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Medication non-compliance
When hard science meets soft science

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Abstract

Drug dosage regimen design is a rational process based on a drug's pharmacokinetics and pharmacodynamics in a specific patient setting and refined by feedback information. This process can be severely affected by medication non-compliance, particularly if the prescriber is unaware of the patient's failure to take medications as directed. Non-compliance takes many forms, including omission or addition of one or more doses, deviation from the prescribed timing of drug administration, and failure to adhere to required dosing conditions with respect to food, water and posture. These problems have many causes, including forgetfulness, lack of motivation, lack of confidence in the medication or prescriber, adverse effects, cost, and dosing complexity. Clinical pharmacology courses should include at least one lecture on medication non-compliance, its patterns, causes, implications and management. From a pharmacokinetic perspective, the impact of missed doses increases with an increase of the medication non-compliance impact factor $\tau/t_{1/2}$ (τ is the prescribed dosing interval and $t_{1/2}$ is the terminal elimination half-life of the drug). The impact of missed doses is decreased by more frequent dosing despite the fact that compliance decreases with increased dosing frequency. Most drug product package inserts do not address compliance issues. Drug-specific pharmacokinetic/pharmacodynamic simulations can yield valuable information for advising patients what to do if they missed one or more doses of their medication.

Keywords: Pharmacokinetics; Pharmacodynamics; Clinical pharmacology; Simulation; Package insert

Rational pharmacotherapy consists of several consecutive processes: diagnosis, selection of one or more drug products and their dosage forms, and definition of an appropriate dosage regimen, which may be modified by subsequent feedback information (therapeutic

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response, adverse effects, plasma concentrations and/or biochemical markers). In the face of medication non-compliance, particularly without the prescriber's knowledge, the feedback signals are corrupted and can become misleading. Utilization of the most sophisticated knowledge of pharmacokinetics and pharmacodynamics can become useless when patients do not take their medication as directed. Unfortunately, medication non-compliance, i.e. the failure to adhere to a prescribed medication regimen, is widespread and often undetected [1,2]. It has three dimensions: (1) omission or addition of doses (at the extreme, failure to take any of the prescribed medication or premature discontinuation of it), (2) deviation from the dosing schedule (improper timing of drug administration), and (3) failure to adhere to proper conditions of dosing (such as food, water, or posture). Examples of the latter are taking tetracycline with milk and taking alendronate with only a sip of water while supine. Dimensions (2) and (3) may occur due to the failure of a physician or pharmacist to instruct the patient adequately; one or both of these professionals then become partners with the patient in medication non-compliance.

There are many different patterns of non-compliance: the prescription is not filled or filled but not used, single doses are omitted randomly, a number of consecutive doses are omitted over several days (the drug holiday), medication is only taken before an appointment with the physician (the "toothbrush effect"), a dose is repeated within a short time due to forgetfulness, a number (perhaps all) of doses are doubled ("more is better"), a course of therapy is terminated prematurely because overt symptoms have disappeared or adverse (though perhaps tolerable) effects have occurred, or people become drop-outs because they are simply tired of taking medication for years (antihypertensives). Most of these patterns first became apparent by medication event monitoring with an electronic device in the closure of the prescription container that registers when the container is opened [3]. There are many reasons for medication non-compliance, some already alluded to, including forgetfulness, concern for experienced or possible adverse effects, cost of medication, lack of confidence in the prescriber or efficacy of the medication, and lack of motivation. Two or more of these reasons may co-exist and their relative frequency is specific to the patient, the health care setting and other variables.

The complexity of the medication regimen is an important determinant of medication error and compliance. While the actual percentages depend on the setting and the definition of compliance, the observations by Jacobs et al. [4], shown in Table 1, are typical: compliance decreases as the dosing frequency increases. Notably, the difference

Table 1
Effect of dosing frequency on medication compliance by arthritis patients[a]

Dosing frequency	Compliance rate, %
1 × day	78
2 × day	72
3 × day	64
4 × day	60
>4 × day	44

[a] Compliance was measured here as the percentage of prescribed amount consumed by the patient per day. From Jacobs et al. [4].

between dosing once or twice a day is relatively small. The situation is reversed when considering overconsumption specifically: it is quite high with once daily dosing and substantially lower when medication is taken two or three times a day (Table 2). Apparently, some people who forget if they have taken their once daily dosage make sure to medicate by taking another dose that day whereas individuals who take their medication more frequently are less concerned with missing a dose. This attitude (though not the practice of overconsumption per se) makes a lot of common sense and differs in that respect from the attitude of the marketing people of many pharmaceutical companies who promote the convenience of once-a-day sustained release products and hint at their better compliance (the FDA does not permit that claim unless proven for the specific product). The purpose of this type of promotion is usually to extend the life cycle (read: monopoly) of the product. In fact, the use of once-a-day medication can be problematic due to the greater impact of a missed dose, as will be shown in the following paragraph on the basis of pharmacokinetic theory [6].

