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Medication regimen complexity and the care of the chronically ill patient

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Abstract

As the population in developed countries ages, patients with multiple chronic conditions are becoming more common. These patients are increasingly being managed with multiple concurrent medications and their medication regimens are frequently described as complex. Despite the significant challenges that complexity poses for clinical decision-making, the adherence of patients to their medication regimens and patient health and wellbeing, a robust understanding of this term in the context of medication regimens, is lacking. Here, it is shown that the essential feature of complex medication regimens is the multiplicity of rules that constitute their basic structure, rather than their intrinsic comprehensibility. Medication regimen complexity is a measure of the size of the consolidated medication script, or the shortest possible list of rules, for that medication regimen. A protocol is suggested for the consolidation of a medication regimen and the measurement and reduction of regimen complexity. This involves simplifying dosing instructions, consolidating the rules for taking medications, determining the number of rules in the consolidated medication script and eliminating or modifying rules towards a more parsimonious treatment plan. Following this protocol may reduce the burden on the patient associated with adhering to the treatment regimen and thus promote patient-centred outcomes, such as improved health and quality of life, key components of the general move towards person-centered medicine.

Keywords

Comorbidity, complexity, consolidation, medication regimen, older patients, patient-centered care, person-centered medicine

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Introduction

> *Mrs. C is a 90-year-old independent, cognitively intact woman with congestive heart failure, hypertension, hypercholesterolemia, fibromyalgia, osteoarthritis, disk degeneration, chronic low back pain, primary hypothyroidism, and a long history of undiagnosed dizziness. Her medication regimen currently consists of 11 medications, each of which should be administered according to one of five unique dosing schedules. Each medication is taken via one of three different routes of administration. Mrs. C's medication regimen demands that she take at least nine pills daily [1].*

The developed world is in the midst of a dramatic demographic transition. The population is aging rapidly [2] and patients like Mrs. C are becoming more common. A substantial number of adults now live with a significant burden of chronic diseases [3].

Pharmacotherapy is a central component of chronic disease management. Studies indicate a significant increase in prescribing for primary prevention of diseases such as osteoporosis and to forestall further deterioration in chronic conditions such as cardiovascular disease [4]. As a consequence, the use of multiple concurrent medications is becoming common [4-6]. Older adults are the population most frequently being prescribed these multiple-medication treatment regimens, often in a context where informative evidence of harm and benefit does not exist [7-9].

The challenges of caring for real patients like Mrs. C would prompt many to label several aspects of this case as complex. *Complexity* is a popular term in modern medical dialogue, yet the variable meaning in different contexts

obscures understanding of the intended meaning in any given instance. Diseases are sometimes considered complex, describing the relatively greater number of genes that determine their expression [10,11]. Patients like Mrs. C are also said to be complex based on the multiple diagnoses they carry [12,13]. Even when describing a single entity, the clinical use of the adjective *complex* is often ambiguous.

To complicate matters further, Mrs. C's medication regimen could also be considered complex in various reports, due to the indicated routes of drug administration [14,15], number of medications [14-17] and dosing frequency of some of the medications [14-18]. Complex medication regimens are difficult for patients to understand and challenging for physicians to manage. Clinicians often rely on clinical practice guidelines (CPGs) to inform clinical decision-making. Recent studies have conclusively shown that CPGs neglect complex medication regimens and often fail to discuss multi-morbidity [19,20].

Adherence, or the extent to which medication-taking behaviour is consistent with the prescribed medication regimen, is often poor in medication regimens described as complex, which may have negative implications for patient health [21]. Yet, even for adherent patients, the considerable burden of following a complex treatment regimen may itself carry negative implications for health and wellbeing, which remain unexplored.

Despite the challenges that complexity poses for decision-making, adherence and patient health and wellbeing, a robust understanding of this term in the context of medication regimens is lacking. Studies that have considered medication regimen complexity have not defined the concept, or have done so inadequately. This includes studies that have constructed indexes to measure medication regimen complexity [14-16] and which have usually either described the factors that contribute quantitatively to regimen complexity, or have defined medication complexity as the sum of these factors.

Here, we seek to define *medication regimen complexity*, which is an important concept for the individualized and thus person-centered care of those burdened by advanced medication regimens. Complexity is an objective, intrinsic property of all medication regimens that is independent of the various constructs used to represent it in the literature. A protocol is proposed for the consolidation of a medication regimen to promote coherence and comprehensibility and the measurement and reduction of regimen complexity to enhance person-centered medicine.

