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Informing the Dosing of Interventions in Randomized Trials

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Abstract

Dosing is potentially the most important decision that must be made when building or refining behavioral interventions. In this paper, we propose standardized terminology and reporting of dosing information, which would inform intervention development, refinement for dissemination, and systematic reviews of dose-response relationships. Dosing of interventions may be characterized by duration, frequency, and amount. To illustrate the value of operationalizing these three parameters to evaluate dose-response relationships, 31 published reports of behavioral interventions to increase adherence to antiretroviral therapy (ART) were reviewed. The ART literature was characterized by under-reporting of dosing parameters, heterogeneity in dosing schedules, and heterogeneity in type of control group, which complicate analysis of dose-response relationships in systematic review and determination of the optimal dose for intervention dissemination. Improved reporting of the three dosing parameters and comparison of intended to actual delivery can inform the identification of the most effective intervention doses and the efficient implementation of efficacious interventions in clinical practice.

Keywords

clinical trial; randomized controlled trial; study characteristics; intervention studies; patient adherence; intervention dose

Among the many decisions to be made when building or refining interventions is choosing the intended dose. Dosing decisions have implications for budgeting, staffing, space allocation, and participant enrollment and retention. Insufficient dosing of a new intervention can lead to premature conclusions about the ineffectiveness of a general intervention approach if a different (but untested) dose would have been effective. Dosing decisions must also be made when translating effective interventions in clinical practice because the complexity and resource intensity of many interventions require dose

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modifications to be feasible in many practice settings. In translating effective and, perhaps, cost-effective interventions for broad dissemination, it would be ideal to provide guidance on ways that the intervention dose could be modified while still retaining the intervention's effect size.

At present, there is little guidance to inform dosing decisions for new interventions or for modifying the dose of existing interventions for translation into clinical practice. To inform dosing decisions, there is a critical need for consensus in standardized terminology and reporting of intervention dose. The goals of this paper are threefold: to propose the use of standardized terminology for intervention dosing parameters, to describe the challenges in comparing those parameters across interventions, and to highlight the intervention dosing information that should be reported to facilitate examination of dose-response relationships for intervention refinement and systematic reviews.

To illustrate the value of operationalizing dosing parameters, published reports of behavioral interventions to increase adherence to antiretroviral therapy (ART) were reviewed. Through this illustrative review, we identify critical issues in the reporting of intervention dosing within and across studies that could be improved to support systematic intervention development, refinement for dissemination, and systematic reviews of dosing elements that are most predictive of patient outcomes. We conclude with recommendations that will facilitate dosing decisions for developing new interventions, refining existing interventions, and systematically reviewing dose-response relationships.

Operationalizing Behavioral Intervention Dose

Dose is defined as the "exact amount of a medicine or extent of some other treatment to be given or taken at one time or at stated intervals."[1] Yet, dose is variously operationalized. Drawing from a concept analysis that was conducted to identify and define nurse dose,[2] three dose parameters—*duration, frequency,* and *amount*—can be defined and operationalized across various types of interventions. *Duration* is the amount of time over which the intervention is intended to be administered (e.g., 12 weeks or 52 weeks). *Frequency* is how often contact is intended to be made with participants per unit of time (e.g., one contact per week or per month). *Amount* is the length of each contact between the interventionist and participant (e.g., 5 minutes, 1 hour). Interactions between *duration*, *frequency*, and *amount* represent another potentially meaningful aspect of dose. The interaction between *duration* and *frequency* is the total number of contacts made. The three-way interaction is the total cumulative number of minutes of intervention delivered.

Given these definitions, one could conduct structured comparative effectiveness trials to evaluate the impact of different dosing schedules. For example, one could hold the intended *amount* fixed (1-hour sessions) and compare whether a more compressed schedule with greater *frequency* (one contact per week) and shorter *duration* (12 weeks) was more effective than a less compressed schedule with lesser *frequency* (one contact per month) and a longer *duration* (12 months). Alternatively, one could hold the intended *duration* fixed (12 weeks) and compare whether less *frequent* contact (one contact every other week) of greater *amount* (2 hours) was more effective than more *frequent* contact (one contact per week) of lesser *amount* (1 hour). In these examples, the total time of patient-interventionist interaction was held constant at 12 hours. One could also compare an intervention requiring 12 hours of patient-interventionist interaction using a variable *frequency*, in which participants receive more frequent contact initially and then less frequent contact over time.

