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Assessing Multiple Medication Use With Probabilities of Benefits and Harms

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Abstract

Objective—A quantitative framework to assess harms and benefits of candidate medications in the context of drugs that a patient is already taking is proposed.

Method—Probabilities of harms and benefits of a given medication are averaged to yield a utility value. The utility values of all medications under consideration are combined as a geometric mean to yield an overall measure of favorability. The grouping of medications yielding the highest favorability value is chosen.

Results—Five examples of choosing between widely used candidate medications demonstrate the feasibility of the proposed framework.

Discussion—The framework proposed provides a simple method for considering the trade-offs involved in prescribing multiple medications. It can be adapted to include additional parameters representing severity of condition, prioritization of outcomes, patient preferences, dosages, and medication interactions. Inconsistent reporting in the medical literature of data about benefits and harms of medications, dosages, and interactions constitutes its primary limitation.

Keywords

adverse effect; utility function; aging; trade-offs; multiple medications

In the United States, adults older than 65 years now take a median of five medications per day (Kaufman, Kelly, & Rosenberg, 2002). Several studies have linked the use of multiple

medications with decreased adherence and increased risk of adverse events (Colley & Lucas, 1993; Monette, Gurwitz, & Avorn, 1995; Nolan & O'Malley, 1988; Tinetti, 1987; Tinetti & Speechley, 1989; Tinetti, Speechley, & Ginter, 1988). Although medications would ideally yield only beneficial effects on the targeted condition or symptom, nearly all medications entail some risk of undesirable adverse effects. One popular set of tools for prevention of adverse drug effects among older patients are the consensus-based Beers's criteria for medication use in older adults (Beers, Ouslander, Rollinger, Reuben, & Beck, 1991). The Beers's criteria for potentially inappropriate medication use in adults 65 years and older in the United States were developed specifically to lower the probability of adverse drug events in this population (Beers, 1997). The Beers's criteria are based on consensus developed through literature review with a bibliography and questionnaire evaluated by experts in psychopharmacology, clinical pharmacology, and geriatrics. Reflecting their popularity, the Beers' criteria were adapted by the Centers for Medicare and Medicaid Services in July 1999 for nursing home regulation. These criteria promote the prevention of adverse drug events in two important ways. First, they list medications or classes of medications that should generally be avoided in patients 65 years and older because of their disproportionately higher risk for adverse events. They also list medications that should not be prescribed to older persons with specific medical conditions. Several studies have shown the Beers' criteria to be effective in decreasing adverse events in older patients (Golden et al., 1999; Mort & Aparasu, 2000). Another important development for preventing adverse drug events in older persons was the exposition of the "prescribing cascade" (Rochon & Gurwitz, 1997). This elegant concept describes how the adverse effects of one medication might be misinterpreted as a new medical condition, which in turn motivates the prescription of additional medication. By making prescribers of medication to older patients conscious of this unfortunate sequence of events, unnecessary augmentation of medication can sometimes be prevented. In this article, we seek to expand the range of tools available to clinicians caring for older patients, by proposing a method to objectively assess the relative merit of a specific candidate medication within the context of drugs the patient is already taking. The proposed framework is offered as a quantitative complement to the Beers' criteria and the prescribing cascade to evaluate the trade-offs between probabilities of harm and benefit when prescribing multiple medications. This is especially important for older adults with multiple morbidities and health conditions (Agostini, 2007).

Background of Proposed Method

When doctors prescribe multiple medications to patients, they rarely have formal quantitative guidelines to assist them. We borrow the concept of combining probabilities from a decision-making framework (Harrington, 1965) routinely used in both aerospace engineering (Jahingir & Huque, 2005) and pharmacology (Narendra, Srinath, & Prakash, 2005) for the design of complex products with highly interrelated outcomes. For example, each medication has a certain probabilistic history of the benefits and adverse effects associated with its use. The combining of probabilities of benefits and adverse effects can be performed via methods that simplify the consideration of competing harms and benefits. Because information on the potential harm of medication usage is usually collected for specific adverse effects, the terms "harm" and "adverse effects" are used synonymously throughout this article.