Complexity as comprehensibility

While few studies have explicitly defined medication regimen complexity, the creators of the Medication Regimen Complexity Index operationalized the definition by declaring that "drug regimen-related factors influencing adherence constitute regimen complexity" [14]. This definition seems too inclusive, as there are many factors related to a medication regimen that may influence adherence, but surely do not constitute complexity, for instance, cost or the tendency to be poorly tolerated by the patient.

Certain medication regimen-related factors may influence adherence specifically by making the regimen less comprehensible and the adjective *complex* is often used as a synonym for *difficult to understand* [22]. We will briefly consider the position that medication regimen complexity consists of the characteristics of the regimen that influence its comprehensibility.

The degree to which patients are able to comprehend their medication regimen is dependent on their particular cognitive status. This does not imply that there are not characteristics of all medication regimens that universally influence comprehension *to varying degrees*. These characteristics might include the clarity of instructions given to the patient or their organization in a format that is easy to navigate. However, clarity and organization are determined by the way in which the information is presented to the patient. These are characteristics not of the medication regimen, but of the verbal or written list of instructions. If comprehensibility is to be an intrinsic property of the medication regimen in and of itself, it must not depend on how the regimen is communicated.

In considering the meaning of *intrinsic complexity*, it was previously suggested that this property is related to how the regimen is structured [18]. It will be argued in the next section that medication regimen complexity is indeed a kind of structural complexity. If structure is the only medication regimen-related factor that determines complexity, then we can dispense with the necessity of *complexity as comprehensibility* in defining medication regimen complexity. Structures are considered complex if they consist of many different, connected parts [22]. Structurally complex entities may sometimes be difficult to comprehend, but this is not their essential feature. In describing a medication regimen, one cannot substitute *difficult to adhere to* or *difficult to comprehend* for the term *intrinsically complex*.

Complexity as multiplicity

A different view of complexity is captured by the use of the term to describe complex diseases as being determined by several genes or complex patients as carrying several diagnoses: *complexity as multiplicity*. With respect to a medication regimen, an important question is: a multiplicity of *what* determines complexity?

A treatment regimen is a set of regular therapeutic actions or behaviours to be followed by the patient and since they are prescribed, these have the form of general rules. For those being treated for chronic illness, many of these rules concern medications. Medication-related rules

constitute the medication regimen, which is a subset of the treatment regimen. The medication regimen is built up from these rules; that is to say that they constitute the basic structure of the regimen. The regimen has the invariant form of a list of rules, each of which is to be independently followed. Thus, it is not the arrangement of rules that determines structural complexity of the regimen, but the multiplicity of distinct rules.

These rules have a similar content and grammar to those written on pill bottles, for instance, "take *x* orally before bed". Each medication-taking rule of a medication regimen contains three parts: the medication to be administered (including dosage), the route of administration and when or under what conditions the rule is to be followed (a qualifier). The qualifier includes either a time, usually one that is relative to the daily routine of the patient ("with breakfast", "every Monday before bed", etc.), or another condition that should trigger taking the medication ("as needed", if blood sugar exceeds a certain value, etc.). These rules are the elementary units of the medication regimen and it is from these that we can understand the meaning of medication regimen complexity proposed in the next section.

Elegant computer programs and consolidated medication scripts

Albert Einstein noted that the fundamental units of a scientific theory were the irreducible rules from which all other rules in the theory could be derived, writing that "Fundamental concepts and postulates, which cannot be further reduced logically, form the essential part of a theory," [23]. While the rules of a medication regimen cannot be reduced to a fewer number of more fundamental rules by the laws of formal logic, they can be consolidated by the laws of common sense. By this, we mean that rules should be merged when the combined rule would present the same instructions in fewer lines. For instance, if two medications are to be taken orally at the same time of day, the rules governing the taking of each can be consolidated into one rule for the taking of both. Not only does this present the information in a concise and palatable form, but consolidation is a necessary step in the creation of the consolidated medication script for a given medication regimen.

In order to formulate the definition of a consolidated medication script, we will turn briefly to the philosopher and computer scientist Gregory Chaitin. His Algorithmic Information Theory (AIT) is a field of theoretical computer science that models theories using computer programs [24]. According to AIT, the complexity of a theory is represented by the size of the computer program needed to generate it, with more complex theories requiring larger programs. This notion of complexity is also one of multiplicity, namely, it considers the number of bits needed to encode the program. While multiple computer programs, each coded differently, could represent the same output, the *elegant* computer program, according to Chaitin, is the smallest program that can produce a given output [24].