For directly acting drugs with rapidly reversible pharmacologic effects (i.e. drugs whose intensity of action at any time is a function of their concentration in plasma at that time),

$$\log C = \log C_\tau - kt/2.302$$

in which t is the time since the last dose minus the dosing interval τ, C is the drug concentration at time t, k is the apparent first-order elimination rate constant of the drug, and C_τ is the steady-state drug concentration at the end of the dosing interval. Converting k to $0.693/t_{1/2}$ and t to multiples of τ yields the following:

$$\log C = \log C_\tau - 0.302 n\tau/t_{1/2}$$

The impact of missed doses on C is therefore primarily a function of the ratio $n\tau/t_{1/2}$. The term $\tau/t_{1/2}$ is the medication noncompliance impact factor. The smaller the noncompliance impact factor, the less pronounced is the impact of one or more omitted doses on C.

Now consider, as an illustration, a drug with a $t_{1/2}$ of 12 h, an apparent volume of distribution of 1 l/kg body weight referenced to plasma, a dose of 10 mg/kg/day (yielding a time-averaged plasma concentration of 7.2 mg/l at steady-state), and a minimum effective plasma concentration of 3 mg/l. In Table 3 are shown dosing frequencies for the daily dose (once to six times a day), the corresponding number of hours beyond the time of the scheduled but omitted dose when the concentration

Table 2
Impact of dosage frequency on patient compliance: overconsumption[a]

Dosage frequency	Patients taking more tablets than prescribed, %
Once daily	40
Twice daily	11
Three times daily	13

[a] Ninety-one patients taking oral antidiabetic drugs. From Paes et al. [5].

Table 3
Effect of dosing frequency on therapeutic coverage with consideration for the relationship between dosing frequency and compliance

τ (h)	t_{min} (h)	t_{min}/τ	$t_{min}/\tau \times$ fractional compliance[a]
24	1.83	0.0763	0.0557
12	8.85	0.737	0.516
8	11.0	1.38	0.716
6	12.1	2.01	0.846
4	13.1	3.29	No data[b]

τ, dosing interval; t_{min}, time beyond the time of a scheduled but omitted dose when concentration becomes less than the minimum effective concentration.

[a] Data from Greenberg [7].

[b] No compliance data reported by Greenberg [7] for this dosing schedule. From Levy [6].

becomes less than the minimum effective concentration, and the same information expressed as a fraction of the dosing interval. Inasmuch as compliance decreases with increasing dosing frequency, the results have been normalized accordingly in the last column of the table. It is evident that once a day dosing provides much less therapeutic coverage beyond the last dose than more frequent dosing schedules. Thus, what is gained by increased compliance is overwhelmed by the decreased therapeutic coverage associated with once a day dosing.

Drug dosing schedules of more than once a day have their own problems. A prescription of one tablet three times a day is taken by patients at widely variable and asymmetric dosing intervals [8]. If patients limit dose taking to a period of 12 h per day (for example 8 AM, 2 PM, and 8 PM), it results in a gradual increase of plasma concentrations from morning to evening, followed by a pronounced decline of concentrations overnight. The magnitude of these fluctuations increases with decreasing elimination half-life of the drug. The daily concentration maximum may be associated with adverse effects (example, carbamazepine) and subtherapeutic concentrations at night may result in loss of efficacy (example, theophylline in nocturnal asthma). Good sustained release products can minimize this problem.

It is important for physicians to be fully aware of all aspects of medication noncompliance. Clinical pharmacology courses should include at least one lecture on this subject, including its patterns, causes, consequences, assessment in individual patients, and management. Much information is available on these subjects [1,2]. I believe that it would be useful for physicians to explore a patient's medication compliance attitude and experiences as part of health history taking. This can guide the need for and direction of subsequent counseling and the choice of drug and/or drug delivery system to minimize compliance problems. When prescription insurance is limited or not available to the patient, an assessment of the economic impact on the patient and cost-conscious prescribing are in order. However, one must be aware that even the most energetic efforts to achieve compliance may yield limited results except for directly observed dosing or even enforced institutionalization (some patients with active tuberculosis).

