

# Polypharmacy:

## The Cure Becomes the Disease

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IN THE PAST, when an apothecary individually compounded medications, polypharmacy referred to the mixing of many drugs in one prescription.<sup>1</sup> Today, polypharmacy implies the prescribing of too many medications for an individual patient, with an associated higher risk of adverse drug reactions and interactions. How many medications constitute too many—four,<sup>2</sup> five,<sup>3, 4</sup> ten<sup>5</sup>? Quantitative definitions vary, and the answer to this question may ultimately depend on the individual patient. Situations certainly exist where the use of multiple medications is justified in order to yield effective pharmacotherapy. To the degree that any medication potentially increases the risk of iatrogenic illness, however, any regimen with at least one unnecessary medication may be considered polypharmacy.<sup>6</sup> It is a problem of substantial importance, in terms of both direct medication costs and indirect costs resulting from drug-related morbidity. Moreover, it is a preventable problem. In this article, we describe how polypharmacy might occur and what complications ensue, we review studies evaluating interventions to reduce unnecessary prescribing, and, finally, we identify practical means for the busy physician to avoid this problem.

### HOW POLYPHARMACY COMES ABOUT

Many factors contribute to the problem of polypharmacy (Table 1). The incidence of polypharmacy increases with age. As one ages, the prevalence of both somatic complaints and chronic diseases increases, yielding more indications for drug therapy. Elderly ( $\geq 65$  years old) patients are prescribed twice as many medications as are younger patients,<sup>7</sup> and nonprescription drug use among the elderly is sevenfold that of the general adult population.<sup>8</sup> In a study of elderly patients in family practice clinics in the United Kingdom, Nolan and O'Malley found an average of 2.5–5.3 prescriptions per patient.<sup>9</sup> The highest numbers of prescriptions per person written for the elderly are for those over 80 years of age<sup>10</sup>; 35% of office visits by those over 85 years of age resulted in the prescription of three or more medications.<sup>11</sup>

Independent of the age of the patient, multiple symptoms and diseases can result in polypharmacy as well. As the number of somatic complaints and diseases increases, so do the indications for pharmacotherapy, and thus the problem list can be a predictor of polypharmacy. In a study of potential medication-related problems in therapeutically complex patients, Shimp and colleagues found an average of five active medical problems and a mean of 11 medications per patient.<sup>12</sup> A Canadian study of drug-related hospital admissions also demonstrated a strong correlation between the number of diseases and the number of drugs used.<sup>13</sup> Even when no organic cause for disease is determined, symptoms can be multiple, and somatization can contribute to unnecessary prescribing in an attempt to address these complaints.

In addition to multiple symptoms and diseases, copious prescribing can lead to polypharmacy. Melmon estimated that 75% of physician visits in the United States terminate in a written prescription.<sup>14</sup> Part of this tendency to frequently address problems with prescriptions may stem from patient expectations: modern medicine should provide an antidote for every symptom. The prescription is a tangible end to the office visit, and may be perceived by the patient as having greater value than education or reassurance. It may also be easier for the busy practitioner to provide the former than the latter two, which may take considerably more time. Newer medications may be added to the expanding regimen without re-evaluation of the need for older ones. Any textbook of pharmacotherapy defines appropriate indications for starting drugs, but, outside of adverse drug reactions, how many discuss indications for stopping them? A study of physician-initiated recommendations to reduce polypharmacy found that discontinuation of medications was the recommendation least likely to be implemented.<sup>5</sup> Pharmaceutical marketing to physicians, and, increasingly, to patients, exerts additional pressure for the pen to meet the prescription pad. This marketing can be both overt, such as journal advertisements, notepads, pens, and other trinkets, and covert, including celebrity endorsements on talk shows and information about new “wonder drugs” in the print and broadcast media.