In analogy to Chaitin's elegant program, the consolidated medication script is the shortest list of rules that can produce a given medication regimen, assuming perfect adherence. A necessary requirement of the consolidated medication script is that it represents the medication regimen in its entirety. A second important requirement is that it must represent only one unique medication regimen, or in other words, it cannot permit multiple interpretations. Thus, in communicating dosing frequencies, phrases like *once daily*, *twice daily*, and so on, should be avoided, as it has been shown that patients vary in how they interpret these kinds of ambiguous instructions [25].

Drafting the consolidated script, a task that few patients presently undertake on their own [25], requires consolidating rules that govern different medications when these medications are to be taken via the same route of administration and when the same conditions are met. As a consequence, the consolidated medication script facilitates understanding of the medication regimen and may be helpful in promoting adherence and reducing the burden of interpreting the regimen. Medication regimen complexity is a measure of the size of the consolidated medication script, or the shortest possible list of rules, for that regimen. It is equal to the number of rules in the consolidated script. More complex medication regimens require that the patient adhere to a greater number of rules. The process for creating a consolidated medication script and measuring medication regimen complexity is summarized in Figure 1, steps 1-4.

Opening case revisited

> *Mrs. C routinely takes the following medications: Nitro-Dur (0.4mg/hr patch once daily), enalapril (5mg tablet twice daily), nitroglycerin (0.4mg/dose aerosol spray as needed), diltiazemXc (360mg tablet once daily), furosemide (40mg tablet once daily), simvastatin (40mg tablet once daily), levothyroxine (0.088mg tablet once daily), clopidogrel (75mg tablet once daily), amitriptyline (10mg tablet at bedtime), zopiclone (5mg tablet, half tablet at bedtime), and alendronate (70mg tablet once weekly) [1].*

Mrs. C's primary care physician or pharmacist should ask her when it would be most convenient to take her medications. She might decide that it is easiest for her to remember to take most of her medications in the morning before breakfast, the second dose of enalapril before dinner and the alendronate at the start of the week when she is preparing her pillbox. The consolidated script for her

Figure 1. Steps in the creation of the consolidated medication script for a medication regimen and the reduction of medication regimen complexity

1. Decide on the medication regimen, based on benefits, harms and patient preferences concerning medications to be taken and dosing schedules to be followed. This must be done with attention to all the available evidence and the uncertainty concerning prescribing multiple medications, especially in populations where the evidence for their use is limited.

2. Determine a qualifier that is not open to interpretation for each rule that governs the administration of medications ("medication-taking rules"). This should be done with patient input as to when they would prefer to take their medications.

3. Draft the consolidated medication script for the medication regimen, including medication-taking rules that each have the following form.

<medication(dosage)$_1$, medication(dosage)$_2$,…medication(dosage)$_n$>, <route of administration>, <qualifier: when the rule is to be followed>

Rules that govern when to take medications can only be consolidated if they contain an identical route of administration and qualifier. There is no limit to how many medications may be included in a single rule, so long as they are all to be taken at once by the same route. Rules that do not govern when to take medications but are included in the medication regimen (such as dietary restrictions) should be included in the consolidated medication script.

4. Calculate the medication regimen complexity, where

Complexity = number of rules in the consolidated medication script

5. Reduce the complexity of the medication regimen by (a) eliminating rules, and (b) modifying rules so they may be subsequently consolidated, where the predicted benefits for the patient outweigh the predicted harms.

medication regimen would then appear as written in Figure 2. In absolute terms, the medication regimen complexity is 6 (Figure 2). Relative to another patient with hypothyroidism and no other comorbid conditions who is taking one tablet of levothyroxine each day, Mrs. C's medication regimen is very complex.

