# Understanding Barriers to Oral Therapy Adherence in Adults With Acute Myeloid Leukemia

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#### **Abstract**

Acute myeloid leukemia (AML) is a disease of older adults, with a median age at diagnosis of 68 years. The availability of oral anticancer medications has increased, although the standard treatment for AML remains in intravenous form. We aim to identify barriers to adherence to oral medications in patients with AML and proposed solutions for improvements, Following institutional review board approval, patients with AML and their caregivers were recruited to participate in focus groups. Sessions were digitally recorded, transcribed verbatim, and analyzed for thematic content using Dedoose qualitative software. 11 patients (five < 65 years; six ≥ 65 years) and 4 caregivers participated in these sessions. Three central themes emerged: 1) medication adherence challenges, 2) managing an oral adherence plan, and 3) strategies to improve oral adherence. Participants recommended written schedules, taking medications around meals, and using pillboxes and alarms. We believe that patients are an important source of insight into barriers and solutions to oral medication adherence.

n 2020, there will be an estimated 19,940 new cases of acute myeloid leukemia (AML) and 11,180 deaths in the United States (Siegel, Miller, & Jemal, 2020). The incidence of AML is increasing, in part due to the overall aging population; the median age at presentation is 68 years (American Cancer Society, 2019; Siegel, Miller, & Jemal, 2020). Overall 5-year survival rates are as

low as 5% to 10% in adults > 60 years (Wang, 2014).

Treatment for AML has historically remained unchanged; standard induction treatment for AML is intravenous (IV) chemotherapy with a prolonged hospitalization of 3 to 4 weeks due to treatment- and disease-related symptoms (American Cancer Society, 2019). These symptoms are associated with decreased activity, distress, and fluc-

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tuating psychosocial needs, directly impacting quality of life (Albrecht, 2014; Albrecht, Boyiadzis, Elswick, Starkweather, & Rosenzweig, 2017; Leak Bryant, Lee Walton, Shaw-Kokot, Mayer, & Reeve, 2015). Adults with AML are more likely to have received different types of chemotherapies (IV and oral) due to risk of relapse, leading to a longer period of myelosuppression and physical deconditioning (Ramos, Mo, Karp, & Hourigan, 2015). It is difficult to achieve long-term remission with current AML intensive treatment. The best curative treatment option for adults with AML in remission who have adequate physical, psychological, and performance status is a hematopoietic stem cell transplant (Pohlen et al., 2016).

The availability of oral medications has increased in recent years (Foulon, Schoffski, & Wolter, 2011), providing both significant benefits and risks to patients. The burden of daily adherence has shifted from the provider to the patient (Foulon et al., 2011; Ruddy, Mayer, & Partridge, 2009). With this shift, patients are responsible for taking their oral medications. However, the associated side effects and symptoms that accompany them may decrease oral adherence (Ruddy et al., 2009). Since 2017, eight novel agents have been introduced for AML, six of which are oral: midostaurin (Rydapt), enasidenib (Idhifa), ivosidenib (Tibsovo), gilteritinib (Xospata), glasdegib (Daurismo), and venetoclax (Venclexta). This significant growth in AML agents is changing how adults with AML are treated.

A 2016 metareview of 63 adherence studies found that as few as 46% of patients take their prescribed dose on the correct schedule (Greer et al., 2016). Identifying potential barriers to adherence is critically important for adults with AML to achieve favorable health outcomes. There is limited evidence for optimizing adherence to oral cancer agents for adults with AML. In particular, older adults (≥ 65 years) with AML may have more barriers to adhering to oral cancer agents than younger adults due to other prescribed oral medications and the associated side effects (Mislang et al., 2017). A clear understanding of barriers to adherence with oral medications in the AML population as described by the patients themselves is essential. We aimed to 1) identify barriers to adherence to oral medications in younger (< 65 years) and older

adults ( $\geq$  65 years) with AML and 2) propose solutions for improvement in oral adherence.

### **METHODS**

### **Setting and Participants**

The focus groups were conducted at the North Carolina Cancer Hospital (NCCH) at the University of North Carolina at Chapel Hill Lineberger Comprehensive Cancer Center. This center is a referral site for adults with probable AML and sees approximately 130 to 150 new cases of AML annually. Participants with a history of AML (active treatment and remission) were included.

