small sample sizes affected their ability to assess the relationship between all potentially influential characteristics and medication adherence rates, or limited the amount of power necessary to detect a difference. This lack of a comprehensive assessment of

characteristics associated with medication adherence may explain why some characteristics that would typically be thought to affect medication adherence rates, such as time since diagnosis, and treatment and disease related side-effects, were not identified in studies focusing on ALL patients but were identified in studies of CML patients. However, several studies focusing on ALL patients did identify some characteristics that may be considered somewhat related to these concepts. For example a number of studies found medication adherence in ALL patients declined with study time or over time, which may be indicative to time since diagnosis[4, 60, 61]. In another study of ALL patients hepatic side effects and disease relapse were identified as being related to patient medication adherence rates,[64] which again these variables may be considered related to or indicative of treatment and disease related side effects. To adequately support hematological cancer patients' adherence to self-administered treatments it is vital that we have an accurate understanding of the adherence rates and factors affecting adherence in the whole population. It is necessary that future research be undertaken with the whole population of hematological cancer patients taking self-administered medications, using rigorous methodologies, consistent definitions and valid and reliable measures of adherence.

#### 4.4 Limitations of the review

Several limitations should be considered when interpreting the results. First, although we employed an extensive search strategy encompassing four of the most prominent medical databases it is possible that relevant publications were missed. In addition, inconsistencies in the terminology used to define adherence (e.g. adherence vs. compliance) made it difficult to determine if studies were assessing adherence or not.

#### 4.5 Directions for future research

Medication adherence is an important issue for a wide range of hematological cancers. Despite this, all but one of the identified studies focused on assessing medication adherence in CML and ALL patients[69]. It is essential that future research investigates the occurrence and characteristics associated with medication adherence in hematological cancers other than CML and AML, particularly as several studies in this review have found adherence rates to vary across treatment types.[28, 39, 49, 54]

A number of characteristics, including age, sex, treatment duration, treatment concomitant and type of treatment were identified by several studies as impacting on ALL or CML patient's adherence rates; however the direction in which these characteristics affect medication adherence was not always clear, i.e. whether it was positive or negative, with inconsistent findings reported across several studies. It may be that other factors, not yet identified, are confounding the impact that such characteristics have on patient's medication adherence rates. It is likely that there is a complex relationship between many patient, disease, treatment and health care characteristics affecting patient medication adherence rates. This notion is supported by the findings of one study, which identified time since diagnosis and length of time on imatinib treatment as significantly associated with patient adherence in a multivariate analysis, but yet failed to find a significant association in the univariate analysis.[5]

Further research is needed to investigate the complexity of medication adherence and the factors affecting it. The inconsistent findings between studies further highlight the difficulties health care providers face when trying to understand and support patients in

regards to medication adherence. As a result, further empirical investigation is needed to tease out the complex relationship these characteristics have on CML and ALL patients medication adherence.

Methodologically rigorous intervention studies are needed to progress our understanding of how to improve medication adherence for hematological cancer patients. Intervention strategies should include carefully chosen (e.g. theory-based and empirically informed) multiple-component[22] approaches to guide providers in the best suite or combination of strategies to address medication adherence in CML and ALL patients. Such approaches may include: use of reminders, information, counselling, follow-ups[22] and involvement of family members and support persons.[74] CML and ALL are relatively low incidence cancers, each making up only 0.3% of all cancers diagnosed in Australia in 2009.[81] The small number of patients may pose difficulties in recruiting sufficient sample sizes to power the traditional gold standard intervention study design, of a randomised controlled trial (RCT) to be undertaken. Consequently, researchers may need to consider alternate intervention research designs that allow for smaller sample sizes to be used.

#### 4.6 Conclusions

To accurately understand and improve medication adherence among hematological cancer patients it is vital that systematic and robust research is carried out in this area. The limited data currently available suggests health care providers can improve medication adherence among individuals with CML and ALL by addressing patient understanding and knowledge of their medication, assisting patients to remember to

take their medication as prescribed, ensuring good communication with their patients about the importance of their treatment, and facilitating patients' available support networks.