Method

Conceptual Description

We propose a utility function that additively combines the probabilities of benefits and harms of a particular medication to yield its utility value. The utility values of the different medications taken by an individual are then multiplicatively combined to yield an overall

favorability value that represents the relative benefit of that person's total group of medications. Whereas formal decision-making processes incorporate both subjective (i.e., preferences and priorities) and objective information (i.e., clinical data), the method proposed here only uses objectively measured clinical data and assumes that the severity of all medical conditions, as well as the overall utility of each medication, are of equal preference and priority to the patient. This framework is thereby not limited by the particular technique used to elicit patient preferences (Brennan & Strombon, 1998; Ruland, 1999). The utility values proposed here are calculated from statistical information representative of study populations rather than individuals. In the Results section, we demonstrate how the utility values of the different medications might be weighted to yield something closer to an individual decision-making process.

Mathematical Description

The utility function has possible values between 0 and 1, where the former represents a medication with a probability of harm of 1.0 and probability of benefit equal to 0 and the latter represents the converse. A medication with equal probability of harm and benefit yields a value of .50. Probabilities of benefit reported by randomized controlled trials (RCTs) are typically from an "intent to treat" analytical strategy and represent population-level effects. Medications are often prescribed for a directly measurable condition, such as a diuretic for hypertension. Whereas there may exist a relatively high probability of controlling hypertension in an individual patient, the hypertension is ostensibly being treated to reduce that person's risk of cardiovascular morbidity. Randomized clinical trials and metaanalyses of hypertension medications often present the absolute risk reduction (ARR) in cardiovascular morbidity over a 5-year period, which for some diuretics is approximately 0.053 (Applegate et al., 1994; Hulley et al., 1985; Mulrow, Lau, Cornell, & Brand, 1998; Perry et al., 1989; SHEP Cooperative Research Group, 1991).

Procedure

We demonstrate our decision-making framework by calculating utility values for a medication based on its documented probabilities of benefits and harms. Table 1 presents information on the probabilities of benefits and harms on several medications or classes of medications widely used by older patients. All probabilities of benefit are at the population level and are from the best data sources available; when multiple sources existed, we chose the most recent.

The values in the last column of Table 1, labeled "Utility Value," are a simple average of the probability of benefit and the probability of no adverse side effects. The latter probability is calculated as one minus the sum of the probabilities of all known adverse effects. The utility value is the average probability of two positive characteristics, namely, that of benefit and that of no adverse effects. The lowest utility value (0.452) is for beta-blockers, reflecting a higher probability of adverse effects than its ARR.

Regarding calculation of utility values, the diuretic in Table 1 has a reported ARR in cardiovascular morbidity of 0.053 over a 5-year period. This small effect coupled with a low risk of adverse effects yields an overall utility value of 0.505 for the diuretic, representing nearly equal chances of harm and benefit. Thus, the reduction in risk of cardiovascular morbidity, if weighed on an equal basis, has nearly the same magnitude of the probability of harm, so the net benefit is approximately 0.50. In the Results section, we present one approach to weighting the probabilities of benefits and harms of particular medications and show how this may affect the choice of medication for a particular condition.

The probabilities of adverse effects are often simply reported as the proportion with adverse effects in the treatment and the control arms of the trials. We limited our calculation of risk of adverse effect for diuretic to the two trials using it as the primary treatment. Some estimates are derived from meta-analyses (e.g., Cochrane meta-analyses) that pool data from multiple studies. The use of meta-analytic results is increasingly seen as a useful source of information in clinical decision making (Lenert & Cher, 1999).

