


Why Individual-Level Interventions Are Not Enough: Systems-Level Determinants of Oral Anticancer Medication Adherence

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Nonadherence to oral anticancer medications (OAMs) in the United States is as low as 33% for some cancers. The reasons for nonadherence to these lifesaving medications are multifactorial, yet the majority of studies focus on patient-level factors influencing uptake and adherence. Individually based interventions to increase patient adherence have not been effective, and this warrants attention to factors at the payor, pharmaceutical, and clinical systems levels. Based on the authors' research and clinical experiences, this commentary brings fresh attention to the long-standing issue of OAM nonadherence, a growing quality-of-care issue, from a systems perspective. In this commentary, the key driving factors in pharmaceutical and payor systems (state and federal laws, payor/insurance companies, and pharmaceutical companies), clinical systems (hospitals and providers), and patient contexts that have trickle-down effects on patient adherence to OAMs are outlined. In the end, the authors' recommendations include examining the influence of laws governing OAM drug pricing, OAM supply, and provider reimbursement; reducing the need for prior authorization of long-approved OAMs; identifying cost-effective ways for providers to monitor nonadherence; examining issues of provider bias in OAM prescriptions; and further elucidating in which contexts patients are likely to be able to adhere. These recommendations offer a starting point for an examination of the chain of systems influencing patient adherence and may help to finally resolve persistently high levels of OAM nonadherence. **Cancer** 2020;126:3606-3612. © 2020 The Authors. *Cancer* published by Wiley Periodicals LLC on behalf of American Cancer Society. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

KEYWORDS: endocrine therapy, health insurance, oral anticancer medications, social determinants.

INTRODUCTION

Nonadherence to oral anticancer medications (OAMs) is a persistent challenge for cancer survivors in the United States¹: Adherence is as low as 33% for some cancers.² Many of the most common incident cancers, including breast, prostate, and lung cancers,³ are treated, at least in part, with OAMs. For example, nonmetastatic, hormone receptor–positive breast cancers are treated with 5 to 10 years of postoperative (adjuvant) OAMs. For metastatic prostate cancer, 2 of the category 1 recommended treatments are OAMs,⁴ and most targeted therapies for lung cancer are also OAMs. OAM treatment for metastatic cancers usually continues until the drug or drugs stop working or side effects become intolerable; therefore, patients may be on these OAMs for months to years. Some less common cancers such as chronic myelogenous leukemia are nearly exclusively treated with OAMs, and this makes adherence a vital issue.

Patient-level factors such as treatment-related toxicities/side effects,⁵ race/ethnicity,⁶ lack of insurance,^{7,8} and transportation issues^{9,10} drive adherence, but multilevel system factors are also implicated in patient receipt of OAMs, delays in access to OAMs, and adherence to OAMs. Nonadherence issues have not been resolved by interventions on individual patient-level factors, such as increasing patient education and removing patient-level barriers¹¹⁻¹⁵; this warrants attention to barriers at the patient-provider, payor, and systems levels. Although it is critical to remove patient-level barriers, these barriers exist within a larger context that must be addressed if we are to increase use of these lifesaving treatments.

In this commentary, we advance the discussion of OAM nonadherence by focusing on drivers of nonadherence in pharmaceutical and payor systems (state and federal laws, payor/insurance companies, and pharmaceutical companies), clinical systems (hospitals and providers), and patient contexts (see Fig. 1). This commentary is informed by the literature,

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See editorial on pages 3613-6, this issue.

DOI: 10.1002/cncr.32946, **Received:** October 21, 2019; **Revised:** January 15, 2020; **Accepted:** January 30, 2020, **Published online** May 21, 2020 in Wiley Online Library (wileyonlinelibrary.com)

