Improving Adherence in the Polypharmacy Management of Disease

a report by
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Introduction

While the developments within the pharmaceutical field in recent decades have improved the efficacy of chronic disease management, the complexity of treatment has also increased proportionally. In many cases, this complexity has taken the form of polypharmacy regimens for comorbidities among disease states and higher risk demographics – patients being treated for diabetes are often being simultaneously treated for hypertension and hyperlipidemia, and elderly patients often require treatment for a myriad of conditions including hypertension, arthritis and depression. The treatment of such comorbid disease states is further complicated by polypharmacy regimens within a single disease state – many of the same diabetes and hypertension patients require combinations of drugs to effectively manage glycaemic levels or blood pressure.

Adherence to the ever-more complex drug regimens prescribed by physicians charged with polypharmacy therapy of multiple diseases is not merely an issue of moral compliance with physician requests, but an element intrinsic to successful disease management. Non-adherence to polypharmacy regimens may be defined as overutilisation, underutilisation, discontinuation or abuse of medication, and is most often associated with preventable increases in morbidity and mortality. Studies have estimated that nearly half of all patients in the US and Europe display some level of non-adherence. Adherence to hypertension medications in the US is only 51%, while adherence to anti-depression medications ranges from 40% to 70% and asthma medications 30% to 70%. In the developing world, adherence rates are even lower and are complicated by the growing level of chronic diseases (including mental health and non-communicable disease), which are expected to rise to 56% of the total disease burden in those countries by 2020.[1]

Polypharmacy in Elderly Patient Populations

Among the populations most impacted by the challenges of polypharmacy are the elderly. In the US, the elderly consume over one-third of all pharmocotherapeutics, and as the number of individuals within the over-65 demographic is expected to double again by 2030 to 20% of the total US population, issues of polypharmacy and adherence will become increasingly relevant to national healthcare policy. A Council of Scientific Affairs Report concludes:

> *"polypharmacy is problematic for older persons because it is the greatest risk factor for ADRs [adverse drug reactions], drug interactions, reduced compliance and increased emergency room visits, hospitalizations, and nursing home admissions. It contributes to the development of several "geriatric syndromes" such as cognitive impairment, delirium, falls and hip fractures, urinary incontinence, and diminished functional status, and it increases health care costs."*[2]

The same report reveals incredibly high levels of medication among the elderly – 66% of men and 88% of women consume at least one prescription medication per week, and when over-the-counter (OTC) drugs and nutritional supplements are included, 89% of men and 94% of women consume at least one medication per week. The elderly also constitute a significant population of individuals undergoing polypharmacy disease management – 15% of elderly men and 25% of elderly women consume more than five prescription medications per week. This population increases dramatically when OTC drugs are included, rising to 43% of men and 57% of women, and perhaps surprisingly, more than one-in-ten elderly persons of either sex consume 10 or more medications per week.

Such high volume polypharmacy consumption is of great concern because adverse drug reactions among

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1. *World Health Organization, "Adherence to Long-Term Therapies: Evidence for Action", 2003.*
2. *American Medical Association, Report 5 of the Council of Scientific Affairs (A-02), "Improving the Quality of Geriatric Pharmacotherapy", 2002.*

the elderly are twice as high as for younger patients, including almost 18% of all elderly individuals treated in an outpatient setting.[3] Elderly patients in high-risk polypharmacy groups (>5 medications per day) are twice as likely as their peers to experience preventable ADRs – thus over one-third of elderly polypharmacy patients are likely to experience an ADR.[4] This high rate of polypharmacy is of even greater concern because the rate of ADRs has been shown to increase exponentially, rather than linearly, with the number of medications taken.[5] Unfortunately, common comorbidities occurring in elderly patients also require use of medications with higher rates of ADRs, so avoiding higher-risk polypharmacy isn't a realistic option. While some level of ADRs may be inevitable, much can be done to reduce their occurrence through patient education and adherence intervention.