When considering the use of aspirin as a protective measure against myocardial infarction (Lip & Felmeden, 2004), the probability of a major hemorrhage with aspirin is higher than its ARR of myocardial infarction, which yields a utility value of 0.499. Assuming that greater importance is assigned to reducing the risk of myocardial infarction, weighting the two conditions by importance would result in a higher utility value than that produced by equal weighting.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a widely used medication with recognized benefits and harm. The probabilities assigned for overall relief of pain are based on a Cochrane meta-analysis (Towheed et al., 2006) providing comparisons of the efficacy of pain relief of acetaminophen relative to placebo and of NSAIDs relative to acetaminophen. A standardized mean difference of the treatment effect was reported that facilitates assignment of a consistent measure of probability of benefit. We added the standardized mean difference between acetaminophen and placebo to that between NSAIDs and acetaminophen to approximate a probability of relief of overall pain for NSAIDs referent to placebo. The probability value of .141 assigned to the sum of these standardized mean differences was obtained from a table of standard normal probabilities.

A recent Cochrane meta-analysis (Jayaram, Hosalli, & Stroup, 2006) that compared risperidone and olanzapine, two treatment choices among the new generation of antipsychotic medications, contained comprehensive information regarding a variety of adverse effects. The data quantified efficacy of relief of psychotic or schizophrenic symptoms as well as the risk of several adverse side effects. The probabilities of relief of psychotic or schizophrenic symptoms for both medications were not directly given. The values assigned represent the proportions of patients in each treatment arm who experienced no clinically important deterioration in symptoms, and the difference between these proportions was not statistically significant. The utility value of risperidone is slightly higher than that of olanzapine because of its overall lower probability of adverse effects. Exclusion of the probability of the negative sexual side effect for males from risperidone still results in a slightly higher utility value than olanzapine.

The Cochrane meta-analysis comparing four types of adverse effects (Jayaram et al., 2006) highlights the importance of rigorously quantifying multiple adverse side effects in addition to the primary efficacy of two medications. Even with these data, however, only those adverse effects that were explicitly reported can be incorporated into that medication's utility value. Thus, a consistently detailed documentation of adverse effects in clinical trials is needed to properly compute informative utility values.

Results

Medication Regimens of Five Hypothetical Older Persons

Table 2 presents the medication regimen for five hypothetical older persons, three males and two females. They are assigned gender because of the gender-specific effects of certain medications, such as risperidone's reported effect of male abnormal ejaculation (Jayaram et al., 2006). Each person takes four different medications corresponding to the distinct

medical conditions listed. The last column of the Table 2 is a multiplicative combination of the utility values of each medicine and is called the favorability value.

The favorability value is calculated by multiplying the utility values of the individual medications and taking a root corresponding to the total number of medications. For example, the favorability value for patient A is the fourth root of the product of his corresponding utility values or

$$\text{Favorability} = [0.499 \times 0.452 \times 0.521 \times 0.530]^{1/4} = 0.500 \quad (1)$$

Because the four utility values are centered around 0.50, the resulting favorability value is also 0.50.

The multiplicative combination of utility values to derive the favorability value is known formally as a geometric mean. When considering clinical trade-offs, the geometric mean possesses an attractive mathematical property. Namely, if any one of the medications has a very low utility value (i.e., highly unfavorable), the favorability value will also be low. This property prevents the choice of a medication that resolves one clinical problem while causing an unacceptably high risk of adverse effects. Our approach provides a framework for evaluating the relative favorability values of the addition of different alternative medications to a person's current regimen of medications. The combination of medications yielding the highest favorability value is the preferred option.

Our framework also allows for the consideration of the harms and benefits of medication interactions. If there were data showing a probability of effect modification by the presence of another medicine, that information would be included in the calculation of the utility value. For example, if there were data showing that the risk of stomach ulcers associated with the use of NSAIDs is modified by the use of another medication, for example, a protein pump inhibitor, then the probability of harm assigned to NSAID would be modified accordingly. Although this type of detailed information has not been routinely reported in the literature, there is a growing recognition of the need to collect information about medication interactions in RCTs.

Based on our framework for calculating an overall favorability value of an individual's current medications, we now consider a decision-making scenario for each of the five hypothetical patients where there is need to augment their current medical regimen, a common occurrence for many people as they age.

Choosing Between Candidate Medications for a New Condition

Table 3 shows each of the five patients having a new medical condition requiring intervention. In each case, we assume that all preexisting medical conditions continue. The new conditions for patients A, B, C, D, and E are, respectively, arthritic pain, hypertension, and symptoms of schizophrenia, depression, and Parkinson disease.