In addition to copious prescribing by an individual physician, multiple providers, especially when there is no primary provider to coordinate drug therapy, can contribute to polypharmacy. Meyer and colleagues<sup>5</sup> noted a significant correlation between the number of providers and the number of medications. This study of

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polypharmacy was set in a Veterans Affairs population, where the patient's medical record and prescription profile are available to all providers. Consider how problematic the situation can become in the private setting where the patient may be seeing multiple providers who do not have access to a common medical record and may be unaware of other medications the patient is prescribed. One should also consider the patient who visits multiple pharmacies, thereby losing this check in the system to prevent potentially adverse combinations of medication.

Unclear changes in drug regimens can lead to polypharmacy. Frequent alterations in medication regimens can confuse patients, who may not retain verbal instructions to discontinue one drug when starting another, or to change the dosage. Nomenclature can also complicate the picture and contribute to duplication, such as the inadvertent consumption of two different calcium channel blockers, or the concomitant use of both generic and brand-name drug, such as verapamil and Calan, by a patient. Many patients recall drug appearance more vividly than drug name, as in "I take a blue pill for my blood pressure and a white pill for my heart." Loss of these visual cues, such as when a pharmacy changes generic suppliers of a product or a patient visits a different pharmacy and receives an alternate brand, may confuse patients as well. Omori and colleagues<sup>2</sup> demonstrated medication errors resulting from regimen changes in 50% of recently discharged hospitalized patients. Overall, 32% of patients had incorrectly added or deleted a drug, and 18% were taking the correct drugs but committed errors in dosing, with 12% of these errors being potentially serious. The patients for whom drug regimen errors were detected were discharged with more medications prescribed (6.1 versus 5.1 prescriptions) and had more drug changes (2.7 versus 1.9) during hospitalization.<sup>2</sup>

Unnecessary medication use by patients may also stem from hoarding old drugs and from self-treatment. Patients may stockpile medications that they no longer actively use in the event they may need them again, either by their own perceptions or by re-ordering by their physicians. When one considers the cost of many drugs, it is easy to comprehend the reluctance of patients to part with such "investments." Patients should be encouraged to discard all unused medications to avoid confusion and potential adverse consequences of self-treatment. A 1977 campaign in Birmingham, England, to dispose of unwanted medications and poisons yielded a third of a million tablets and capsules, which was estimated to comprise only 3% of the total.<sup>15</sup> Self-treatment can also contribute to polypharmacy via the plethora of over-the-counter products available to consumers, including "natural remedies" sold through health food stores. Medications borrowed or shared among well-intentioned but misinformed friends or family members can further add to this problem.

TABLE 1

## Factors Contributing to Polypharmacy

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Increasing age
Multiple symptoms
Multiple medical conditions
Copious prescribing
Multiple providers
Lack of a primary provider to coordinate drug therapy
Use of multiple pharmacies
Drug regimen changes
Hoarding of medications
Self-treatment

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TABLE 2

## Complications of Polypharmacy

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Increased side effects
▪ Adverse drug reactions
▪ Drug-drug interactions
Noncompliance with the medication regimen
Increased costs
▪ Directly due to medication
▪ Indirectly due to hospitalization or other treatment for adverse drug events

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## COMPLICATIONS OF POLYPHARMACY

The complications of polypharmacy are multiple—increased problems with medication side effects, adverse drug reactions, drug-drug interactions, non-compliance with the medical regimen, and direct drug costs, as well as indirect costs resulting from hospitalization for iatrogenic illness (Table 2). Side effects, although minor enough to allow continuation of treatment, can be uncomfortable for the patient. Side effects of two or more drugs can be additive and, in some cases, synergistic. Consider the potential anticholinergic effects in a patient taking amitriptyline for depression and diphenhydramine for sleep, and who self-treats with chlorpheniramine for rhinitis. Such pharmacologic gumbo can be especially problematic in elderly patients because of physiologic changes that decrease their ability to metabolize and excrete medication and that can alter organ sensitivity to pharmacodynamic effects.<sup>6, 16</sup> For example, decreased baroreceptor sensitivity in the elderly, which increases susceptibility to orthostasis, may worsen the side effects of a medical regimen that includes hydrochlorothiazide and trazodone.