Figure 2. Consolidated medication script for a patient taking 11 different medications

1. Nitro-Dur 0.4mg/hr patch before breakfast
2. enalapril 5mg tablet, diltiazemXc 360mg tablet, furosemide 40mg tablet, simvastatin 40mg tablet, levothyroxine 0.088mg tablet, and clopidogrel 75mg tablet before breakfast
3. enalapril 5mg tablet before dinner
4. amitriptyline 10mg tablet and zopiclone 2.5mg (half tablet) at bedtime
5. alendronate 70mg tablet in the morning on Mondays
6. nitroglycerin 0.4mg/dose aerosol spray as needed

It should be noted that the enalapril's two daily doses constitute two distinct rules, each of which determines a unique time of day when the medication should be taken (Figure 2). The qualifier "twice daily", for Mrs. C, would mean "before breakfast *and* before dinner". As a general rule, a qualifier may not contain the conjunction *and* when this precedes a second condition that could independently be met to trigger execution of the rule. However, it may contain *and* if and only if both conditions separated by this conjunction must be met to trigger execution of the rule. For instance, the qualifier in the rule for taking alendronate could be written less succinctly as "in the morning *and* only on Mondays" (Figure 2).

Other rules that are part of the medication regimen, but do not govern when and how medications are to be taken, should also be included in the consolidated medication script. These may include dietary restrictions, such as "avoid grapefruit", or other precautions, such as "do not operate heavy machinery". These rules need only be prescribed if they are relevant to the patient. If the patient would never reasonably operate heavy machinery, this rule need not be included in the medication regimen or the consolidated medication script. All rules listed in the consolidated script, whether or not they determine medication-taking behaviour, contribute equally to medication regimen complexity.

Reducing complexity and forming habits

The final step in the process of creating a patient-centred consolidated medication script is to find ways to reduce the complexity of the medication regimen that it reflects (Figure 1, step 5). Referring to the fundamental

rules of a theory, Einstein believed that "it is the grand object of all theory to make these irreducible elements…as few in number as possible" [23]. This is in line with the philosophy that it is the *raison d'etre* of science to simplify nature so that it may be made intelligible. Surely, the simplification of the patient's medication regimen should be considered one of several worthy pursuits of the prescriber. This process requires patient input and careful trade-offs, often between treatment efficacy on the one hand and simplicity and convenience on the other.

The complexity of the medication regimen can be reduced through editing the consolidated medication script. The first way to do so is by eliminating rules. Although some prescribers might be concerned that reducing the number of doses or discontinuing certain medications would cause harm, there is little evidence to justify the concurrent use of frequently prescribed medications, or even their individual use in certain patients, especially those with comorbidities or the elderly [7-9]. In fact, a group that has followed a systematic approach to reducing the number of medications used by elderly patients has produced marked benefits for their patients [26,27].

Another mechanism of potentially reducing medication regimen complexity is substituting longer acting preparations for preparations that require multiple dosing. For instance, in Mrs. C's case, substituting a delayed release preparation of enalapril that could be taken in the morning instead of the two doses she currently takes would decrease her medication regimen complexity by one (Figure 2). Finally, medications that were formerly taken at different times could be taken at the same time of day. While we can predict that reducing medication regimen complexity would make it easier for a patient to adhere, the success of these changes should be evaluated only after a trial with that patient.

We suspect that reducing the number of rules to be followed benefits the patient by lowering the number of habits they must form. When the information is presented as a consolidated list of rules, the burden on the patient has less to do with understanding their regimen and more to do with remembering the rules and the inconvenience of adhering to them.

Rules are more likely to become engrained habits when they are constant. In contrast, high complexity may disproportionately lower adherence and quality of life in new medication regimens or those that are adjusted frequently. As a tool for personalized care, medication regimen complexity is best assessed in the context of chronically ill patients, who are more likely to be taking their medications for an extended period of time. This is also the population that would most benefit from its use, as the burden of complex medication regimens is often the greatest.

Comparison with previous measures of complexity

Medication regimen complexity is a property that is intrinsic to the structure of the medication regimen. In comparison, medication regimen complexity indexes are constructs and were validated based on their consistency with the expert opinion of physicians and pharmacists [14-16]. As an absolute value, medication regimen complexity does not depend on the clinical judgment of the prescriber or the cognitive status of the patient, although its influence on a particular patient will be relative.

Contrary to previous ways in which it has been conceived [14-17], medication regimen complexity does not necessarily increase if one adds more medications to the regimen. This is because medication regimen complexity is not influenced by the content of medication-taking rules. Just as the complexity of a disease may depend on the number of genes that are implicated or the complexity of a patient may depend on the number of comorbid conditions, medication regimen complexity depends only on the number of rules to be adhered to. It would seem bizarre to consider the number of nucleotide base pairs in each gene when assessing the complexity of a disease, or the number of letters in each diagnosis when assessing the complexity of a patient. It should seem equally strange to consider the number of medications in each rule when determining the complexity of a regimen.