We present two candidate treatments for each condition with their corresponding utility values from Table 1. Not surprisingly, the medication with the higher utility value yields the higher favorability value when combined with the preexisting medications. It is noteworthy that for patients B and D, the favorability values for the regimen of five medications are lower than that of the current regimen of four medications. Thus, the favorability value can be viewed as a measure of the collective balance between the probabilities of benefit and harm within the entire group of medications a person is taking. Patients A, C, and E increase their favorability values by adding fifth medication candidates with utility values higher than the favorability value of their current regimens of four medications.

Weighting Probabilities of Benefit and Harm Within Utility Values

A completely unweighted evaluation of the probabilities of benefit and harm of a particular medication may not be realistic in every situation. Furthermore, because the probability values in Table 1 regarding probabilities of benefit and harm are population based, a completely unweighted evaluation will always yield a utility value representative of the study population rather than any individual patient. Methods to measure the preferences of the individual and the physician might be used to derive relative weights of the respective benefits and adverse effects of the medication being considered. Table 4 shows how the calculation of the utility values of the two candidate medications for treatment of Parkinson disease, levodopa and pramipexole, are modified based on a weighting of the probabilities of benefit and harm.

As a demonstration, we assume that patient or physician preferences have been elicited and result in the weights applied to the probabilities of benefits and harms in the first two columns of Table 4. The last two columns show the weighted utility values of levodopa and pramipexole, based on these weights. Equal weighting of the probabilities of benefits and harms yields the same unweighted values reported for these medications in Table 1. The trend of an increase in utility values when benefits are weighted higher than harms and vice versa is consistent for both medications. Pramipexole has higher utility values than levodopa when benefits are weighted higher than harms. In contrast, levodopa is favored by weights that place more emphasis on harms over benefits. In summary, a weighting of this sort allows for the utility value to reflect the preferences of the patient or physician with respect to the probabilities of benefit and harm. This, in turn, may drive a different choice of medication based on those preferences.

Discussion

This approach to quantifying the harms and benefits of medication use has a number of strengths worth highlighting. First, it represents a mathematically straightforward approach to directly combining the probabilities of benefits and harms using data from published sources. Second, because the method is computationally simple, it can be easily updated within electronic databases on receipt of new sources of information, similar to the update that occurred with the Beers' criteria that are used to evaluate inappropriate prescribing (Fick et al., 2003). In addition to being updated since their development, the Beers' criteria have also been implemented in an electronic database to evaluate types of medication errors in North Carolina nursing homes (Hansen et al., 2006). A third strength is that the utility values can incorporate different weights for benefits and harms to reflect individual patient or physician preferences or severity of events. Reviewing the favorability values in Table 2, it is natural to question whether the narrow range of favorability values (0.50 to 0.657) reflects clinically meaningful differences. As demonstrated in Table 4, the incorporation of preferences affords these favorability values a greater range. We recommend first calculating utility and favorability values based on equal weighting of the benefits and harms, and then incorporating different weights to reflect individual patient or physician preferences or severity of events.

Limitations

This approach is limited by the availability of clinical data. Because most data come from RCTs or meta-analyses, our approach is restricted to the sample populations from which inferences are made and represents population results, whereas medical decisions are made at the patient level. Integration of patient preferences and priorities, however, can transform these utility and favorability values from population metrics into patient-specific measures.

Furthermore, dose–response relationships and medication interactions are rarely reported in the clinical literature and need to be integrated into the calculation of the utility and favorability values. Last, the proposed utility values are point estimates for which measures of variability need to be developed.

Future Research

The proposed framework needs to be modified to accommodate two levels of weighting, that is, are corresponding to within and among individual medications. There is a need to precisely determine how common methods of eliciting patient preferences can be quantitatively scaled into the weights. Together, these modifications will enable the proposed framework to yield measures descriptive of individual cases. Finally, covariance measures need to be derived for the utility values to allow statistical inference.

