Interventions to Improve Adherence and Persistence to Oral Medications: A Targeted Literature Review

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Objective

- A targeted literature review (TLR) was undertaken to describe interventions for improving long-term adherence to oral medications and to summarize their effectiveness.

Conclusions

- Studies of pharmacist/physician-led interventions were more likely to report improvement in adherence/persistence to oral medications compared with studies of other interventions.
- Future adherence/persistence interventions should consider the inclusion of contact with pharmacists, side-effect or symptom management, daily or weekly reminders, and patient education as part of the intervention package.

Plain language summary

Why did we perform this research?

- Not taking medication as prescribed can worsen health and increase healthcare costs in patients with chronic medical conditions, such as cancer or diabetes.
- Knowing which methods help patients take their oral medications as prescribed (adherence) can help healthcare professionals (HCPs) and healthcare organizations select better interventions to support patients' medication taking.

How did we perform this research?

- Published literature from the past 10 years identified from biomedical databases was reviewed to summarize methods to help patients stay on their medications and to determine which methods are effective in helping patients stay on medication long term.
- Methods were categorized by who or what provided assistance to patients, e.g., the type(s) of HCPs; an electronic contact (app, device, voice messages); or education about medications only.

What were the findings of this research?

- Among the studies in this review, most studies of interventions led by pharmacists found significant improvements in patients taking medications as prescribed, whereas fewer studies of interventions led by nurses or any/other/unspecified HCPs or involving electronic contact showed significant improvements, and none of education-only intervention studies found significant improvements.
- Studies with large improvements in adherence included multiple intervention components that addressed patient knowledge, side-effect and symptom barriers, forgetfulness, and communication with an HCP.

What are the implications of this research?

- The findings of this review can help inform development of future programs that help patients stick to their medications and ultimately improve their health. Those programs might consider the inclusion of contact with pharmacists, side-effect or symptom management, daily or weekly reminders, and patient education as part of the overall program.

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Objective

- Medication nonadherence is associated with worsening of health outcomes and increasing healthcare costs among patients with both oncological and non-oncological chronic conditions.[1,2]
- New, self-administered, targeted therapies in oncology have led to improvements in survival, but patients need to adhere to these therapies over a long period.[3]
- Some of the most common patient-reported barriers to medication adherence include forgetfulness, side effects, complicated regimens, and depressive symptoms.[4-7] In addition, difficulty accessing medications due to prior authorizations, high cost sharing, or need to obtain drugs from specialty pharmacies may lower adherence rates.[8-9]
- To our knowledge, no literature review has previously captured a broad array of interventions designed to improve adherence to oral medications prescribed long term, and there is no summarized evidence on the effectiveness of the interventions.
- A TLR was conducted to summarize published interventions for improving adherence to oral medications and their effectiveness.

Methods

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The TLR was conducted using the following criteria:

- Papers from 2 databases: MEDLINE via the PubMed platform and Embase via the Elsevier platform
- Search dates: 8 August 2014 to 8 August 2024
- Language: Articles published in English (but no country limitations)

Patients	Interventions	Outcomes	Study design

Aged ≥ 18 years with medical conditions requiring daily or frequent oral medications
 	
Exclude: Provider administers medication at clinic, office, etc.
	• Interventions to improve long-term (≥ 3 months[a]) adherence to oral medications
	• Comparator not required
		Adherence measures, including
		• % of patients reaching adherence threshold
		• % of taken prescribed doses or filled prescriptions
		• Scores on self-reported adherence questionnaires
		• Persistence of appropriate dosing or taking minimum quantity
			• Observational
			• RCT
			• Crossover
			• Qualitative
			• Bibliography review only:
			  • Systematic reviews
			  • Comprehensive reviews

RCT = randomized controlled trial.
[a] Minimum time selected to ensure adequate number of studies.