#### **Procedures**

We recruited a convenience sample of participants from the NCCH, which has a large population of adults with AML. Interested participants were made aware of the study through fliers posted in the hematology/oncology clinic and by word of mouth by nurse navigators. The study was reviewed and approved by the University of North Carolina at Chapel Hill institutional review board.

# DATA MANAGEMENT AND ANALYSIS Data Collection Procedure

The focus groups lasted approximately 60 to 75 minutes and took place in conference rooms on the inpatient hematology and oncology unit at the NCCH. Each focus group was led by an experienced moderator from Communication for Health Applications and Interventions (CHAI) Core's Qualitative Research group. These focus groups followed a focus group discussion guide that the project and research team worked together to develop and finalize. Couples (or single participants) were given \$50 or \$100 gift cards for taking part in the discussion.

## **Analysis**

All sessions were digitally recorded and files were transcribed verbatim by a professional service. Research team members developed a codebook based on the research questions and imported the transcriptions and codes into Dedoose, a qualitative management software tool, to facilitate analysis. Three coders independently applied codes to the transcripts. A thematic qualitative analysis was conducted based on the code reports that

were generated, and a summary of the findings that emerged are presented in this article.

### **RESULTS**

### Sample

The mean age was 61.5 years (standard deviation [SD]: 9.9), with six females and five males. The majority of participants were retired. Among the 11 participants, level of education ranged from high school (n = 3), general educational degree (n = 1), 4-year college degree (n = 3), and graduate school (n = 4). The sample was racially diverse, with six Caucasian, three African-American, one American Pacific Islander, and one American Indian participants. The mean age of the  $\geq$  65 age group was 68 (SD: 3.7) and the mean age of the  $\leq$  65 age group was 53 (SD: 7.7).

Four focus groups were organized. Two groups consisted of participants under the age of 65 and their caregivers (focus group 1: N=2 with 1 participant and 1 caregiver; focus group 2: N=5 with 4 participants and 1 caregiver) and two groups of participants consisted of participants over the age of 65 and their caregivers (focus group 1: N=5 with 3 participants and 2 caregivers; focus group 2: N=3 with 3 participants only). Eleven participants (5<65 years;  $6\geq65$  years) and 4 caregivers participated in sessions.

Three central themes emerged from the focus groups: medication adherence challenges, managing an oral adherence plan, and strategies to improve oral adherence. Adherence challenges such as number and size of pills, different medication instructions, cost, availability of oral medications, and side effects are presented. An adherence plan was recommended, including written schedules, medications (including information on whether to take with or without food), and the use of pillboxes and alarms. The main sources of information were the health-care team and bottle instructions. Recommendations for providing adherence assistance included better instructions, assistance with oral medication scheduling, making pills smaller, and consistency in packaging (Table 1).

# Theme 1: Challenges of Adhering to Oral Medications

The first theme we identified was challenges of adhering to the oral medications and the impact it could have on overall outcomes. One participant commented, "When I organize her pills, I'll do 2 weeks at a time. It's hard to take pills at different times with as many as she has. Some of them look the same. Sometimes you're loading them up, and you'll spill them out, and you've got pills everywhere and you say, 'Which pill is this?' Have you ever done that?"

Regardless of age, a common theme expressed was the impact of side effects of oral medications on daily life, including lack of appetite, nausea, and stomach issues. "I've lost over 60 pounds already. I started out at 230, and now I'm down to 160, 165. I used to cook every day. I don't enjoy eating at all," said one patient over 65.

"My doctors have given me several different medications for nausea, and none of them have helped," another patient commented.

"The midostaurin definitely makes me nauseous. They have implemented a pre-dose regimen where I'm taking the antinausea medication 30 minutes prior, and that seems to help," reported one patient under 65.

Another patient said, "It took me probably a week, maybe even 10 days, to feel empowered enough to advocate for myself that I'm not taking the potassium on top of the valacyclovir, because the potassium sits in my stomach like a brick. Like literally within 10 minutes, I'm going to start getting stomach cramps."

"I definitely think that it has to be all of the chemo, including midostaurin, that is contributing to my diarrhea," said a patient under 65.

Participants were asked to discuss their thoughts and experiences related to oral medications compared with IV medications and what they perceived as being most effective. In general, adults with AML in both age groups felt that the IV method for receiving medications was more effective, both in terms of the drug's efficacy and in getting patients to take their medications. Concordantly, several participants pointed out reasons they think IVs are harmful or are less effective when compared to taking medications orally.