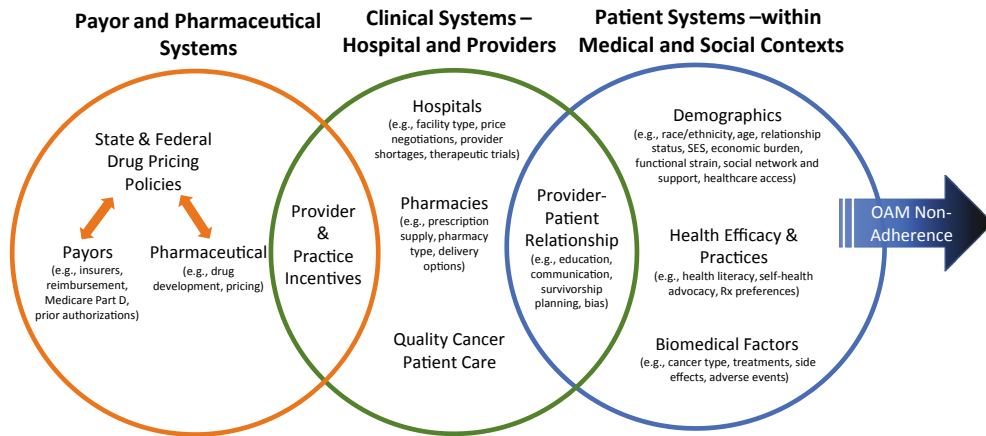


FIGURE 1. Chain of systems influencing OAM nonadherence. This figure includes a diagram of how pharmaceutical, payor, patient, and provider systems are linked and intersect to form a context for individual-level patient nonadherence to OAMs. OAM indicates oral anticancer medication; SES, socioeconomic status.

our research,¹⁶⁻¹⁸ and clinical practice. In the end, we provide recommendations for addressing nonadherence behaviors in the context of the patient-provider relationship and health care landscapes in which they occur.

PAYOR AND PHARMACEUTICAL SYSTEMS

Rising cancer incidences increase the demand for OAM drug procurement and operational costs for hospitals and practices,^{19,20} which are driven by the US system of payors and pharmaceutical systems. Timely approval of prescriptions by payors (ie, insurance companies) is the first stage of access for patients, yet barriers remain in the form of requirements for prior approval²¹ or a lack of insurance coverage for specific classes of medication.²² In a 2017 American Society of Clinical Oncology survey of clinical practices, prior approvals (78%) and coverage denials/appeals (62%) were named as key bottlenecks to OAM receipt. Prior approvals may be required even for OAMs that are recommended in treatment guidelines.²² With 78% of practices reporting that prior approval requirements have frequently led to OAM abandonment,²² the need for prior approvals is a clear system-driven barrier to patient OAM nonadherence.

Both prior approvals and formulary coverage are managed by pharmacy benefit managers, who negotiate which prescriptions are on what health plan's formularies, which manufacturer provides them, and what the prices will be. Pharmacy benefit managers also use policies such as step therapy, which steers patients to use formulary-preferred prescriptions (which must fail) before they can use the provider-recommended treatment.²³ The trade-offs of

step therapy include delayed time to optimal treatment, patient suffering and costs due to the management of side effects and discontinuation of the ineffective first-step drug, and erosion of the provider-patient relationship.²⁴ Delays in optimal cancer treatment that are exacerbated by step therapy positions the pharmaceutical industry in the driver's seat for care decisions, and this may lead to increased stressors and life-threatening events. Because the link between pharmacy benefit management and cancer health outcomes is understudied, there is a knowledge gap that undermines our clinical scholarship to address disparities caused by this process.

High out-of-pocket costs, rooted in the insurance and political systems, remain a barrier to OAM adherence.²⁵⁻²⁸ The costs are expected to grow.²⁹⁻³¹ Estimated monthly insurance payments per patient for OAMs have more than doubled in 10 years, and they surpass payments for intravenous anticancer medications.²⁹ Pharmacy benefit managers are reimbursed a percentage of a drug's list price and can contribute to high OAM costs through two practices. One is by recommending higher cost drugs to a formulary (ie, rebate pumping), which increases the amount of their rebate. Another is by charging the health plan or employer a higher cost than what is paid to the pharmacy for prescriptions (ie, price spreading), which leads to higher premiums and cost sharing for patients.³² Pharmacy benefit managers have attempted to address critiques of rebates that they receive by offering tiered formulary options and giving health plans and employers an option to choose between formularies with and without rebates, yet information is not available to compare tier lists and costs.³³