Compliance Versus Adherence

The issue of non-adherence has been a topic within medical literature since the inception of pharmacotherapy, usually centred on compliance or non-compliance with physician recommendations. Recent discussions of non-adherence have tended to discriminate between 'compliance' and 'adherence' – 'compliance' is assumed to mean obedient following of a specific directive (e.g. "take this tablet three times a day, 30 minutes before meals"), while 'adherence' entails not only the following of literal medical advice, but more broadly associated behavioural changes in lifestyle, mutually agreed upon by both the patient and the physician.

The World Health Organization (WHO) has strongly emphasised this aspect of patient buy-in concerning their own healthcare and agreement with treatment regimens, describing adherence as "the extent to which a person's behaviour – taking medication, following a diet and/or executing lifestyle changes, corresponds with agreed recommendations from a healthcare provider."[1] This emphasis is not merely a matter of semantics or broad-minded regard for the physician-patient relationship, but an important element in fulfilling the healthcare system's goal of improving patients' disease states, given that the majority of patients self-manage, and thus self-medicate, their conditions.

When issues of polypharmacy and chronic care are introduced into this essentially out-patient model of disease management, the importance of patients being educated about adherence within their specific clinical context is further heightened – in short, patients who not only conceptually understand their treatment regimens but believe that adherence to those regimens is in their own best interest are less likely to discontinue treatment. This statement is borne out by multiple studies which cite lack of perceived therapeutic effectiveness as one of the most common reasons for discontinuation of therapy.[1,2,6,13,14] Given the subtlety of the symptoms associated with conditions such as hypertension and hyperlipidemia, discontinuation of pharmacotherapy may result in serious morbidity or mortality by the time the patient presents gross symptoms.

Educational and Behavioural Adherence Interventions

Patient education by health providers often takes the form of either educational or behavioural intervention, or a combination of both. Educational intervention is usually conducted through verbal audiovisual intervention, with or without written aids. Quantifying the effectiveness for such interventions by themselves is complex and studies have produced mixed results, however, when coupled with behavioural interventions such as drug regimen changes (e.g. reduction in dosing frequency, combination therapy and formulation or dosage form changes), intervention is almost always effective to some degree. This combination of educational and behavioural interventions is often most effective in chronic disease conditions such as hypertension and hyperlipidemia, diabetes, asthma, schizophrenia and depression, and HIV/AIDS. The supporting medical literature within each of these

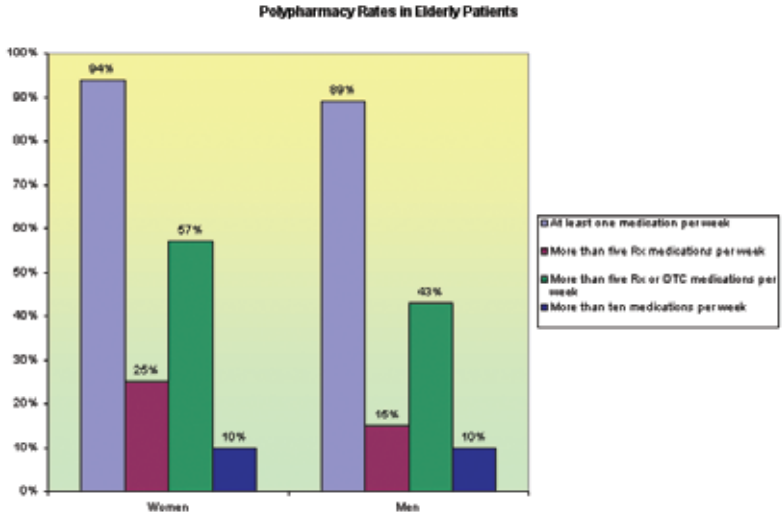
3. *Gandhi T K, Burstin H R, Cook E F, et al., "Drug complications in outpatients",* J. Gen. Intern. Med. *(2000), 15: pp. 149–154.*
4. *Hanlon J T, Schmader K E, Koronkowski M J, et al., "Adverse drug events in high risk older outpatients",* J. Am. Geriatri. Soc. *(1997), 45: pp. 945–948.*
5. *Hutchinson T A, et al., "Frequency, severity, and risk factors for adverse drug reactions in adult outpatients: A prospective study",* J. Chronic. Dis. *(1986), 39: pp. 533–542.*
6. *Peterson A M, Takiya L and Finley R, "Meta-Analysis of Interventions to Improve Drug Adherence in Patients With Hyperlipidemia",* Pharmacotherapy *(2003), 23 (1): pp. 80–87.*
7. *Brown B G, Bardsley J, Poulin D, et al., "Moderate dose, three-drug therapy with niacin, lovastatin, and colestipol to reduce low-density lipoprotein cholesterol below 100 mg/dl in patients with hyperlipidemia and coronary artery disease",* Am. J. Cardiol. *(1997), 80: pp. 111–115.*
8. *McCrindle B W, O'Neill M B, Cullen-Dean G and Helden E, "Acceptability and compliance with two forms of cholestyramine in the treatment of hypercholesterolemia in children: a randomized, crossover trial",* J. Pediatr. *(1997), 130: pp. 266–273.*