"I know there are added issues of potential infection and all that stuff every time. But if you switch, you plug in and unplug when you're lying there, and it's just easier," said a patient under 65.

Table 1. Themes of Challenges to Adhering to Oral Medications		
Theme	Patient comment	
Challenges to Adhering		
General challenges	<ul> <li>Number of pills to take</li> <li>Competing demands/other life priorities</li> <li>Different pills have different directions</li> <li>Financial</li> <li>Size of pills</li> <li>Smell of pills</li> <li>Medications not available in the pharmacy</li> <li>Shut down at night and skip taking medications</li> </ul>	
Side effects of chemotherapy and medications	<ul> <li>Nausea and/or stomach issues</li> <li>Losing fingernails and peeling skin</li> <li>Light headed or dizzy</li> <li>Drowsiness</li> <li>Diarrhea</li> <li>Headaches</li> <li>Elevated sugars</li> </ul>	
Effectiveness	<ul> <li>IV method is easier</li> <li>IV is more potent, hits the bloodstream faster</li> <li>IV means no swallowing "horse pills"</li> <li>Less skips with IV</li> <li>No stomach issues with IV</li> <li>Don't have to be awakened with IV</li> <li>IV takes a toll on the body</li> <li>IV more inconvenient</li> <li>IV feels like it is one and done for the day, but felt worse</li> <li>More tired with IV</li> <li>Loss of control using IV</li> </ul>	
Oral Adherence Plan		
Inpatient strategies	<ul> <li>Delivered to room</li> <li>Follow discharge checklist</li> <li>Advocate for self</li> <li>Space out the dosage</li> </ul>	
Outpatient strategies	<ul> <li>Make it part of daily routine</li> <li>Create a schedule and tracking system</li> <li>Use pillboxes and containers</li> <li>Involve others</li> <li>Count the number of pills</li> <li>Involve the pharmacy</li> </ul>	
Medication directions	<ul><li>Directions from health-care team</li><li>On the bottles</li><li>None given</li></ul>	
Forgetfulness	<ul> <li>Skip it</li> <li>Seek advice from health-care team</li> <li>Seek advice from pharmacist</li> <li>Depends on what it is and when you remember</li> <li>Take the next day</li> </ul>	

Table continued on following page.

"I don't know, maybe the IV is more effective because it's immediately in your bloodstream...I don't know how long it takes for the oral medication to get in your system," commented one patient under 65.

"I'm so tired of swallowing so many pills. I was vactually in a trial, but then two times a day

there were two very large pills. I did that for about 4 days. Then with all the other pills, I opted out just because of the size of the pill," one patient under 65 responded. There were several participants from both age groups who mentioned negative issues with IVs when comparing them to oral medications, such as feeling worse and being fatigued.

Table 1. Themes of Challenges to Adhering to Oral Medications (cont.)		
Theme	Patient comment	
Suggestions for Improving Oral Medication	Adherence	
Have a specific oral adherence plan	<ul> <li>Plan dictated by nurse at discharge</li> <li>Plan revolves around time of day</li> <li>Plan revolves around meals and food</li> <li>Plan incorporates physical activity</li> <li>Just do it</li> </ul>	
Adherence assistance	<ul> <li>Better directions or a guide on when and how to take pills</li> <li>Make pills smaller</li> <li>Be consistent with the way the medications look</li> <li>Not have to take pills all at the same time</li> <li>Pill boxes with alarms</li> <li>Need visuals or a chart format</li> <li>Reconceptualize how pills are packaged</li> <li>Specific directions when you throw up</li> <li>Ask more questions</li> </ul>	

"I can tell it's taking a toll on my body. Well, it's taken away my sense of taste, my smell. I may eat once a day. I've gone down 43 pounds now. I don't care if I eat or not because it doesn't taste right. Food mostly tastes like cardboard or paper," one patient over 65 reported.

One participant commented, "Mentally, I'm done for the day. I just felt so much worse on the IV medication," and another said, "I don't know what I would choose if I had to choose one over the other. You do get a little bit more fatigued with the IV."

Participants were asked to discuss times when they had purposely stopped taking oral medications and what the result of the decision looked like. Almost all said they would never purposely stop taking their medications, mainly because they want to feel better.