Nonetheless, cancer drugs are often placed on specialty tiers, and this still shifts costs away from health plans directly to patients through high cost sharing.²³

OAM costs are passed on to patients directly through cost sharing among various benefit plans. OAMs are often covered under an insurance plan's pharmacy benefits rather than the medical benefit portion of the plan, and patients are subjected to out-of-pocket coinsurance, deductibles, and caps on annual drug benefits.³⁴ Even legislated solutions have not resolved issues of high patient cost sharing for OAM therapy.²¹ Cost-containment policies in the form of state-level chemotherapy parity laws³⁴ apply only to private insurance plans²¹ and, though available in a plurality of states, have not reduced OAM costs for those with the highest out-of-pocket expenditures.³⁵ Prohibitively high costs are expected to persist even after the 2020 closure of the Medicare doughnut hole because there is currently no limit on out-of-pocket spending for outpatient prescription drugs under Medicare Part D.³⁰ Although the Affordable Care Act instituted limits on out-of-pocket spending for commercial insurers, patients still face high deductibles and coinsurance that they cannot afford.³⁶ Further contributing to high costs are laws that prohibit federal negotiation of drug pricing with pharmaceutical companies.³⁷

In some cases, the lack of generics can allow a pharmaceutical company to keep OAM prices high. Many targeted cancer therapies are relatively new to the market, so there are not yet generics for many OAMs.³⁸ For example, of the 5 OAMs used to treat chronic myelogenous leukemia, only 1 is available as a generic in the United States. Notable exceptions to the lack of generics are the endocrine OAMs for the adjuvant treatment of hormone receptor-positive breast cancer, for which these 3 OAMs are all available in generic form. The availability of generics has implications for adherence because patients on generic OAMs have less discontinuation than those on brand-name OAMs³⁹ on account of the lower cost of generics in comparison with brand-name drugs.

Charity assistance has not been a remedy for high OAM costs to patients, in part because of insurance eligibility requirements, and it has even been associated with delays in uptake because of the time that it takes to apply for aid.⁴⁰ Cancer medications are the most common therapeutic area for which copay or health insurance premium assistance programs are available⁴¹; however, charitable assistance has been found to be used for only 12% of OAMs, and when used, it covers only a median of 15% of an OAM prescription's cash price.⁴² Most programs require patients to have some form of insurance

to be eligible for assistance. The insurance requirement poses a problem for Medicare Part D patients and especially for those ineligible for the low-income subsidy, who face high coinsurance costs for specialty drugs, lack insurance coverage when they are in the doughnut hole, and have no out-of-pocket spending cap. Although charitable assistance provides a needed service that can remove some cost barriers,^{40,42} it is a downstream solution for which upstream systems-level barriers still need to be removed.

CLINICAL SYSTEMS: HOSPITALS AND PROVIDERS

How individual hospital systems negotiate with payors and OAM suppliers may contribute to clinician prescribing practice as well as patient access to and use of OAMs. At the hospital level, changes in payments models for hospitals have led to changes in what clinical practices offer and what costs are passed down to providers and to patients. The regulation of hospital payments for cancer services has been gaining momentum across the United States because it provides standardization of pricing for cancer treatment. This has led to a nationwide shift in recent years from cancer service provision at physician practices in the community (nonregulated setting) to the hospital (regulated setting).⁴³

The Centers for Medicare and Medicaid Services currently reimburses Part B drugs, such as intravenous or injected oncolytics, administered by a health provider proportionally to the cost of the drugs.^{44,45} This reimbursement model has been shown to increase utilization of more expensive oncolytics.⁴⁶ However, there is no similar Part D reimbursement for oral drugs such as OAMs, and it is not clear how this difference in reimbursement models influences the use of intravenous oncolytics in comparison with their equivalent OAMs. The literature is mixed with respect to the influence of pharmaceutical manufacturer payments on prescriber practices. Although a recent review found that in some cases, incentives of various types may steer oncologists to recommend more profitable cancer drugs,⁴⁴ one study of OAMs used to treat prostate cancer found no association between pharmaceutical manufacturer payments to prescribers and use of a specific OAM.⁴⁶