Adverse drug reactions, of greater severity than side effects, necessitate discontinuation of the suspect drug and often necessitate treatment for the adverse event. Multiple medication use is the factor most strongly and consistently associated with an increased risk of adverse drug reactions.<sup>16</sup> An exponential, rather than linear, increase in the incidence of adverse drug reactions is observed with the addition of more drugs to the regimen.<sup>16, 17</sup> With increased numbers of medications, the probability for an adverse drug reaction in-

**TABLE 3**  
How to Simplify the Medication Regimen

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Eliminate pharmacologic duplication
<ul style="list-style-type: none"> <li>■ Avoid combinations that augment side effects</li> <li>■ Avoid combinations that duplicate therapy</li> <li>■ Use monotherapy to manage multiple diseases when possible</li> <li>■ Avoid drugs that can exacerbate the patient's other medical conditions</li> </ul>
Decrease dosing frequency
<ul style="list-style-type: none"> <li>■ Choose the best medication for the patient with the least frequent dosing interval</li> <li>■ Consider sustained-release dosage forms (beware of cost)</li> </ul>
Regular review of drug regimen
<ul style="list-style-type: none"> <li>■ Is the patient taking the medication as prescribed?</li> <li>■ Are all agents still needed?</li> <li>■ Can the regimen be simplified?</li> <li>■ "Brown bag" session may be helpful</li> </ul>

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creases,<sup>18</sup> and so too does the difficulty in attributing culpability among the various agents in a patient's regimen. Consistent with the added risk of adverse drug reactions, the opportunity for drug–drug interactions multiplies as more drugs are added.<sup>19</sup>

Noncompliance with the medical regimen, especially the inaccurate use of prescription drugs, may be the most significant problem facing medical practice today. Noncompliance is the main reason for most outpatient treatment failure, as well as a cause of serious medical complications.<sup>20</sup> Estimates of medical noncompliance have ranged from as low as 20% to as high as 82%, averaging about 50% for chronic diseases, and often higher for acute therapy.<sup>20–22</sup> Although noncompliance rates have been estimated at 25–59% in the elderly,<sup>20, 21, 23, 24</sup> noncompliance with medication has been correlated more strongly with the number of medications than with age.<sup>5, 25</sup> In a study of noncompliance as a contributor to hospitalization, Col and colleagues found that the complexity of the medication regimen (as reflected in greater number of doses per day and greater number of both scheduled and as-needed medications) was directly associated with an increased risk of noncompliance; this noncompliance contributed to a more frequent need for hospitalization.<sup>24</sup> In a study of patients recently discharged from the hospital, increased numbers of prescribed medications, more complex regimens, and the availability of previously prescribed drugs also led to medication noncompliance, including inadvertent errors. Patients discharged from the hospital with six or more medications had a particularly high medication error rate of 70%.<sup>2</sup> Complexity of the medication regimen can overload a patient's ability to comprehend instructions, yielding confusion. Medications may not be appropriately prioritized by the patient; as-needed medications may be taken with greater consistency than scheduled medications. A patient may take his bedtime stool softener or an "as-needed" nonsteroidal anti-inflammatory agent regularly at the expense of his or her scheduled antihy-

pertensive. This can become a vicious circle: as a more complex medication regimen leads to noncompliance and therapeutic goals are not attained, the patient or physician may perceive a need for larger doses or additional medications to manage the problem.