## **Acknowledgments**

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## **Conflict of interest**

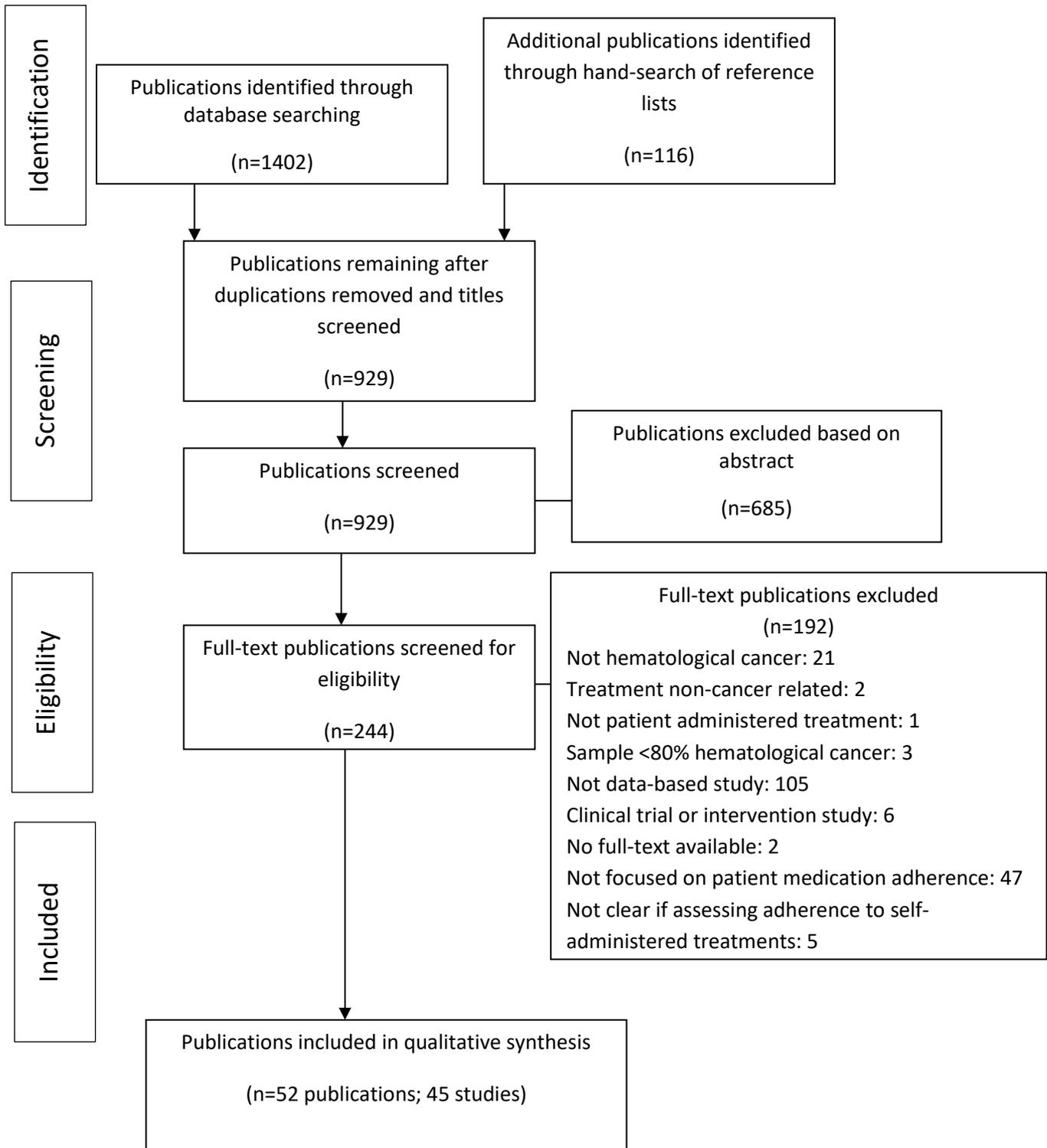
The authors declare they have no conflict of interest.

**Author Vitae:** AH is an early career researcher within the University of Newcastle. AH has experience in longitudinal, cross-sectional and intervention research studies. The majority of her research has focused on methodology and assessing psychosocial outcomes of cancer survivors and their support persons. CP is an associate professor of health behaviour at the University of Newcastle. CP has a strong interest in cancer prevention and control, as well as an interest in the areas of social disadvantage, chronic disease and health service delivery. JB is an early career researcher at the University of Newcastle. JB works across a range of area in cancer control, including prevention, treatment and survivorship. JB is involved in several intervention trials which aim to improve the care of cancer patients. ML is a senior lecturer and researcher in the area of health behaviour. ML's research interests include: health behaviour change, tobacco control and assessment of unmet needs of hematological cancer survivors and their support persons. PR is a professor of medicine at the University of Newcastle and

the director of haematology at the Calvary Mater Hospital in Newcastle Australia. PR has over 20 years' experience in clinical trials, biostatistical analyses and health resources research. AE is a haematologist and clinician scientist at the Calvary Mater Hospital in Newcastle Australia. His research interest predominately lies in combining his clinical experience in hematology with his passion for researching thrombosis and coagulation. HS is a research assistant at the University of Newcastle. Her background is in psychology and health behaviour.