Summary and Conclusion

As the population ages the problem of how to balance the risks and benefits of multiple medications is becoming of crucial importance. The proposed approach takes information on the probabilities of benefit and harm of medications and combines them in an intuitively sensible and mathematically transparent manner. The method can also incorporate patient–physician preferences, priorities, and severity of conditions. Although the approach is limited by the available clinical information, this limitation is shared by any method designed to objectively assess the benefits and harms of medications. Moreover, the simplicity and transparency of our approach provides patients and physicians with a conceptually reasonable and reproducible method to evaluate the trade-offs inherent to the use of multiple medications. The proposed method is offered as a quantitative complement to the screening of medications using the Beers’s criteria and may potentially assist with the prevention of prescribing cascades that lead to unneeded medication (Beers, 1997; Rochon & Gurwitz, 1997).

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Table 1

Associated Probabilities of Benefits and Harms of Medications Commonly Used by Older Patients

Medication	Probability of Benefit (Risk Reduction Referent to Placebo)	Probability of Harm (Increase in Risk Referent to Placebo)	Sources of Statistical Information	Utility Value
Acetaminophen	Overall pain relief (0.052 absolute risk reduction)	Adverse GI effects (0.013)	Towheed et al. (2006)	0.520
Alendronate 5 mg for 1 year	Risk reduction of vertebral fractures (0.48)	All adverse effects (0.15)	Cranney et al. (2002)	0.665
Aspirin	Treatment of clotting to reduce myocardial infarction over 5 years (0.005 absolute risk reduction)	Major hemorrhage (0.007)	Lip and Felmeden (2004)	0.499
Beta-blocker	Prevention of cardiovascular disease (0.007 absolute risk reduction)	Discontinue treatment due to adverse effects (0.104)	Wysonge et al. (2007)	0.452
Diuretic	Treatment of hypertension to prevent cardiovascular morbidity and mortality over 5 years (0.053 absolute risk reduction)	Adverse effects (0.044)	Benefit: Mulrow et al. (1998) Harm: SHEP, Applegate et al. (1994); SHEP Cooperative Research Group (1991) and SHEP-PS, Hulley et al. (1985); Perry et al. (1989)	0.505
Levodopa	Intent-to-treat response rate in 11 months (0.49) Improvement in UPDRS (0.049) ^a in 23.5 months	Somnolence (0.173)	Parkinson Study Group (2000)	0.683
NSAIDs	Overall pain relief (0.141 absolute risk reduction)	Adverse GI effects (0.019)	Towheed et al. (2006)	0.561
Olanzapine	Nonworsening of schizophrenia (0.682)	12-month relapse (0.143) Weight gain (0.143)	Jayaram, Hosalli, and Stroup (2006)	0.698
Pramipexole	Intent-to-treat response rate in 11 months (0.72) Improvement in UPDRS (0.024) ^a in 23.5 months	Somnolence (0.324)	Parkinson Study Group (2000)	0.710
Protein pump inhibitor	Reversal of nonulcerative dyspepsia in 2 to 8 weeks (0.10–absolute risk reduction)	Adverse effects (0.04)	Moayyedi (2006)	0.530
Risperidone	Nonworsening of schizophrenia (0.651)	Insomnia (0.067) Extrapyramidal (0.125) Male abnormal ejaculation (0.05)	Jayaram et al. (2006)	0.705
SSRI	Intent-to-treat response rate (0.48)	All adverse effects (0.25) GI, sexual dysfunction	Steffens, Krishnan, and Helms (1997)	0.615
Statin	Control of cholesterol to prevent major coronary events over 5 years (0.044 absolute risk reduction)	Elevated CK,AST, or ALT (0.003)	LaRosa, Jiang, and Vupputuri (1999)	0.521
TCA	Intent-to-treat response rate (0.486)	All adverse effects (0.30) Sedation, dizziness, anti-cholinergic symptoms	Steffens et al. (1997)	0.593

Note: ALT =alanine aminotransferase; AST =aspartate aminotransferase; CK =creatinine kinase; GI =gastrointestinal; NSAID =nonsteroidal anti-inflammatory drug; SSRI =selective serotonin reuptake inhibitors; TCA =tricyclic antidepressants; UPDRS =Unified Parkinson's Disease Rating Scale; Calculation of utility value for acetaminophen: $[(0.052) + (1 - 0.013)]/2 = 0.520$.