Costs of polypharmacy, both directly, via prescription costs, and indirectly, through hospitalizations for adverse drug events or treatment failures due to noncompliance, are a financial burden for the individual and society. To the individual patient who may have no or only partial insurance coverage for prescriptions, medication costs can be overwhelming. Higher medication costs have been associated with an increased risk of noncompliance.<sup>24</sup> The monthly cost of an angiotensin-converting enzyme inhibitor can well exceed that of the electric bill, and this may hinder compliance when such choices are forced on those with limited budgets and fixed incomes. Any medication that is not absolutely necessary adds to these cost and compliance issues. Institutional and societal costs must also be considered. Health system resources can be squandered through increased clinic visits and hospitalizations because of drug-related morbidity attributable to polypharmacy. Ten percent to 17% of hospital geriatric admissions are related to adverse drug events.<sup>7, 24</sup> Patients admitted for adverse drug events averaged 5.7 medications versus 3.2 medications for patients admitted for other reasons, clearly demonstrating the costs of multiple medications.<sup>7</sup> In the Harvard Medical Practice Study (II), drug-related complications were the most frequent adverse event, constituting 19% of iatrogenic injuries. The authors related this to the quantity and variety of medications in hospitalized patients.<sup>26</sup> Grymonpre and colleagues, in a review of hospital admissions in patients over 50 years of age, noted that, of those patients using medication, 20% of admissions were directly attributable to undesirable effects associated with drug therapy. Over half of these were due to adverse drug reactions, and intentional noncompliance was the next most frequent cause.<sup>13</sup>

### PREVENTION AND TREATMENT OF POLYPHARMACY

Numerous studies have been directed at influencing and reducing the costs of prescribing,<sup>27–33</sup> but few of these have focused specifically on reducing polypharmacy. Increasing awareness of the problem of polypharmacy is the first step, but merely providing physicians with a medication list or profile did not reduce prescribing in two controlled trials.<sup>31, 32</sup> This is consistent with related studies of the impact of peer comparison feedback on physician prescribing trends<sup>33</sup>: written information alone is insufficient to influence prescribing. Meyer and colleagues, however, demonstrated that a simple intervention, consisting of a written notification of the dangers of overmedication and a request to

simplify regimens of polypharmacy patients, was as effective as a more intensive intervention incorporating an individual review and recommendation for each of these patients.<sup>5</sup> Other studies have underscored the effectiveness of "counterdetailing," a face-to-face educational session of the physician by a clinical pharmacist, to reduce prescribing of targeted drugs, though these focused on cost containment, not polypharmacy.<sup>34</sup>

Tamai and colleagues demonstrated that providing medication profiles in conjunction with consultation by a clinical pharmacist was effective in reducing prescribing in a controlled trial in three general medicine clinics in a Veterans Administration teaching hospital.<sup>35</sup> Independent review of targeted polypharmacy patients followed by recommendations to their physicians by other physicians<sup>3</sup> or clinical pharmacists<sup>4, 36, 37</sup> has been demonstrated to reduce prescribing for ambulatory general medicine patients, and the latter method has also been shown to be cost-effective.

As indicated above, physicians can be prompted to reduce prescribing by written cues or consultation. Rather than addressing polypharmacy after it has occurred, however, prevention should be the key; at the heart of this matter is the patient-physician relationship and overall compliance issues. The patient needs to be a responsible partner in his health care; the patient and physician together need to identify the problem, decide on the process to manage the problem, and decide on the goals of treatment. Compliance problems are preventable and can be influenced by the physician. Some of the risk factors for failure to follow recommendations include inadequate communication between physician and patient, with resultant poor patient understanding of what to do and why,<sup>23</sup> patient belief that the problem is not serious or that treatment is ineffective, patient expectations of failure or treatment side effects or patient perception of overmedication, therapeutic benefits that are not immediately apparent to the patient, or a long-term, complex, or costly medication regimen.<sup>38-40</sup> Working collaboratively, the physician can develop a treatment plan, assess comprehension of this plan, and set aside time in the follow-up visit to reinforce and solve problems. By informing the patient of what to expect from his or her medication — desired outcomes as well as side effects — and that the results will be evaluated at the next clinic visit, the physician shares with the patient the control of the treatment plan. On return, asking in a nonjudgmental manner whether the medication was taken or not, and, if not, why (cost, side effects, doubt of need for medication), is crucial in determining the next step. Any medication should be started as a trial and discontinued if ineffective or side effects are intolerable, so that the medication is not "carried along" or, worse, continued, and its side effects managed with yet another drug. If the drug is effective, plans can be made to discontinue other less-effective medications. Substitute instead of add on

new medications for one disease process whenever possible.