**Table 1: Search terms used to identify relevant publications assessing medication adherence in hematological cancer patients**

	<b>Search terms</b>
Hematological cancer terms	multiple myeloma OR myeloma OR leukemia OR leukaemia OR leukemias OR lymphoma OR Hodgkin's lymphoma OR non-Hodgkin's lymphoma OR nonHodgkin's lymphoma OR hematologic neoplasm* OR Haematologic neoplasms OR haematologic neoplasm* OR hematological cancer* OR hematological cancer* myeloproliferative disorder OR hematologic malignancy OR haematologic malignancy
Adherence terms	Patient compliance OR patient adherence OR patient nonadherence OR patient non-adherence OR medication adherence OR Medication nonadherence OR medication non-adherence OR medication persistence OR medication concordance OR treatment compliance OR medication compliance



**Figure 1: PRISMA[82] four-phase flow diagram describing selection process of eligible publications**

**Table 2. Research studies reporting medication adherence rates to self-administered cancer therapies by Chronic Myeloid Leukaemia (CML) patients**

Author (year) Country	Cancer type Treatment type	Sample size  Response rate	Age range	Medication adherence measure	Definition of adherence	Rate of adherence
Almeida (2010)[28] Unclear	CML  Imatinib, Nilotinib, Dasatinib and Bosutinib	122  Not reported	Adults	Observation (not clear)	Unclear	Mean adherence =96%  23% of patients were 100% adherent
Bazeos (2009)[29] Unclear	CML  Imatinib	87  Not reported	Unclear	MEMS	Unclear	Median adherence = 98% (range 23-104%)  26% of patients were <90% adherent  14% of patients were <80% adherent
Casamartina (2010)[30] Unclear	CML  Imatinib	Not reported  Not reported	Unclear	Pill count  SMAQ questionnaire	Unclear	Mean adherence = 98%  11% non-compliant patients according to pill counts  13% non-compliant patients according to the SMAQ questionnaire

Cortes (2011)[31] USA	CML  Imatinib, dasatinib or nilotinib	74  Not reported	Adults (≥18 years)	Morisky Medication Adherence Scale (scores range from 0-8)	Medium/high adherence: scoring between 6 -8 on an 8 point MMAS.	72% (n=51) of patients reported medium/high adherence.
Darkow (2007)[32] USA	CML  Imatinib	267  Not applicable	Adults (≥18 years)	Claims data	Failure to refill treatment within 30 days from end of supply of the previous prescription  MPR – as continuous variable also categorised as low (<50%) intermediate (50%-90%), high (90%-95%) and very high (95%)	First year Mean MPR = 78% (SD=28%).  45% (n=120) had very high MPR (>95%).  9% (n=25) had high MPR (90%-95%).  46% (n=122) had MPR <90%  20% (n=53) had low MPR (<50%)  31% of patients had a treatment interruption
De Almeida (2010)[33] Brazil	CML  Imatinib, Dasatinib or Nilotinib	131  Not reported	Unclear	Unclear	Mean MPR	Mean adherence = 94%  20% of patients were 100% adherent
Doti (2007)[9] Unclear	CML  Imatinib	24  Not reported	Adults	Patient self-report	Quantity of treatment taken/quantity prescribed X 100	Mean adherence for first 12 months=96%