Results and Interpretation

- A total of 243 unique titles and abstracts were screened from PubMed and Embase, and 51 studies (37 oncology; 14 non-oncology) were included.
- Included studies evaluated interventions seeking to improve long-term (≥ 3 months) adherence/persistence; when comparative, comparisons could be a different intervention, no intervention, placebo, or before and after intervention comparisons.
- The interventions were categorized as pharmacist/physician-led, nurse/HCP-led,^ digital app/device/voice response system (VRS), or education only (Figure 1).
- Nearly half (43%) of the studies were conducted in the United States (US; n = 17 oncology; n = 5 non-oncology).
- Nearly two-thirds (63%) of the studies were RCTs.
- Table 1 shows characteristics of the included studies.
- The mix of intervention components varied across intervention categories, but most categories included initial education and follow-up calls or visits that involved adverse event monitoring and management (Figure 2).

^ In Nurse/HCP, HCP means (1) unspecified HCP or a mix of different types of HCPs; or (2) HCP who is not a pharmacist, physician, or nurse.

Figure 1: Oncology or Non-Oncology Studies by Adherence Intervention Category

8 of the 19 nurse/HCP-led^ studies were led by nurses; for another 8 studies, the type of HCP[b] was unspecified or a mix of types of HCPs; in 3 studies, the HCPs were healthcare plan managers, community health workers, or predoctoral clinical psychology students

14 of the 15 pharmacist/physician-led studies were led by pharmacists; only 1 was physician led

[a] One study included 2 intervention groups, both HCP and device interventions, bringing the total adherence interventions to 15.
[b] An HCP is any person that is qualified and authorized to provide healthcare services.
^ In Nurse/HCP, HCP means (1) unspecified HCP or a mix of different types of HCPs; or (2) HCP who is not a pharmacist, physician, or nurse.

Figure 2: Intervention Components Across Studies

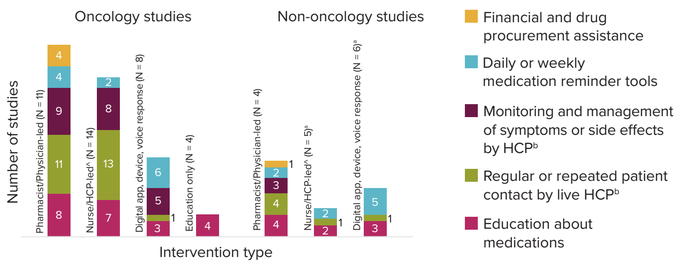

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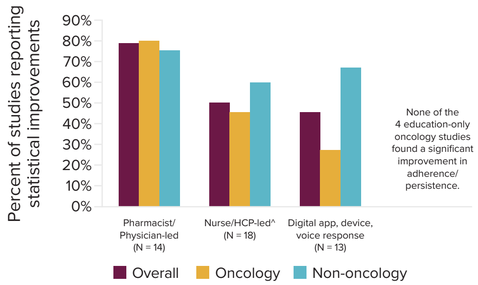
Table 1: Characteristics of Included Studies

Oncology (n = 37)	Non-oncology (n = 14)
Country n = 17: US n = 3: Türkiye n = 2: France, Germany, Spain n = 1: Brazil, Canda, China, Ethiopia, Finland, Israel, Italy, Japan, Singapore, Switzerland, multi-country	**Country** n = 5: US n = 2: Greece, Japan n = 1: Italy, Belgium, Brazil, England, Switzerland
Study design RCT (n = 21) Non-RCT/observational (n = 16) • Prospective (n = 11) vs retrospective (n = 5) • Single center (n = 11) vs multicenter (n = 5)	**Study design** RCT (n = 11) Non-RCT/observational (n = 3) • Prospective (n = 3) vs retrospective (n = 0) • Single center (n = 3) vs multicenter (n = 0)
Follow-up 3-6 months (n = 24) > 6-13 months (n = 7) 24-36 months (n = 4) 60-96 months (n = 2)	**Follow-up** 3-6 months (n = 9) > 6-13 months (n = 4) 24-36 months (n = 1) 60-96 months (n = 0)
Type of medications Any OAA (n = 13), endocrine therapy (n = 14), TKI (n = 7), oral chemotherapy (n = 3)	**Type of medications**[a] Anticoagulants (n = 6), antidiabetics (n = 5), antihypertensives (n = 3), osteoporosis treatment (n = 1)

OAA = oral anticancer agent; TKI = tyrosine kinase inhibitor.
[a] One study involves multiple types of medication.