Part of the problem of overprescribing is rooted in patient expectations of receiving a prescription for every symptom. Although education may consume more time than writing a prescription, by discussing the potential benefits and risks of adding a new medication to a regimen, the physician can make the patient a partner in the decision making process. Consider drug-drug interactions as well as the drug's side effect profile, impact on compliance, and cost to the patient. If there is any doubt, don't prescribe. When possible, manage symptoms and diseases with nonpharmacologic therapy. For example, educate patients with gastroesophageal reflux on antireflux measures<sup>41</sup>; encourage proper sleep hygiene in patients complaining of insomnia.<sup>42</sup>

Prioritize the medication regimen; stress the importance of the regular use of medications to prevent problems or manage disease compared with those medications patients use on an as-needed basis for symptom relief. If the physician does not assist in prioritizing medications, the patient may do so independently, and the medication prescribed for dyspepsia may be taken at the expense of the one prescribed for arrhythmia. Be sure that the patient can tell you what he or she is taking, when the medications are taken, and why. Include the purpose of the medication in the "Sig:" of the prescription. Share results of treatment and whether or not you have achieved desired goals (e.g., control of blood glucose, blood pressure, or cholesterol level).

There are several ways to help simplify drug regimens and facilitate compliance: these include efforts to eliminate therapeutic duplication, decreasing the dosing frequency, and regular review of the drug regimen (Table 3). The goal should be to have each patient on the least complex drug regimen possible, given the constraints of the medical illness and symptoms involved and the cost of therapy. Therapeutic duplication occurs when one drug could take the place of two or more drugs, when more than one drug is used to manage a condition without additional benefit, or when the combination of drugs prescribed potentiates the side effect profile or exacerbates the medical condition of the patient. To eliminate therapeutic duplication, consolidate therapy whenever possible. For example, use medications to manage multiple diseases, such as a beta blocker in a patient with both hypertension and coronary artery disease, or an angiotensin-converting enzyme inhibitor in a patient with hypertension and congestive heart failure. Also consider combinations that may be superfluous because of therapeutic duplication: the combination of sucralfate and H<sub>2</sub> blockers, for example, has demonstrated no advantage over monotherapy in either peptic ulcer disease<sup>43, 44</sup> or reflux esophagitis.<sup>45</sup> Avoid combinations that increase the potential for augmented side effects, e.g., a tricyclic anti-

depressant plus diphenhydramine for sleep; or the addition of lorazepam for daytime anxiety in a patient prescribed triazolam for insomnia. Pursue monotherapy when possible: when a medication fails, replace it with another agent rather than adding a second. Finally, avoid any medication that may exacerbate another problem the patient has, such as the use of verapamil to manage hypertension in a patient known to have problems with constipation, or the use of beta blockers in a patient with underlying reactive airway disease.