Doti (2008)[10] Unclear	CML  Imatinib	24  Not reported	Adults	Patient self-report	Quantity of treatment taken/quantity prescribed X 100	Mean adherence for first 12 months=96%  Mean adherence for second 12 months=91%
Efficace (2012)[34] Italy	CML  Imatinib	413  Not reported	Adults	Adapted version of the Morisky Medication Adherence Scale	Patients who respond to all three questions as never were considered adherers	53% reported optimal adherence behaviour and were defined as adherers
Feng (2006)[36] USA	CML and GIST  Imatinib	878  Not applicable	Unclear	Claims data	MPR	Mean adherence = 76%  28% of patients discontinued treatment for at least 30 consecutive days during the 1 year follow-up
Ganesan (2011)[37] India	CML  Imatinib	516  Not reported	Adults, adolescents and children	Appointment schedule  Self-report	Failing to, or late to report to scheduled appointment to refill prescription  Self-report interruption for more than 1 week	206 patients had dose interruptions of more than 1 week. Of these 30% (n=150) were deemed to be due to non-adherence
Guerin (2011)[38]	CML	521	Unclear	Claims data	PDC	Mean PDC over the study period was 0.79

USA	Nilotinib and Dasatinib	Not applicable				for Nilotinib and 0.69 for Dasatinib
Guerin (2010)[14] USA	CML  Imatinib	1,877  Not applicable	Unclear	Claims data	Adherence = MPR $\geq$ 85% Non-adherence=MPR < 85%	34% of patients were 100% adherent
Guerin (2012)[39] USA	CML  Nilotinib or Dasatinib	878  Not applicable	Unclear	Claims data	MPR PDC	The average MPR was 0.800 (SD=0.246) for nilotinib and 0.739 (SD=0.292) for dasatinib  The average PDC was 0.759 (SD=0.243) for nilotinib and 0.696 (SD=0.283) for dasatinib
Guilhot (2010)[40] Brazil, France, Italy, Spain and Russia	CML  TKIs	405 (physicians ) 1,155 (patient chart reviews)  Not applicable	Unclear	Patient chart review and physician surveys	Not reported	Across the five countries between 43% and 53% of patients were 100% adherent  More than 10% of patients missed $\geq$ 10% of their prescribed daily dose of medication  Russia reported the highest percentage of non-adherent patients (23%) and Brazil the lowest (8%)

Halpern (2007)[41] USA	CML  Imatinib	374  Not applicable	Unclear	Claims data	MPR  Compliance categories were good ( MPR≥ 90%); medium (MPR=70–89.9%); poor (MPR<70%).	Year 1: 44% (n=166 good), 21% (n=79) medium and 34% (n=129) poor adherence  Year 2: 38% (n=143) good, 22% (n=84) medium and 39% (n=147) poor.
Ibrahim (2010)[43] Unclear	CML  Imatinib	87  Response rate = 91%	Adults	MEMS	Not reported	Median adherence = 98%  26% of patients were ≤90% adherent and 14% were ≤80% adherent.
Ibrahim (2011)[42] USA	CML  Imatinib	87  Response rate = 91%	Adults	MEMS	Not reported	Median adherence = 97% (range = 24% - 104%).  26% (n=23) adherence was ≤90%  21% (n=18) adherence ≤85%
Jacobsen (2011)[44] Unclear	CML  Imatinib, Nilotinib or Dasatinib	62  Response rate = 91%	Adults	Self-report questionnaire  Medical chart review	Not reported	In the past 30 days 6% (n=4) patients reported taking more treatment per day than prescribed

						<p>In the past 30 days 37% (n=23) of patients reported taking less treatment than prescribed</p> <p>Among all patients the number of days one or more doses were missed were 1 day (13%), 2 to 3 days (13%), 4 to 6 days (7%) and 6 or more days (5%)</p>
Johnson (2010)[45] US	CML  TKIs	39  Response rate = 49%	Adults	Author developed self-report questionnaire of adherence. Completed by patients and physicians	Patients were classified as true compliant if there was agreement between both patients and physicians	42% of patients were classified as true compliant and 58% as non-compliant
Jonsson (2012)[46] Sweden	CML  Imatinib	38  Response rate = 90%	Adults	MMAS – scores range from 1 to 13	Adherent = MMAS score ≥ 11 Non-adherent = MMAS score < 11	<p>Mean Morisky score 12.3 (range 9-13)</p> <p>97% (n=37) were classified as adherent</p> <p>1 patient was classified as non-adherent (Morisky score &lt; 11)</p>

