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The Unknown Impacts of Combinations of Large Numbers of Drugs

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This editorial shows the lack of an evidentiary basis behind the prescription of combinations of large numbers of drugs. People who take large numbers of drugs are gambling that the net effects will be helpful rather than harmful.

As people get older, they develop chronic illness resulting in an increase in the number of medications they take.[1,2] The effects of taking combinations of medications are varied. Two or more drugs are often used together to treat patients for a single problem. For example, many patients with clinically significant high blood pressure will require two or three drugs to achieve blood pressure control.[3] Drugs in such combinations are usually chosen from different chemical classes that act through different mechanisms. Although, technically, these are pharmacodynamic drug interactions, they are typically beneficial to patients. With a combination of drugs, low doses of each are often chosen, thereby minimising adverse effects. Common clinically significant drug-drug interactions occur when one drug increases or decreases the metabolism of another drug, thereby altering that drug's effect.[4] In other instances, drugs decrease the excretion of other drugs, thereby causing toxicity, or may do the opposite (increase excretion), leading to poor treatment outcomes.[4] Drugs may also interact by antagonising the actions of one another. For example, a drug like ibuprofen can negate some of the blood pressure-lowering effects of antihypertensive medications.[5] In addition, combining drugs can exacerbate the adverse effect profile of the individual agents. For example, combining four or more drugs increases the risk of falling in elderly patients, as does the use of two or more psychoactive medications.[6,7]

All medications have adverse effects with varying clinical consequences and severity. These adverse effects can result from medications taken individually or can result from pharmacokinetic and pharmacodynamic interactions of medications being taken in combination. Hundreds of drug-drug interactions have been identified, with varying degrees of clinical significance.[8] A central question revolves around whether adequate clinical trials exist to provide an accurate picture of potential adverse effects from drugs taken individually or in combination.

The central assumption of the present analysis is that the therapeutic and adverse effects of drugs taken in combination cannot be extrapolated from the therapeutic and adverse effects resulting from drugs taken individually or in pairs because of the synergistic effects of drugs taken in combination. The therapeutic and adverse effects of the combination must be obtained from the administration of the full combination in clinical trials. Thus, the effects of drugs A, B and C taken in combination cannot be estimated accurately from effects of combinations A–B, A–C and B–C, due to the unknown effects of combining multiple agents.

Another assumption is that different doses of any drug will not be considered in this analysis. Thus, a

drug will be associated with one dose only. This is obviously a conservative assumption, since nonlinear dose-related effects can drastically impact the pharmacokinetics and pharmacodynamics of a drug.[9] A third assumption is that the order in which the drugs are taken is unimportant. All that matters is the combination. Again, this is a conservative assumption.

Finally, the following analysis neglects drug-food, drug-herb and drug-disease interactions, and does not examine serum drug concentrations, route of administration, drug metabolism, duration of therapy and patient factors (age, sex, weight, genetic predisposition).[4,10] Inclusion of these factors would only strengthen the conclusions.

Now, let us assume that the maximum number of different drugs taken in combination is ten. This is done for computational simplicity only and is again a conservative assumption. In the geriatric population it is not uncommon to find people using ten or more medications on a daily basis.[1,11]

In order for a comprehensive handbook to exist that identifies the adverse effects of drugs used in combination, it would have to cover all combinations of drugs that could be conceivably taken by individuals. This means that, given our maximum combination of ten drugs, it would have to cover every conceivable combination of ten drugs. Additionally, to address the needs of people who take nine drugs, it would have to cover every conceivable combination involving nine drugs. And so on, down to one drug. Although one could argue that there could be exclusion conditions (e.g. if drugs A and B are known to be unacceptable in combination, they could be excluded in combination from any larger grouping), this may not be valid. If drugs A and B are a bad combination, the addition of drug C may (hypothetically) neutralise some of the negative adverse effects (and may provide others), thus changing the conclusions.

Thus, the analytical problem is to determine the number of combinations of drugs that would have to be examined to provide an evidentiary basis for predicting adverse effects (positive and/or negative).

If there are n total drugs available and if r drugs are taken at a time (during 1 day, for example) and if the order in which the drugs are taken is unimportant, then the number of combinations of n drugs taken r at a time is the binomial coefficient C(n,r) [equation 1]:

$$C(n,r) = n!/r!(n-r)! \quad \text{(Eq. 1)}$$

where n! represents n factorial [$n \times (n-1) \times (n-2)..(1)$].

Table I shows the number of combinations C(n,r), for r = ten drugs, as a function of number of drugs available.

Several thousand different drug entities are available that comprise the >11 000 drug products on the US market. Thus, to provide an evidentiary basis for all combinations of ten drugs, trillions of clinical trials would be required, and the identification of adverse events that rarely occur would require tens of thousands of subjects to be tested in each trial.

To cover all combinations of nine drugs, a similar analysis would have to be repeated, further increasing the already massive numbers. Removing the conservative assumptions by adding dose effects, drug-food interactions, drug-herb interactions, etc., would further increase the numbers of clinical field trials required.

The numbers of clinical trials and study subjects required to provide a full evidentiary basis for the therapeutic and adverse effects of combinations of multiple drugs indicate that drugs are being prescribed (or taken without prescription) in combinations for which there is no evidentiary basis to estimate potential beneficial or harmful effects. This assumes that the total effect of the combination is truly synergistic and that total effects cannot be estimated by combining effects of smaller groupings. Thus, people who are taking large numbers of

Table I. Number of possible drug combinations according to number of drugs available

No. of drugs available	No. of combinations
100	1.73×10^{13}
1 000	2.63×10^{23}
10 000	2.74×10^{33}

drugs are gambling that the net effects will be helpful rather than harmful.

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