Ensuring reimbursement from insurance companies, managing patient payments, and surviving market competition are day-to-day challenges of a small oncology practice. However, large cancer centers and midsize oncology practice groups have less administrative burden because of shared resources among departments, market influences, and flexible resources to adjust to

incidental operational events.⁴⁷ In addition, the Centers for Medicare and Medicaid Services does not allow certain states to participate nationally in payment models such as the Oncology Care Model that would otherwise incentivize providers to serve Medicare patients. Thus, community oncology providers are incentivized to sell their practices to hospitals to gain access to the benefits of practicing in a regulated hospital-based setting. This trend typically causes services to be more centralized in urban metropolitan areas and, consequently, more sparse in rural areas. This phenomenon leads to health professional shortage areas, which have been associated with less OAM adherence.^{48,49} The distance to a cancer center or clinic can be a barrier for patients to the frequent follow-up required for monitoring of OAMs.

Oncology practices may also face barriers due to a lack of resources for managing patient access and adherence to OAMs. Because prescribers are often unaware of OAM coverage by a given insurer and out-of-pocket costs to patients, practices frequently pursue a time-consuming process of sending test orders⁵⁰ for a treatment to learn what OAMs will be covered. Practices that have sufficient staffing to monitor uptake and adherence may have better patient outcomes, but not all practices can afford more support staff. In contrast to intravenous anticancer medications, which are given under supervision, the oncology team does not know how and when a patient is taking OAMs. Follow-up visits for OAMs are usually less frequent than visits for intravenous anticancer medications, and as such, the oncology team has less opportunity to assess side effects or other issues that may lead the patient to be nonadherent. A lack of standardized monitoring can lead to a reduction in treatment efficacy or complications that may result in death.⁵¹

PATIENT SYSTEMS: WITHIN MEDICAL AND SOCIAL CONTEXTS

Patient-level factors interact with systems-level and patient-provider factors to frame the availability of OAMs and delays in patient receipt of OAMs.⁵² OAM nonadherence studies have identified side effects, the competing management of comorbidities, a higher body mass index, and higher dosing frequencies as patient-level medical barriers.^{5,10,14,48,53,54} Racial disparities in adherence may be partially explained by differences in household net worth⁵⁴ and disappear after adjustments for copayments, poverty status, and comorbidities.⁵⁵ Thus, addressing disparities in adherence requires reducing out-of-pocket costs for patients.⁵²

Use of mail-order pharmacies versus retail pharmacies is associated with greater adherence,⁵⁶ and this makes retail pharmacy systems a target for reducing nonadherence, although challenges remain. A recent study found that delayed pharmacy processing times (median delay of 6 days) due to challenges in determining OAM insurance coverage was the rate-limiting step for timely availability of OAMs.²² Even 1 week of delays may lead to patient anxiety and can result in a loss of retention of information that increases the risk of adverse effects, complications, and nonadherence.

In addition to the patient-level factors, patients may receive inadequate treatment in areas where retail environments, policies, or interventions lead to differential OAM access⁴⁹ or where patients are isolated from care because of transportation limitations^{9,10} or low oncology provider access, although the latter has yet to be tested. Studies on how clinician bias influences OAM prescribing behaviors are yet to be conducted. Patient-provider communication may be devoid of the patient's home and family context, so functional well-being, family demands, ethnocultural beliefs, religious beliefs, and other factors are not considered when OAM treatment recommendations are being made. However, the socioenvironmental and lived contexts in which patient-level nonadherence occurs have been understudied because of a preoccupation with examining patient-level factors.

RECOMMENDATIONS

Payor and Pharmaceutical Systems

Understanding the systems-level levers requires research that examines the patient in the context of the entire system, which includes the perspectives and experiences of patients, stakeholders from pharma, clinicians, hospital leaders, and others. Researchers and policy analysts should conduct simulations of how changes in federal and state laws governing drug pricing, supplies, and access might influence patient-level adherence. State and federal legislators should act to close loopholes in chemotherapy parity laws and directly address the appropriateness of high-cost medications when equally viable lower cost alternatives are available.^{34,35} Programmatic changes could be made on the basis of the mounting body of evidence of systems-level barriers. For example, insurers, states, and employers could enhance tools on OAM cost transparency, insurance coverage, and availability to be more easily accessible to providers and patients and revisit whether long-used OAMs should still need prior authorization.