fields is replete with examples concerning improvements in patient adherence, but in nearly all cases there exists common themes of education and drug regimen changes that are applicable to concerns of polypharmacy, both within the specific disease states and within comorbid conditions.

In one meta-analysis concerned with improving adherence to anti-hyperlipidemia medication, switching patients from immediate release (IR) niacin four times a day (qid) to controlled release (CR) niacin twice a day (bid) was shown to be highly effective in lowering LDL cholesterol – 83% of patients taking the CR formulation reached the desired level after eight months, while only 52% of patients on the IR formulation achieved the desired level.[6,7] In the same analysis, there was a 25% improvement in adherence when paediatric patients were switched from a powder formulation to a tablet formulation of cholestrymine viii and changes in dosing frequency (once-a-day versus bid or qid) and dose formulation (powder versus tablet) for cholestyramine/pravastatin therapy were also shown to be statistically significant.[9]

The rigorous lifestyle management of diabetes and the severe consequences of poor self-management of the disease create considerable adherence issues, including complex dosing regimens, dietary restrictions, negative social stigma surrounding insulin injections and fear of weight gain and gastrointestinal (GI) side-effects associated with pharmacotherapy,[10] however, educating patients about the importance of self-maintenance of glycaemic control is one of the most significant interventions capable of improving adherence.[11] A study concerned with increasing adherence among diabetic patients showed significant improvements when patients received reductions in dosing frequency or were switched to therapies with lower levels of GI side-effects.[12] Among the most significant developments in diabetes care are the emergence once-a-day insulin secretagogues such as Glucotrol XL®, a once-per-day controlled release Glipizde formulation. Because of its dosing convenience and improved side-effects profile which alleviates the weight gain and other symptoms often

Figure 1:



associated with diabetic pharmacotherapy, it and similar drugs have been shown to dramatically improve patient quality of life.[13]

The issues surrounding adherence to asthma pharmacotherapies are similar to those of diabetes – self-medication is complicated by social stigma and inconvenience of the treatment regimen. This is especially true of paediatric asthmatics, 50% of whom are self-medicating at age 12 and 17% of whom are doing so by age six.[14] Such high rates of self-medication in children are disconcerting, since up to 70% of adult and paediatric asthmatics misuse their inhalers, and a similar number fail to adhere to preventive therapies such as theophylline.[15,16] However, through patient education and counselling, intervention programmes have shown significant improvements in adherence.

The combination of patient education and the development of controlled release drug formulations have also been shown to significantly improve the adherence rates of another difficult area of pharmacotherapy, mental illness. In the example of schizophrenia, the self-medication of complex antipsychotic medication regimens is often untenable, yet the consequences of non-adherence are severe. In a recent American Medical Association

9. *Eriksson M, Hadell K, Holme I, et al., "Compliance with and efficacy of treatment with pravastatin and cholestyramine: a randomized study on lipid-lowering in primary care",* Intern. Med. *(1998), 243: pp. 373–380.*
10. *Thompson C J, Cummings J F, Chalmers J, Gould C and Newton R W, "How have patients reacted to the implications of the DCCT?",* Diabetes Care *(1996), 19: pp. 876–879.*
11. *Blaum C S, Velez L, Hiss R G and Halter J B, "Characteristics related to poor glycemic control in NIDDM patients in community practice",* Diabetes Care *(1997), 20: pp. 7–11.*
12. *Dey J, Blond L and Guthrie R Jr, "Factors Influencing Patient Acceptability of Diabetes Treatmnent Regimens",* Clinical Diabetes *(2000), 2 (18): pp. 61–66.*
13. *Testa M A and Simonson D C, "Quality of life and health economic benefits of improved glycemic control in patients with non-insulin dependent diabetes mellitus",* JAMA *(1998), 280: pp. 1,490–1,496.*
14. *Kattan M, "Challenges in Asthma Medication for Inner City Kids. Engaging the Patient: Improving Communication and Adherence",* American Medical Association media briefing, *4 March 2004.*