With few exceptions, drug product package inserts (drug labeling) provide no instructions or inadequate instructions to patients who have missed one or more doses

of their medication [9]. The exceptions include the low potency oral contraceptives for which detailed instructions ("What to do if you miss pills") are provided. For drugs whose pharmacologic effect at any time is a function of their plasma concentration at that time, a knowledge of the drug's pharmacokinetics and its usual minimum effective concentration in plasma can provide the basis for suitable instructions to patients concerning compliance problems. For drugs with indirect pharmacologic effect such as the anticoagulant warfarin [10], this issue is more complicated. These drugs typically exhibit hysteresis in that their onset and time course of effect lag behind the time course of their plasma concentrations [11,12]. Depending on the pharmacokinetic/pharmacodynamic characteristics of a drug, onset and offset of action may be relatively rapid or quite slow. For example, the antiplatelet action of aspirin is produced within minutes after drug ingestion but persists for days, long after aspirin has been eliminated by hydrolysis ($t_{1/2}$ about 15 min). From a compliance perspective, drugs with rapid onset and prolonged duration of effect (due to a long $t_{1/2}$ and/or a shallow effect versus concentration relationship) confer "forgiving" characteristics on a drug.

The clinical impact of missed doses depends also on the steepness of a drug's concentration versus response curve and the region of that curve encompassed by the usual therapeutic concentration range. The impact of a missed dose may be minimal in the flat (maximum effect) portion of the concentration versus response curve [13]. Another consideration is drug compartmentalization in the body with the site of action in a real or apparent effect compartment [14] and/or an indirect mechanism of action. Both have a dampening effect on pharmacologic effect intensity fluctuations relative to the fluctuations of drug concentrations in plasma [15]. This can mitigate the impact of deviations in the timing of dosing and problems due to unintentional asymmetric dosing.

For indirectly acting drugs, pharmacokinetic/pharmacodynamic simulations based on a well-defined structural model and a good understanding of a drug's mechanism of action and clinical pharmacology can be powerful tools to assess the impact of missed doses, drug holidays and overdosing. This can provide the basis for rational compliance sections in drug package inserts. The definition of structural models should in any event be an essential component of drug development because it, in conjunction with population data, can lead to the elaboration of safe and effective drug dosage regimens.

Finally, medication compliance does not only relate to taking the right dose of the right drug at the right time. Warfarin is a case in point. The need to control diet (intake of vitamin K), physical activity and other lifestyle variables, and for avoidance of or adjustment for interacting drugs is at least as important as proper drug dosage. Special clinics staffed by clinical pharmacists or nurse practitioners for anticoagulation, antihypertension or immunosuppression control can provide a comprehensive approach to all aspects of medication compliance, often with spectacular results [16].

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Appendix A. Discussion 11

A. Breckenridge: I guess from what you said that therapeutic drug monitoring has got a relatively limited role in picking out the chronic non-complier.

G. Levy: You're quite correct, I failed to point that out. In the simulations it's apparent that, particularly considering the normal fluctuation in plasma concentrations, that plasma concentrations reflect poor compliance for only about one to two half-lives. And that's not very long, so that kind of monitoring is unfortunately not very diagnostic.

S. Jackson: Coming back to your comment on once versus twice-daily and to my comment yesterday, I wanted to expand on that a little bit. Your said that twice-daily is a more appropriate way of dealing with dosing because of the insurance it provides. One could argue that because of this the burden of tablet-taking, that why should one expose those patients who will do it right, is causing a pharmacological loss of effect?

G. Levy: Let me point out that FDA does not permit making a claim for better compliance of once-a-day medication, unless that has been shown for that medication. If you go through the product literature, the only claims that are made for once-a-day are convenience. But the best signal of convenience that the patient gives us is the compliance history. And compliance is essentially the same, once-a-day and twice-a-day. The chance of a loss of adequate exposure to a drug is so much greater once-a-day, and then you have this added problem of overdosing, which is quite frequent, and I think that from a medical point of view, twice-a-day is the way to go. I agree with Pieter Joubert that it has come to the point where marketing people in industry have been so successful in brainwashing physicians, that most of them think that once-a-day medication is better. It has to do mainly with the extension of patent coverage as the generics came on the scene. And I think that from a medical point of view it's unfortunate.

M. Reidenberg: Many years ago the group at McMaster University working with Canadian steelworkers and their families did a series of controlled experiments on compliance. What they concluded was that compliance will depend partly on how serious the patient thinks their illness is and on how effective they think the medication is. And most of the other interventions that they tried, including counselling, were found to make very little difference in the compliance rate. When they gave the steelworkers sphygmomanometers and had them measure their own blood pressure to see the effect of the drugs, then they took medication regularly. Other interventions made little difference. At our institution, it appears that when renal transplant patients stop taking their antirejection therapy, it is often depression and attempted suicide rather than "forgetting" to take the medicine.