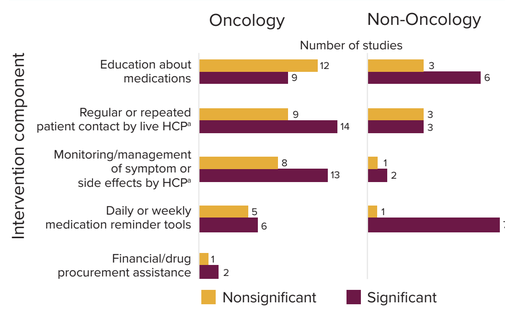
- Of studies reporting statistical comparisons, 79% (11/14) of the pharmacist/physician-led intervention studies showed a statistically significant improvement in adherence/persistence when compared with either pre-intervention levels or usual care (Figure 3), and 60% of these studies were observational studies.
- Of studies reporting statistical comparisons, adherence/persistence improved in half (50%; 9/18) of nurse/HCP-led^ interventions and nearly half (46%; 6/13) of digital/device/voice response interventions. Notably, none of the education-only interventions resulted in significantly improved adherence (Figure 3).
- Intervention components most commonly found in studies with significance outcomes in oncology were regular or repeated contact with an HCP and side-effect management or monitoring, and in non-oncology were daily or weekly reminder tools and education about medications (Figure 4).
- Studies with large (≥ 10% increase) statistically significant improvements in adherence/persistence included multidimensional interventions addressing patient knowledge, side effects and symptoms, forgetfulness, and communication with an HCP (Table 2).

Figure 3: Percentage of Studies With Statistically Significant Adherence/Persistence Outcomes



Note: The denominators are the number of studies per intervention category that reported statistical comparisons.
^ In Nurse/HCP, HCP means (1) unspecified HCP or a mix of different types of HCPs; or (2) HCP who is not a pharmacist, physician, or nurse.

Figure 4: Number of Studies With Significant or Nonsignificant Adherence or Persistence Outcomes by Intervention Component



[a] An HCP is any person that is qualified and authorized to provide healthcare services.

Table 2: Intervention Features of Studies With Large and Significant Differences

Intervention leader/disease	Ref/location	Study type	Education	HCP contacting patient	Side-effect/ symptom management	Daily or weekly reminders	Medication reconciliation	Drug interactions	Lab monitoring	Collaboration between pharmacist and primary care physicians	Refill reminders	Financial/drug procurement assistance	Motivation
Pharmacist Oncology	Lam (2016)[10] US	Cohort	●	●	●		●	●	●			●	
Pharmacist Oncology	Moulin (2017)[11] Brazil	Cohort	●	●	●				●				
Pharmacist Oncology	Curry (2020)[12] US	Cohort	●	●	●	●		●				●	
Pharmacist Non-oncology	Ho (2014)[13] US	RCT	●	●	●	●	●			●	●		
Pharmacist Non-oncology	Singleton (2017)[14] US	Cohort	●	●	●	●						●	●
Nurse Oncology	Başoğlu (2024)[15] Türkiye	RCT	●	●	●								●
Nurse Oncology	Kekäle (2016)[16] Finland	RCT	●	●	●	●							
HCP (unspecified) Oncology	Gönderen Çakmak (2021)[17] Türkiye	RCT		●									●
Digital app Non-oncology	Senoo (2022)[18] Japan	Prospective observational study	●			●							
Total			8	8	7	5	2	2	2	1	1	3	3

Most common intervention features

Note: Large differences in adherence were defined as those with difference of ≥ 10 percentage points or other units.

Limitations

- As almost all studies in this TLR had multiple features, it is unclear if any individual feature aided adherence/persistence or whether the specific mix of features was the key factor.
- Over a third (37%) of the studies were not RCTs and were, therefore, subject to selection bias.
- The study was also subject to publication bias, as positive or significant findings are more likely to be published than those with negative or null results. This can skew the effectiveness of adherence interventions summarized from the literature.

Disclosures

MS, RS, and YL are employees of AstraZeneca and hold stock in the company. AC, SN, and SK are employees of RTI Health Solutions, an independent nonprofit research organization, which was retained by AstraZeneca to conduct the research that is the subject of this abstract. Their compensation is unconnected to the studies on which they work.

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