briefing, gaps in refilling prescriptions were cited as dramatically increasing the rates of hospitalisation: gaps of one week increased the risk of hospitalisation two-fold; gaps of two weeks increased the risk four-fold, and gaps of four weeks or more increased the risk eight-fold.[17] The simplification of dosage regimens through the use of long-acting therapeutics may allow for improved accuracy of self-medication and dramatically lessen the chances that gaps in prescriptions would occur. Non-adherence in patients taking selective-seratonin reuptake inhibitors (SSRIs) usually results in discontinuation of therapy during the first three months of use – a 1995 study showed that 28% of patients discontinued treatment within 30 days and 44% discontinued treatment after 90 days, usually due to poor tolerance and unwanted side-effects.[18] The development of controlled release dosage forms in recent years, including buproprion (Wellbutrin SR®), paroxetine (Paxil CR®) and venlafaxine (Effexor XR®) have improved adherence and patient tolerability due to their ability to reduce the side-effects associated with peak plasma levels of the immediate release forms.[19]

The Role of Institutional Providers and the Pharmaceutical Industry in Improving Adherence

While patient education and alterations in dosing regimens by physicians will likely always be the primary actors improving adherence, the roles of institutional providers and the pharmaceutical industry are equally important because they define the level of access individuals have to such resources. By encouraging educational outreach programmes to high-risk polypharmacy demographics, increasing use of pharmacy counselling services, and including improved dosing regimes on insurance formularies, institutional providers can support and augment the efforts of physicians to improve the chronic disease management of their patients. In return, institutional providers are rewarded with lower healthcare costs, related reductions in the number of ADRs and unnecessary hospital admissions.

Similarly, the pharmaceutical industry not only plays a critical role in the development of more efficacious, safe and convenient pharmacotherapies, it is also the primary distributor and marketer of those therapies. Through improvements to and clarification of product labelling, package inserts and direct-to-consumer advertisements, the industry may aid in patient education, pharmacokinetic-pharmacodynamic research specific to high-risk polypharmacy populations and chronic disease states, and the continued development of less complex dosing regimens and combination therapies, the industry can improve the number of options available to physicians to facilitate improved adherence. The industry benefits from such contributions through positive branding to both physicians and patients, strengthening of intellectual property portfolios and improved brand loyalty of chronic medications once patients discern an optimal treatment regimen.

Conclusion

Given the growing population of elderly patients and individuals living with chronic conditions, the use of polypharmacy in disease management will dramatically increase in the coming decades, and the goal of reducing morbidity and mortality through improvements in polypharmacy adherence will become a necessary and fundamental measurement of an effective treatment regimen. ■

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15. *Bender B, Milgram H and Rand C, "Nonadherence in asthmatic patients: is there a solution to the problem",* Annals of Allergy, Asthma & Immunology, *(1997), 79; pp. 177–185.*
16. *Reid D et al., "Management and treatment perceptions among young adults with asthma in Melbourne: the Australian experience from the European Community Respiratory Health Survey",* Respirology, *(2000), 5: pp. 281–287.*
17. *Conley R, "Improving Outcomes for People with Serious Mental Illness. Engaging the Patient: Improving Communication and Adherence",* American Medical Association media briefing, *4 March 2004.*
18. *Lin E H, VonKorff M, Lin E, et al., "The role of the primary care physician in patients' adherence to antidepressant therapy", Med. Care (1995), 33: pp. 67–74.*
19. *Nemeroff, C B, "Improving Antidepressant Adherence",* J. Clin. Psychiatry *(2003), 64 (suppl 18).*