In general, an increase in the number of daily doses of a drug may increase complexity, consistent with previous measures [14-18]. This is not guaranteed, however, as adding a second dose that is to be taken with another medication already in the regimen would not increase complexity as defined here.

Medication regimen complexity and personalized care

Previous conceptions of medication regimen complexity have decontextualized components of unique regimens, such as the number of medications or routes of administration, computed them to generate a number and often compared this score to patient adherence at a population level. Not only does this approach ignore the structural complexity of a particular regimen as a whole, but it cannot tell you how an individual patient will adhere to their regimen and it neglects the burden of adherence experienced by the patient, as a unique, patient-centred outcome.

Medication regimen complexity should be manipulated by clinician and patient together in the context of patient-specific characteristics and values with a motive to improving mutually agreed-upon goals of therapy. Insofar as adherence may improve the clinical

effectiveness of medications and enhance patient health and wellbeing, this is one laudable goal. Yet, adherence may also be a crutch for patients that lament the loss of time, energy and freedom associated with following their medication regimen. Reducing medication regimen complexity may address all of these determinants of patient health and quality of life.

Further, the process of creating a consolidated medication script is itself valuable to the delivery of patient-centred care as it involves removing ambiguous instructions, simplifying dosing times based on patient preference and consolidating the list of medications to promote better comprehension. Those who use this approach to medication regimen complexity will find that its elegance lies in its simplicity. Parsimony is an often overlooked principle in the approach to ethical, conscientious clinical decision-making, but in an age of complex diseases, patients and medication regimens, it will surely serve physicians and their patients reliably.

Conclusion

Medication regimen complexity is a property intrinsic to the structure of a medication regimen that relates to the number of rules patients must adhere to. The process suggested here for consolidating the rules for administering medications and minimizing medication regimen complexity may decrease the burden of adherence and, consequently, improve adherence itself, as well as other downstream outcomes. Future studies could test this hypothesis by subjecting the approach to experimental trials and may reveal important deficiencies in its design or challenges to its execution.

Medications are only one component of treatment regimens for the chronically ill. The general approach suggested offers a heuristic for thinking more broadly about treatment regimen complexity and a consolidated treatment plan that can render therapy less taxing for the patient. The best treatment plan for an individual patient contains the absolute fewest number of rules necessary to meet all of the goals of treatment. In all components of therapy, parsimony is a prerequisite for optimal patient-centred care and of the move towards person-centered medicine.

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References

[1] Smirnova, A., Bell, S.H., Tracy, C.S. & Upshur, R.E. (2011). Still dizzy after all these years: a 90-year-old woman with a 54-year history of dizziness. *BMJ Case Reports* [Epub ahead of print]. doi:10.1136/bcr.05.2011.4247.

[2] Centers for Disease Control and Prevention. (2003). Trends in aging--United States and worldwide. *Morbidity and Mortality Weekly Report* 52 (6), 101-104,106.

[3] Upshur, R.E. & Tracy, S. (2008). Chronicity and complexity: is what's good for the diseases always good for the patients? *Canadian Family Physician* 54 (12), 1655-1658.

[4] Bajcar, J.M., Wang, L., Moineddin, R., Nie, J.X., Tracy, C.S. & Upshur, R.E. (2010). From pharmaco-therapy to pharmaco-prevention: trends in prescribing to older adults in Ontario, Canada, 1997-2006. *BMC Family Practice* 11 (75).

[5] Cole, A. (2008). Over 60s' use of prescription drugs has doubled in past decade in England. *British Medical Journal* 337, a1132.

[6] Qato, D.M., Alexander, G.C., Conti, R.M., Johnson, M., Schumm, P. & Lindau, S.T. (2008). Use of prescription and over-the-counter medications and dietary supplements among older adults in the United States. *Journal of the American Medical Association* 300 (24), 2867-2878.

[7] Boyd, C.M., Darer, J., Boult, C., Fried, L.P., Boult, L. & Wu, A.W. (2005). Clinical practice guidelines and quality of care for older patients with multiple comorbid diseases: implications for pay for performance. *Journal of the American Medical Association* 294 (6), 716-724.

[8] Tinetti, M.E., Bogardus, S.T. Jr. & Agostini, J.V. (2004). Potential pitfalls of specific disease guidelines for patients with multiple conditions. *New England Journal of Medicine* 351 (27), 2870-2874.