"I would never not take it, because clearly it has a purpose. I don't want to do anything that deters my ability to go home," one patient under 65 said on the topic. Another patient commented, "If you want to be healthy, you will take it. There is no option."

A few participants mentioned that it would be easier to forget to take oral medications at home compared to going to the hospital, but forgetting was not the same as deliberately stopping medications. One general statement from participants was, "Here at the hospital, they're standing right there. I thought one time, 'Well, there's a reason why that lady's standing there, because they want to make sure that you take these pills.'

Then I saw some nurses who wouldn't stand guard as much."

### Theme 2: Oral Adherence Plan

Participants were asked to discuss any techniques or strategies they have used over the years to help them adhere to their oral medication regimen. For patients still receiving care in the hospital, strategies were more simplified with the assistance of a health-care team. However, participants also shared several strategies that work for them at home, including routines, tracking systems, and pillboxes. A few participants also brought up strategies they have heard about or would like to try to assist them with their medications.

"I take eight in the morning, three at lunch time, and three at night...[the nurses] just tell me what it is, and I take it," one patient over 65 said.

"When they give you this whole cup of pills, you feel obligated that you must swallow this cup of pills while the nurse is standing there. What I have found is you actually don't...now that I've added oral chemo to what I'm doing, they are still bringing me this cup of pills on top of my chemo. I've just started saying, "No, I'm going to do my chemo, and then I'm going to wait an hour." Then I'll do the other pills that I need to take. Then, I'll push the potassium to later in the day," a patient under 65 explained.

The outpatient strategies for oral medications adherence were clearly stated by both age groups as making oral medications a part of the daily routine.

One patient under 65 said, "I always make sure I do it at a certain time every day. If I do it that way then I get into a routine. Once I get into a routine, then it's like second nature to just do it." Another patient said, "I just know I need to do it when I first wake up. Then, right before I go to bed I take them."

One patient over 65 commented, "I always take the morning meds, and the other meds when I get here [to the hospital]," and another participant said, "I do mine in the morning, and then before I go to bed at night. The pills stay right beside my bed, and that's always the first and last thing I do."

# Theme 3: Suggestions for Improving Oral Medication Adherence

Participants were asked to discuss what types of assistance they could use to better adhere to their oral medication regimen. Both groups of participants (under and over 65) shared similar suggestions on ways to improve or help them follow their oral medication regimen (Table 2).

Participants were also asked to discuss what they felt should be the major takeaway messages from the discussion, and what kind of general recommendations they could draw from their own experiences that may help other AML patients when it comes to taking oral medications (Table 3).

### **DISCUSSION**

To our knowledge, this is the first study to explore oral adherence solely in younger and older adults with AML. It provides a detailed picture of the challenges to adhering to a prescribed schedule and suggestions for improving oral medication adherence.

Oral adherence is a major challenge for adults with AML (Theme 1) and is likely to be problematic in the outpatient setting. Forgetfulness contributes to decreased oral adherence. One patient stated, "If I were here (inpatient), I would ask the nurse what I needed to do," compared to remembering one's own oral medication schedule.

Patients are an important source of insight into barriers and solutions to oral medications adherence. In our study, quotes from younger and older adults with AML highlight the uniqueness of the disease and oral medications' impact, such as nausea and diarrhea. These symptoms can deter an individual from taking their oral medications.

Spoelstra and colleagues examined feasibility, preliminary efficacy, and satisfaction with a nurse practitioner intervention known as ADHERE as one practical intervention to increase adherence (Spoelstra et al., 2017). This intervention had sev-

Table 2. Participant Responses on Providing Assistance With Oral Medication Adherence		
Idea	Quote	
Better directions or a guide on when and how to take pills	"I take them all at one time, in the morning. It would be helpful if they would say specifically, take this one at bedtime, or do not take this with that."—Patient over 65 "A guide on which medications you can stretch out throughout the day and try to pace yourself in order to be kind to your gut would be helpful. Also, which medications are better to be taken with food and which are not?"—Patient under 65	
Make pills smaller	"I would ask that somehow those huge monster pills could be made smaller. I would much rather take two small round pills then one huge pill with angles on it." —Patient over 65	
Be consistent with the way the medications look	"Be consistent. The purple pill has been purple ever since we got it, but there are some pills that we get that are different colors and different sizes, and it really throws you off. It's hard to keep up with sometimes."—Patient over 65  "What I found is that CVS goes with the cheapest brand of that particular pill, like sometimes the pill is orange, and sometimes it's white and they will say, this is what you're used to, but just know that now the pill is white. It's the same medicine, it's just they've changed providers, or changed something, and the pill looks different."—Patient over 65	
Not to have to take all pills at the same time	"Only because I have to take so many pills, that at some point, I kind of gag after a certain number of pills. If I can wait an hour, or half an hour, then I can take it then, but it's all within the same time of the day, like the morning, even though I can take them any time. I can take them all at night, except for a couple. For me, it's easier to remember just to try and get them all out of the way in the morning, except for the ones that I have to take at night."—Patient over 65	