Cost-reduction strategies are essential to helping to reduce disparities in nonadherence. Policymakers should limit or eliminate management strategies that put cost or revenue as the primary driver for OAM usage, such as rebates to pharmacy benefit managers, or require pass-throughs that directly benefit patients. Instead, hospitals and practices could engage in direct price negotiations with pharmaceutical companies. Policy options to increase generic drug competition might include Food and Drug Administration action to: accelerate timelines for fast-track generic approvals; allow cross-country importation of generics; and permit preclearance of generics for drugs that have experienced recent price spikes. Congressional action is needed to replicate the Medicaid reimbursement caps for Medicare Part D.⁵⁷

Clinical Systems: Hospitals and Providers

Further research is needed on the unanswered questions of how federal reimbursement models and pharmaceutical manufacturer payments influence which OAMs providers prescribing, and how prescribing might differ at for-profit and nonprofit practices. Research on the role of clinician ethnic bias in OAM prescription may also be warranted. There is a dearth of publications on outcomes of for-profit cancer centers; this is also likely due to the proprietary nature of their data. We may need to use tax records to identify which cancer centers are for-profit in combination with population-based studies to assess outcomes of patients attending for-profit centers. Studies on prescriber bias are feasible and could follow the patterns of other diseases that have used implicit bias testing and vignettes to assess prescribing behavior for patients of different backgrounds.

At the practice level, having dedicated staff to manage and monitor patients and OAM prescriptions is ideal but may not be feasible. Electronic monitoring innovations may be a cost-effective way to address this issue. More interventions for these tools are needed so that oncology teams can check whether patients are having any problems accessing OAMs or are experiencing side effects and can ensure that they are tolerating their OAMs. Greater provider-patient interaction around OAMs, including standardized patient monitoring processes,⁵¹ and the use of bidirectional communication (information plus patient navigation or follow-up phone calls)⁵⁸ can increase adherence.⁵⁹

Patient Systems: Within Medical and Social Contexts

There is a substantial and rich body of research on patient-level factors.^{5-9,10,14,48,53,60} We now need to identify

systems in which nonadherence is low and the characteristics of the patients within those systems. There is little research on how for-profit cancer centers versus nonprofit cancer centers (academic and community practices), the density of oncology providers, pharmacy retail environments, and other contexts influence nonadherence. For these studies to happen, we need to have data sets that are accessible and affordable to researchers: Most pharmaceutical claims data sets are proprietary and expensive or are not linked to oncology records, and this precludes understanding how and why decisions about OAMs are made. Although Surveillance, Epidemiology, and End Results–Medicare claims data are available, they still represent an age- and insurance-limited population, and this precludes our study of these relationships across a span of age and insurance groups. These lines of research should be pursued, and we hope that our commentary spurs greater interest in having multidisciplinary teams assess these topics.

This commentary brings fresh attention to the long-standing issue of OAM nonadherence, a growing quality-of-care issue, from a systems perspective. These recommendations offer a starting point for an examination of the upstream multilevel factors influencing downstream patient adherence that may finally resolve persistently high levels of and disparities in OAM nonadherence.

FUNDING SUPPORT

This work was supported by the National Cancer Institute (grant K01CA184288), the National Institute of Mental Health (grant R25MH083620), the National Heart, Lung, and Blood Institute (grant T32HL139426), and the Sidney Kimmel Cancer Center (grant P30CA006973).

CONFLICT OF INTEREST DISCLOSURES

Kimberley T. Lee reports a grant from Pfizer Global Medical Grants that was awarded to her institution (not to her personally) in January 2020 and preceded the development of this commentary. The other authors made no disclosures.

AUTHOR CONTRIBUTIONS

Lorraine T. Dean: Contributions to all aspects of the article from conceptualization through final revision and editing. **Marshalee George:** Contributions to all aspects of the article from conceptualization through final revision and editing. **Kimberley T. Lee:** Contributions to the writing and revision of drafts. **Kimlin Ashing:** Contributions to all aspects of the article from conceptualization through final revision and editing.

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