Koren-Michowitz (2012)[6] Israel	CML Imatinib	200  Not reported	Adults	Self-report patient logs  Medical history	Percentage sum of actual dose taken divided by percent sum of the planned dose for all of the days that were logged	Self-reported compliance was 98% of prescribed dose  76% (n=144) received the standard dose throughout the study
Lee (2009)[11] US	CML Imatinib	19  Not reported	Unclear	Chart review and patient history	Unclear	67% of patients with a trough level of 780ng/ml reported poor compliance  20% of patients with a trough level of 1885ng/ml had poor compliance
Marin (2010)[8, 47] UK	CML Imatinib	87  Unclear	Adults	MEMS	Unclear	Median adherence = 98% (range 24% to 104%)  27% of patients had adherence <90%  14% of patients had adherence ≤80%
Noens (2008)[48] Belgium	CML Imatinib	169  Not reported	Adults (>14 years)	Pill count	Percentage of prescribed medication taken over 90 day study period	Pill count ranged from 29% to 202%

<p>Noens (2009)[5] Belgium</p>	<p>CML Imatinib</p>	<p>169 Not reported</p>	<p>Adults (&gt;14 years)</p>	<p>Physicians used the 4 item Basel Assessment of Adherence Scale (BAAS) to assess perception of adherence by the patient and a third person.</p> <p>Physicians, patients and a third person rated patient's adherence on a 0-100 point visual analogue scale (VAS)</p> <p>Pill count</p>	<p>Adherence with appointments was assessed as a ratio of appointments scheduled to appointments kept.</p> <p>A "yes" on any of the four items in the BAAS constitutes non-adherence</p>	<p>Physician believed on average 93% (<math>\pm 13</math>) of patients in the first month after diagnosis were adherent and 87% after the first year.</p> <p>Physician, patient and third person VAS ratings ranged from 95 to 97 out of 100 at baseline and follow-up.</p> <p>On the BAAS 36% of patients at baseline and 33% of patients at follow-up reported at least one of the four non-adherence behaviours in the last four weeks. The most common behaviours included, occasionally not taking a dose (16% at baseline and 13% at follow-up) and taking a dose with a delay of more than 2 hours (22% at baseline and 25% at follow-up)</p> <p>Mean pill count scores for the 90 day period =</p>
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						91% of prescribed dose (range 29% to 202%)
Oliveria (2011) [49] Unclear	CML  Dasatinib, Nilotinib or Imatinib	2,145  Not applicable	Unclear	Claims data	MPR	Sample size too small to calculate
StCharles (2009)[50] USA	CML  Imatinib	430  Not applicable	Adults (<65 years)	Claims data	MPR over 12 month period  Adherent behaviour was classified as an MPR >85%	Mean MPR = 80%  60% of patients were categorised as adherent
van Lierde (2007)[52] Belgium	CML  Imatinib	169  Not reported	Adults (>14 years)	Physician, patient and third person VAS  Patients BAAS  clinic appointments kept  Pill count	% of clinic appointments kept  % of treatment taken per pill count	VAS – Approximately 1 in 3 patients (33%) exhibited non-adherence in the 4 weeks prior to baseline and follow-up  BAAS 36% at baseline and 33% at follow-up  Pill counts – approximately 1 in 7 were perfectly adherent (14%) with under and over taking
Wu (2009)[53] USA	CML  Imatinib	1,877	Unclear	Claims data	MPR	Of the 1,877 patients evaluated there were 6,175 adherent and

		Not applicable				3,163 non-adherent intervals  34% of patients were 100% adherent throughout the observation period.
Wu (2010)a[54] USA	CML  Nilotinib or Dasatinib	521  Not applicable	Unclear	Claims data	PDC	The average PDC over the study period was 0.79 for nilotinib and 0.69 for dasatinib
Wu (2010)b[13] USA	CML  Imatinib	592 (592 eligible out of 2840)  Not applicable	Mix Those aged <65 years	Claims data	MPR – categorised as low MPR (<85%) and high MPR (>=85%)	Mean MPR over 365 days of treatment = 79%  41% (n=242) were identified as low MPRs  59% (n=350) had high MPRs
Yood (2010)[57] USA	CML  Imatinib	216  Not applicable	Mean age 51 years	Claims data and medical records	MPR and treatment interruptions (failure to refill prescription within 30 days of end of supply from previous prescription or clinician-directed discontinuation)	51% had a mean MPR <85%  57% experienced at least one treatment interruption