[9] Upshur, R.E. (2005). Looking for rules in a world of exceptions: reflections on evidence-based practice. *Perspectives in Biology and Medicine* 48 (4), 477-489.

[10] Zhao, Y., Clark, W.T., Mort, M., Cooper, D.N., Radivojac, P. & Mooney, S.D. (2011). Prediction of Functional Regulatory SNPs in Monogenic and Complex Disease. *Human Mutation* 32 (10), 1183-90.

[11] Lyon, G.J., Jiang, T., Van Wijk, R., et al. (2011). Exome sequencing and unrelated findings in the context of complex disease research: ethical and clinical implications. *Discovery Medicine* 12 (62), 41-55.

[12] Naik, A.D. & Singh, H. (2010). Electronic health records to coordinate decision making for complex patients: what can we learn from wiki? *Medical Decision Making* 30 (6), 722-731.

[13] Petersen, L.A., Woodard, L.D., Henderson, L.M., Urech, T.H. & Pietz, K. (2009). Will hypertension performance measures used for pay-for-performance programs penalize those who care for medically complex patients? *Circulation* 119 (23), 2978-2985.

[14] George, J., Phun, Y.T., Bailey, M.J., Kong, D.C. & Stewart, K. (2004). Development and validation of the medication regimen complexity index. *Annals of Pharmacotherapy* 38 (9), 1369-1376.
[15] Martin, S., Wolters, P.L., Calabrese, S.K., Toledo-Tamula, M.A., Wood, L.V., Roby, G. & Elliott-De Sorbo, D.K. (2007). The Antiretroviral Regimen Complexity Index. A novel method of quantifying regimen complexity. *Journal of Acquired Immune Deficiency Syndromes* 45 (5), 535-544.
[16] DiIorio, C., Yeager, K., Shafer, P.O., Letz, R., Henry, T., Schomer, D.L. & McCarty, F. (2003). The epilepsy medication and treatment complexity index: reliability and validity testing. *Journal of Neuroscience Nursing* 35 (3), 155-162.
[17] Muir, A.J., Sanders, L.L., Wilkinson, W.E. & Schmader, K. (2001). Reducing medication regimen complexity: a controlled trial. *Journal of General Internal Medicine* 16 (2), 77-82.
[18] Corsonello, A., Pedone, C., Lattanzio, F., Lucchetti, M., Garasto, S., Carbone, C., Greco, C., Fabbietti, P. & Incalzi, R.A. (2009). Regimen complexity and medication nonadherence in elderly patients. *Journal of Therapeutics and Clinical Risk Management* 5 (1), 209-216.
[19] Mutasingwa, D.R., Ge, H. & Upshur, R.E. (2011). How applicable are clinical practice guidelines to elderly patients with comorbidities? *Canadian Family Physician* 57 (7), e253-262.
[20] Cox, L., Kloseck, M., Crilly, R., McWilliam, C. & Diachun, L. (2011). Underrepresentation of individuals 80 years of age and older in chronic disease clinical practice guidelines. *Canadian Family Physician* 57 (7), e263-269.
[21] World Health Organization. (2003). Adherence to long-term therapies: Evidence for action. Geneva: World Health Organization.
[22] Oxford Dictionaries. (2010). Definition of complex from Oxford Universities Online. Available at: http://oxforddictionaries.com/definition/complex (last accessed 16 August 2011).
[23] Einstein, A. (1994). Ideas and Opinions. New York: Random House, Inc.
[24] Chaitin, G. (2002). On the intelligibility of the universe and the notions of simplicity, complexity and irreducibility. Available at: http://www.umcs.maine.edu/~chaitin/bonn.html (last accessed 16 March 2011).
[25] Wolf, M.S., Curtis, L.M., Waite, K., Bailey, S.C., Hedlund, L.A., Davis, T.C., Shrank, W.H., Parker, R.M. & Wood, A.J. (2011). Helping patients simplify and safely use complex prescription regimens. *Archives of Internal Medicine* 171 (4), 300-305.
[26] Garfinkel, D., Zur-Gil, S. & Ben-Israel, J. (2007). The war against polypharmacy: a new cost-effective geriatric-palliative approach for improving drug therapy in disabled elderly people. *Israel Medical Association Journal* 9 (6), 430-434.
[27] Garfinkel, D. & Mangin, D. (2010). Feasibility study of a systematic approach for discontinuation of multiple medications in older adults: addressing polypharmacy. *Archives of Internal Medicine* 170 (18), 1648-1654.