Table 3. Recommendations from Participants for Improving Oral Medications Adherence		
Topic	Quote	
Pillbox type	"Pillboxes with alarms. We have some at homeyou can buy them online." —Patient over 65	
Chart format	"For me, my Excel spreadsheet is the best, because it lists the medication's generic name, brand name, what it's for, and the time of day to take it because sometimes I can't remember."—Patient over 65	
Reconceptualize how pills are packaged	"One good thing would be if the pharmacy had all your prescriptions for each day, a 30-day supply, assembled in one package so that you didn't have to do it yourself." —Patient over 65	
Adherence	"I would say just stick to it. Don't, if you feel better one day, think, 'Oh I don't have to take my medicine.' "—Patient over 65	
Directions when you vomit pills	"I think it would be good for people to know whether they should wait to take a dose until the next day if they throw something up. I know a lot of that depends on what the medication is."—Patient under 65	
Ask more questions	"I didn't realize it, or maybe take advantage of it as much at the time, but there are opportunities for the patient to ask questions. I also know that when you've been here for 4 or 5 weeks, you just want to get out. You aren't thinking about what questions you could ask."—Patient over 65	

eral components, including motivational interviewing, brief cognitive therapy, and systematic patient education that promoted adherence and symptom management (Spoelstra et al., 2017). ADHERE was most beneficial for those who were newly prescribed oral medications, and those patients reported fewer and less severe symptoms (Spoelstra et al., 2017). Participants who participated in face-to-face 30-minute ADHERE intervention sessions followed by telephone calls were more likely to complete the intervention compared to the control group.

This study has some limitations. First, this single-site study focused on interviewing a small number of adults with AML and their caregivers during and after treatment in a large academic comprehensive cancer center. Second, we were limited by the diversity of race/ethnicity and sex, although our sample was representative of the AML population. Third, we interviewed participants once and did not use serial assessments. Serial assessments provide for additional data that were not captured in the first interview. Fourth, we did not ask participants about other factors that could potentially lead to low adherence such as poor vision and decreased cognitive alertness. Despite these limitations, this study was novel in its exploration of understanding barriers to oral adherence in younger and older adults with AML. The qualitative design allowed authors to comprehensively explore patient and caregiver experiences by gaining a deeper understanding of their perceptions of oral medications.

# IMPLICATIONS FOR THE ADVANCED PRACTITIONER

Oral medications pose both challenges and opportunities for patients and clinicians. Proposed solutions for the improvement of oral adherence are needed (Theme 3). Oncology advanced practitioners can review patients' prescribed oral adherence plans (Theme 2) to help them create a written schedule that considers timing, food ingestion (with or without), and number and size of medications. They can ask patients at every encounter about associated side effects from oral medications and remind them of the importance of taking their oral medications. Oncology advanced practitioners can strongly reinforce to adults with AML that relying on pill color is not a safe way to administer and ingest oral medications. Providing or recommending aides such as medication boxes with or without alarms and ensuring patients and caregivers understand how to use them reinforce the importance of adherence. Oncology advanced practitioners should provide written instructions about what to do if doses are missed or vomited and when to re-dose, along with role-playing several scenarios with patients and caregivers to ensure understanding.

Adults with AML should also be provided with information on how they can reach their advanced practitioners or leukemia team if questions arise and who to contact after clinic hours. Addressing these barriers frequently and quickly can increase oral adherence. Future studies would benefit from developing an adherence tool or modifying the ADHERE intervention to meet patient and caregiver needs. •

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### **Disclosure**

Ms. Richardson has served on an advisory board for Roche. Ms. Owenby and Dr. Wujcik are employees of Carevive Systems, Inc. The remaining authors have no conflicts of interest to disclose.

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