Yood (2012)[56] USA	CML  Dasatinib and Nilotinib	250  Not applicable	Adults (>18 years)	Claims data	Poor adherence=MP R<85%	Adjusting for confounders, quantified rates of poor adherence between nilotinib and dasatinib users yielded hazard ratios of 1.6 overall, and 1.9 for <100 mg/day and 1.2 for >=140 mg/day
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CML=Chronic Myeloid Leukaemia; MEMS=Medication Event Monitoring System; ALL=Acute Lymphoid Leukaemia;  
USA=United States of America; SMAQ=Simplified Medication Adherence Questionnaire; UK=United Kingdom;  
MPR=Medication Possession Ratio; MMP=Matrix Metalloproteinase; TG=Thioguanine; MP=Mercaptopurine;  
MTX=Methotrexate; PDC=Proportion of Days Covered; TKI=Tyrosine Kinase Inhibitors; MMAS=Morisky Medication  
Adherence Scale; BAAS=Basel Assessment of Adherence Scale; VAS=Visual Analogue Scale

**Table 3. Research studies reporting medication adherence rates to self-administered cancer therapies by Acute Lymphoid Leukaemia (ALL) patients**

Author (year) Country	Cancer type Treatment type	Sample size  Response rate	Age range	Medication adherence measure	Definition of adherence	Rate of adherence
Bhatia (2012)a[59] Unclear	ALL 6-MP	462  Not reported	Children	MEMS  Biological indicators	<95% - based on authors clinical work as the rate of adherence associated with an unacceptable increase in relapse	Month one adherence = 94%  Month 6 adherence = 89%  45% of patients were <95% adherent after a median follow-up time of 5.4 years
Bhatia (2012)b[4] USA	ALL Oral mercaptopurine	327  Not reported	Children (≤21 years)	MEMS	Unclear	Adherence decreased from 95% in month 1 to 90% in month 6.
Christiansen (2008)[60] UK	ALL Oral mercaptopurine	55 parents/car egivers  Not reported	Children (<18 years)	Self-report	Assessed frequency of forgetting doses using three-point Likert scale	4% (n=2) stated they forgot a dose more than once a month.  27% rarely forgot a dose.  69% never forgot a dose.
Jaime-Perez (2009)[61] Mexico	ALL MTX or 6MP	49	Children (<15 years)	Self-report	Failure to take medication on two or more	Self-report 10% (n=5) at least one episode of

		Not reported		Medical chart review  Serum concentration assay	occasions without medical advice  MTX not detected in serum in at least one of three random samples	non-compliance was reported  Medical chart review 16% (n=8) referred skipping treatment  Serum assay 29% MTX was not present in at least one measurement
Mancini (2012)[64] France	ALL  Imatinib	52  Response rate = 96%	Children (<11 years), adolescents (11-17 years) and adults (>17 years)	Self-report by patients	Unclear	12 (23%) patients were clearly non-adherent.
Oliveria (2004)[65] Brazil	ALL	39  Not reported	Children (<18 years)	Parent report  Medical chart review  Serum concentration assay	Indication that child failed to receive medication on two or more occasions without medical advice  Two or more records of irregular administration of treatment	Self-report 33% (n=13) were non-compliant  Medical chart review 31% (n=12) had irregular or incorrect dosage or interruption of treatment without medical advice  Serum assay 17% (n=6) were non-compliant

					Significant and simultaneous decrease of 6-TG and MMP concentration in relation to other samples without decrease in prescribed 6-MP dosage in previous four weeks	Overall 54% (n=21) were considered non-compliant through at least one method
Oliveria (2005)[68] Brazil	ALL 6-MP MTX	73  Not reported	Children (<18 years)	Self-report  Medical chart review	Failure to take medication on two or more occasions without medical advice  Not receiving 6-MP or MTX three times or more without medical instructions	27% (n=20) were non-compliant when defined as missing two or more treatments  16% were non-compliant when defined as missing three or more treatments
Pai (2008)[66] USA	ALL  6MP	51  Consent rate = 93% completion rate =77%	Adolescents (12-19 years)	Self-report using an author developed measure  Biological measure	General adherence score calculated (0-5) with higher scores indicating higher adherence	Mean general adherence score was 4.39 (SD=1.19) at day 56 and 4.37 (SD=1.11) at day 112

						<p>At day 56 20% of patients reported missing a dose in the last week and 18% reported doing so at day 112</p> <p>At day 56 35% of patients reported missing a dose in the two weeks and 35% reported doing so at day 112</p> <p>53% of patients had bioassay indicators that represented non-adherence for at least one of the three time points</p>
Sitairesmi (2009)[67] Indonesia	ALL MTX, vincristine, dexamethason , l- Asparaginase, doxorubicin and 6-MP	51 Response rate = 71%	Parents of children patients	Self-report using an author developed measure	Not reported	<p>4% (n=2) reported sometimes changing the dose because of side effects</p> <p>6% (n=3) stopped treatment because of side effects</p>