G. Levy: I certainly agree with the first part of what you say, that trust in the physician, trust in the efficacy of the medication are the major determinants, and that has become difficult as patients are seen for shorter and shorter periods of time—3, 4, 5 min in many settings. The second part, it turns out that compliance problems are quite pronounced with anti-rejection drugs, at least those have been the reports. The seriousness of the impact of non-compliance seems to have only modest influence in the reports I've seen on the extent of compliance. Again, all these things depend on the setting and it's difficult to generalise.

L. Sheiner: John Urquhart classifies "non-compliers" into those who don't initiate their therapy, those who don't take it properly when they take it, and those who decide to

terminate prematurely. I think those are three different behavioural phenomena. Non-initiation and premature termination may be motivated actions: either you have lost faith in the medicine or you have side effects or some such. Failing to take medications properly despite the unambivalent intention to do so, at least from my own personal experience, is pretty much a matter of forgetting or not having the right habits. If you can get it into habit—take your med when you take your daily orange juice, or when you brush your teeth, or whatever, then you can be pretty regular. But then sometimes you may be travelling and things aren't quite the same: no orange juice, and hence no meds. I think there's very little evidence that forgetting, or failing to have reliable drug-taking habits are deliberate choices. Let me add just one more thought about dosage selection. If we knew someone was a non-complier and he wasn't responding to medication, we probably would not raise his dose. We'd do something else, like urging he pay more attention, whether or not it would be effective. If that's true, then we have to ask ourselves why we approve a dose that gives an acceptable average outcome in a group of people who are a mixture of compliers and non-compliers. That's the dose we come up with in our dose ranging clinical trials, and the one we test in phase III, but it clearly isn't the right dose, either for compliers, for whom it may be too large, or non-compliers, who won't take it anyway.

G. Levy: My first experience with non-compliance was before the advent of NSAIDs; I was working with people at Buffalo Children's Hospital trying to find ways of indirect plasma concentration monitoring using saliva; we used theophylline and did quite well. I went to the Juvenile Rheumatoid Arthritis Clinic and asked the chief for permission to do a study there with aspirin, and he said, "I don't believe in plasma concentration monitoring" I said, "Alright, but would you let us do it if we promise not to tell you the results" He accepted, and I had my assistant interview patients while waiting to be seen, and a good number agreed to have blood sample and saliva taken. We saw more and more zero levels—no drug at all—to the point where we would ask the parents, "if you don't give the child the aspirin, you can tell me, I'm not part of this group, and then we don't have to bother drawing a blood sample". About half did not give the medication, yet they came every month to the clinic, and every month the nominal dose was increased—of course it was never taken—but it was increased. And finally, the chief of service asked me, "Well, what are the results?", and I told him, since then they are monitoring plasma concentration.

A. Breckenridge: Should the product information which we give to patients be explicit about the problems of non-compliance? If someone is taking an anti-malarial like, mefloquine once a week for example, and he forgets it; what should people be doing if they've forgotten it for 2 days? Surely there should be someone's concrete advice for that as well.

G. Levy: Product information is certainly very important for oral contraceptives. I think when you have drugs with rebound effects, some of the beta-blockers and so on, it may be extremely important. The other issue is one of the reinitiation of therapy—with antiarrhythmics—where you can't just omit doses and then start again as before. So it's very drug-specific, and yes indeed we have to own up to the fact that many people simply are forgetful. Those people need advice for a number of drugs, but for other drugs, I don't think it's as important. I think most of the anti-malarials have a very long terminal half-life, and to the best of my knowledge, that might not be as critical for those agents.

L. Sheiner: Part of the problem is that we don't have the information that we would like to offer people, whether the patient himself or the physician, on what the effect of non-compliance might be. It's not studied. This seems to me similar to the paediatric situation, and I offer the same solution: start with observational phase IV studies. Given that people do, in fact, take their drugs erratically, if we could document compliance, at least among some sub-set of patients in phase IV, we might discover whether they have rebound effects, whether they have first dose effects, etc. We might then be able to offer some rational advice. Once more, I'm on my learn–confirm hobbyhorse, claiming that it's our exclusive preoccupation with approval, and the fact that only an intention-to-treat analysis is required of a phase III study to obtain that approval that has caused us to not get this information. We simply do not think about designs that would allow us to get this information at the same time as—not instead of—the information that we need for approval.

P. Joubert: I have not been keen on including these devices for looking at compliance into clinical trials during drug development. My opinion is that if you want to control for compliance in a phase III study, you introduce an artificial situation during drug development versus the real world of phase IV. If you need to ensure compliance in phase III to obtain an efficacy label, then you probably will require a labelling that will require you to ensure compliance once you are on the market. I see the sophisticated analysis of compliance as a very strong phase IV issue to be studied, but I'm very reluctant to bring it into the drug development process.

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