^aIndicates mean improvement over maximum value of 188.

Table 2

Common Medication Profiles of Older Patients With Overall Favorability Values

Patient Profile	Current Medications	Motivation for Treatment	Utility Value of Each Medication	Overall Favorability of Current Medication Regimen
A (male)	Aspirin	Clot prevention	0.499	0.500
	Beta-blocker	Hypertension	0.452	
	Statin	Cholesterol	0.521	
	Protein pump inhibitor	Nonulcerative dyspepsia	0.530	
B (male)	Acetaminophen	Arthritic pain	0.520	0.545
	Protein pump inhibitor	Nonulcerative dyspepsia	0.530	
	SSRI	Depression	0.615	
	Statin	Cholesterol	0.521	
C (female)	Alendronate	Prevent osteoporosis	0.665	0.629
	Levodopa	Parkinson	0.683	
	NSAID	Arthritic pain	0.561	
	SSRI	Depression	0.615	
D (female)	Alendronate	Prevent osteoporosis	0.665	0.657
	NSAID	Arthritic pain	0.561	
	Pramipexole	Parkinson	0.710	
	Risperidone	Treat schizophrenia	0.705	
E (male)	Diuretic	Hypertension	0.505	0.544
	NSAID	Arthritic pain	0.561	
	Statin	Cholesterol	0.521	
	TCA	Depression	0.593	

Note: NSAID = nonsteroidal anti-inflammatory drug; SSRI = selective serotonin reuptake inhibitors; TCA = tricyclic antidepressants; Calculation of favorability value for patient A: $(0.499 \times 0.452 \times 0.521 \times 0.530)^{0.25} = 0.500$.

Table 3
Choosing Between Candidate Medications for a New Condition With Utility Values

Patient	Favorability of Current Regimen of Medications	Additional Treatment Needed For:	Candidate Medications Being Considered:	Utility Value	Favorability Updated to Include Candidate Medication	Candidate Medication Chosen
A (male)	0.500	Arthritic pain	Acetaminophen	0.520	0.504	NSAID
			NSAID	0.561	0.511	
B (male)	0.545	Hypertension	Beta-blocker	0.452	0.525	Diuretic
			Diuretic	0.505	0.537	
C (female)	0.629	Symptoms of schizophrenia	Olanzapine	0.698	0.642	Risperidone
			Risperidone	0.705	0.644	
D (female)	0.657	Depression	SSRI	0.615	0.649	SSRI
			TCA	0.593	0.644	
E (male)	0.544	Parkinson disease	Levodopa	0.683	0.569	Pramipexole
			Pramipexole	0.710	0.574	

Note: Bold value numbers indicate higher in comparison of two candidates; NSAID = nonsteroidal anti-inflammatory drug; SSRI = selective serotonin reuptake inhibitors; TCA = tricyclic anti-depressants. Calculation of updated favorability value for Patient A from adding acetaminophen: $(0.499 \times 0.452 \times 0.521 \times 0.530 \times 0.520) 0.20 = 0.504$.

Table 4

Weighting of Benefits and Harm in Calculation of Utility Values for Levodopa and Pramipexole

Weights Assigned to Probabilities of Benefits and Harms (Sum to 1)		Weighted Utility Values	
Benefits	Harms	Levodopa	Pramipexole
		Probability of benefits = .539	Probability of benefits = .744
		Probability of harms = .173	Probability of harms = .324
.80	.20	0.897	1.00^a
.60	.40	0.754	0.817
.50	.50	0.683 ^b	0.710^b
.40	.60	0.612	0.603
.20	.80	0.469	0.390

Note: Calculation of first weighted utility value for levodopa: $[(0.80/0.50)(0.539) + 1 - (0.20/0.50) \times (0.173)]/2 = 0.897$. Bold values indicate the higher weighted utility value of the two candidates.

^aCalculated value of 1.03 truncated at 1.00.

^bEqually weighted utility values given in Table 1.