MEMS=Medication Event Monitoring System; ALL=Acute Lymphoid Leukaemia; USA=United States of America; UK=United Kingdom; MMP=Matrix Metalloproteinase; TG=Thioguanine; MP=Mercaptopurine; MTX=Methotrexate

**Table 4. Summary of Chronic Myeloid Leukaemia (CML) patients at potential risk of medication non-adherence**

<b>Patient characteristics</b>
Education level lower than secondary school[5]
Lack of knowledge on the impact of their disease and treatment[5, 27]
Low self-efficacy in relation to medication behaviour (i.e. confidence in their ability to take medication)[5]
High self-reported functional status (i.e. self-perceptions of performing normal activities)[5]
High self-reported quality of life[5]
Taking medication independent of meals[35]
<b>Disease and treatment characteristics</b>
Not participating in a clinical trial[28, 33]
Further time from diagnosis[5, 27]
Longer time between diagnosis and medication being filled[50]
Higher rates of treatment side-effects[8]
High cancer complexity[32]
High number of cancer related complications[36]
<b>Social characteristics</b>
Low levels of social support[34]
Living alone[5, 27]
Low socioeconomic status[50]

<sup>a</sup>Characteristics identified in this table are based on characteristics identified by quantitative studies as being statistically significantly related to medication adherence (or non-adherence) in CML patients

<sup>b</sup>Due to differences in the specific adherence outcome assessed by each study (e.g. some studies adherence, others non-adherence) the information in this table should be used as a basic guide to assist health care providers in easily identifying potential sub-groups of hematological cancer patients at risk of medication non-adherence

**Table 5. Summary of Acute Lymphoid Leukaemia (ALL) patients at potential risk of medication non-adherence**

<b>Patient characteristics</b>
Hispanic, Asian or African American background[4, 59]
Older age[4, 59, 64]
<b>Disease and treatment characteristics</b>
Experiencing hepatic side effects[64]
Disease relapse[64]
<b>Social characteristics</b>
Fewer people residing at home[64]
Single parent families[4, 59]

<sup>a</sup>Characteristics identified in this table are based on characteristics identified by quantitative studies as being statistically significantly related to medication adherence (or non-adherence) in ALL patients

<sup>b</sup>Due to differences in the specific adherence outcome assessed by each study (e.g. some studies adherence, others non-adherence) the information in this table should be used as a basic guide to assist health care providers in easily identifying potential sub-groups of hematological cancer patients at risk of medication non-adherence

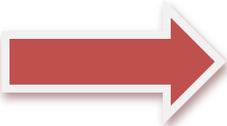
**Appendix 1. Health care provider checklist to help support medication adherence  
in hematological cancer patients**

Patient name	
Date	
Medication type	
Time on medication	

<b>Step 1: Identify patients at potential risk of non-adherence to offer additional support</b>		
<input type="checkbox"/> Patient lives alone		<b>Additional support and assistance may be needed</b>
<input type="checkbox"/> Patient does not have a regular and reliable support network		
<input type="checkbox"/> Patient was diagnosed >12 months ago		
<input type="checkbox"/> Patient is of low SES		

<b>Step 2: Reinforce importance of medication adherence on disease control to all patients</b>
<input type="checkbox"/> Explain when patients should take their medication
<input type="checkbox"/> Explain the correct dosage of medication patients should take
<input type="checkbox"/> Explain specific effects medication has on the disease

<b>Step 3: Assess all patients medication adherence</b>
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<input type="checkbox"/> Has the patient intentionally non-adhered	<p style="text-align: center;"><b>Suggested strategies</b></p> 	<input type="checkbox"/> Assess why and address barriers <input type="checkbox"/> If possible offer adherence counselling
<input type="checkbox"/> Has the patient forgotten to take their medication anytime since their last appointment	<p style="text-align: center;"><b>Suggested strategies</b></p> 	<input type="checkbox"/> Pill boxes <input type="checkbox"/> Medication schedule/diary <input type="checkbox"/> Invite assistance of support persons <input type="checkbox"/> Reminder alarm <input type="checkbox"/> Couple medication behaviour with events in normal everyday routine

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