Decreasing the frequency of dosing may help simplify the drug regimen and improve compliance. Eisen et al. found that once- or twice-daily dosing improved compliance in hypertensive men significantly over three-times-daily dosing.<sup>38</sup> In the elderly, once-a-day dosing may be of even greater importance to achieve compliance.<sup>46-48</sup> Lower compliance levels with antihypertensive medication result in less effective blood pressure control<sup>46</sup> and may lead to the addition of another antihypertensive agent. Therefore, when selecting the optimal drug for the patient at the least cost, consider the medication with the least frequent dosing schedule. When possible, avoid a regimen that includes twice-a-day, three-times-a-day, and four-times-a-day dosing frequencies together; if three-times-daily dosing is necessary for one medication, adjust the other medications to coincide with this pattern. Some drugs that are frequently administered in divided doses can be given less frequently; for example, spironolactone has an active metabolite with a sufficiently long duration of action to allow once-daily dosing; bile acid-binding resins can be given to patients once or twice rather than three times daily with meals as tolerance allows, with the added benefit of decreasing the opportunity for binding interactions, which reduce absorption of concurrent medications. Consider the use of sustained-release dosage forms in selected patients to reduce the complexity of a medication regimen. Bear in mind, however, that these preparations tend to be more costly and therefore could provide a disincentive to compliance. Ask the patient which would be preferable when a more expensive but more convenient agent is available.

Regular review of the drug regimen can help prevent problems associated with polypharmacy. Review all medications the patient is taking, not only the ones you are prescribing. Important questions to ask include: Are all agents still needed? Is the patient using the medications as prescribed? Could the regimen be simplified? Interviewing the patient with open-ended questions and review of the refill history, if available, can assist in this. Medications should be prioritized in order of relative importance to achieve therapeutic goals; this will help determine which agents could be eliminated first when simplification is necessary. All of this, admittedly, is time-consuming in the context of a brief clinic visit. Incorporating a review of medications

into a review of the problem list may allow these issues to be addressed more efficiently. For example, addressing issues of noncompliance and goals for treatment of congestive heart failure can easily incorporate discussions of diet as well as medication. The assistance of a nurse or clinical pharmacist to educate and review drug therapy with the patient can decrease physician time commitment. Of particular importance is to review and verify patient understanding when several medications have been changed at once (additions, deletions, or dosage adjustments), which commonly occurs in the hospital setting.<sup>2</sup> At outpatient visits, making as few changes at one time as possible is preferable for evaluating outcome (efficacy and side effects) at subsequent visits. Written instructions can be a helpful adjunct to verbal counseling.<sup>40, 49</sup> Much of the information given to the patient verbally is not recalled at a later time. A simple way to assist the patient in understanding his or her regimen is to make sure he or she has a current medication list, including name, dosage, directions, and reason for taking the medication. Again, a nurse or clinical pharmacist can review this information with the patient and assist in identifying methods to facilitate compliance (such as taking the medication with a daily activity such as toothbrushing; keeping the medication in a highly used area of the house instead of hidden in a drawer, with consideration to precautions when children may be present; or the use of a reminder pillbox).

An excellent way to review the medication regimen as taken by the patient is a "brown bag session"; Colt and Shapiro described this method of "therapeutic débridement" to reduce polypharmacy.<sup>7</sup> Have the patient bring in all medications at the next clinic visit—this is an excellent opportunity for both physician and patient education. The patient's comprehension of and compliance with the prescribed regimen can be effectively assessed in this fashion. Medications that are seldom used because of perceived lack of efficacy or intolerable side effects can be identified, as well as those obtained from other providers. This interview can also be conducted by a clinical pharmacist.

## SUMMARY

Polypharmacy occurs when a medical regimen includes at least one unnecessary medication. Factors that contribute to this problem include: patient characteristics of increasing age, multiple medical problems, therapy expectations, and decisions to self-treat; physician factors such as excessive prescribing; and system problems of multiple providers and lack of a coordinating provider. Complications include increased adverse drug reactions and noncompliance, which can lead to increased hospitalization and associated costs. Polypharmacy can be avoided by patient education and sharing the decisions for making the treatment goals

and plan. The medication regimen can be simplified by eliminating pharmacologic duplication, decreasing dosing frequency, and regular review of the drug regimen. The goal should be to prescribe the least complex drug regimen for the patient as possible, while considering the medical problems and symptoms and the cost of therapy.

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