Given that comparative effectiveness trials manipulating intervention dosing parameters are relatively infrequent, a potentially more accessible way to understand which dosing parameters and which levels of each parameter generate more effective interventions is

through systematic review. Examinations of dose-response relationships in systematic reviews typically involve only one aspect of dose and do not jointly consider *duration*, *frequency*, and *amount*. For example, in a meta-analysis of behavioral interventions to increase adherence to highly active ART,[3] a dichotomous covariate representing *5 or more sessions* versus *fewer than 5 sessions* did not account for a significant proportion of variance in the effect size. More variance may have been explained if other dosing parameters had been examined. Ideally, people designing, refining, and disseminating interventions would like to be informed about all parameters of dosing as these parameters may work in concert, may interact with one another (the whole is greater than [or less than] the sum of its parts), or some parameters may be more predictive of patient outcomes than other parameters.

Illustrative Data Set

To experience firsthand and illustrate the challenges in comparing interventions along these three dosing parameters, we systematically reviewed 31 reports of randomized controlled trials that evaluated interventions to improve patient adherence to ART. The data set was assembled as part of a larger study to develop and evaluate methods for conducting mixed-methods research syntheses [4] and was based on a search of six databases (Academic Search Premier, CINHAL, PubMed, PsychINFO, Sociological Abstracts, and The Cochrane Library). Inclusion criteria for this search included: conducted in the US, published between 2000 and 2009, medication adherence as an outcome, and sufficient information to calculate the effect size. For this paper, we excluded studies that involved minimal human contact (e.g., provision of educational materials or pill boxes) or in which the only difference between intervention and control groups was something other than human contact (e.g., reminders from a pager). For the purposes of this paper, we chose to assess only on the dose of the human contact portion of the intervention even if human contact was supplemented with devices or intervention materials such as videos or written materials because dosing parameters for these intervention components would be difficult to determine.

To use dosing data in a meta-regression to examine dose-response relationships, the data must be reduced to a common denominator. To illustrate, *duration* was calculated in weeks, *frequency* in times per week, and *amount* in minutes (Table 1). Values were averaged across components in the case of multi-component interventions (e.g., comprising in-person group sessions and individual telephone interviews). In a meta-regression, the dependent would be the effect size representing the difference in outcomes between intervention and control groups; the independent variables would be between-group differences in the dosing parameters, which could be calculated from the information provided in Table 1.

Challenge 1: Under-Reporting of Dosing Parameters

One challenge to comparing interventions along dosing parameters is under-reporting of dosing information. As shown in Table 1, there was inconsistency in the completeness of reporting across the three parameters. Intended *duration* was always reported. Intended *frequency* was reported less often; commonly, authors reported the total number of contacts without reporting the interval at which the contacts occurred. Therefore, *frequency* was calculated by dividing the total number of contacts by the *duration*.

Data were least likely to be reported for *amount* (missing in 12 out of 31 reports). Moreover, *amount* tended to be reported as delivered rather than as intended, often as a mean or median and sometimes accompanied by a standard deviation or range. Although reporting of intended delivery is necessary to evaluate the efficacy or effectiveness of an intervention on the basis of intent-to-treat principles, comparison of actual to intended delivery enables the evaluation of mediators and provides information on whether some intervention doses are

likely to be infeasible because the intended delivery is rarely provided. Significant differences between intended and actual delivery may indicate that interventionists have practical difficulty with fidelity to the protocol and/or that patients have difficulty adhering to the prescribed intervention. In the reports that included data on actual delivery, the authors indicated that actual delivery was somewhat less than intended. Such differences may suggest that a more modest intervention dose may reduce the risk of challenges with fidelity to the intended intervention, patient attrition due to drop out, and excess intervention costs.

Challenge 2: Heterogeneity in Dosing Schedules

Another challenge to comparing interventions along dosing parameters is that dosing schedules may vary between studies and between participants in the same study. Dosing schedules may be fixed (i.e., the schedule is constant throughout the study duration) or variable (i.e., the dose changes during the study) and may be tailored (i.e., delivered according to participant needs or progress) or untailored (i.e., applied similarly to all participants). In Ma (2008), the directly observed therapy intervention was delivered 5 times per week for the first 12 weeks, 4 times per week for the next 3 weeks, 3 times per week for the next 3 weeks, twice per week for the next 3 weeks, and once per week for the final 3 weeks to all participants (variable, non-tailored). In Rathbun (2005), participants had in-person visits at baseline and then 2 weeks later, with an intervening telephone call and then additional follow-up for participants who needed it (variable, tailored). Because mean values for *frequency* and *amount* obscure these subtle differences in dosing schedules, additional variables may be created representing fixed versus variable and tailored versus untailored dosing schedules (last two columns of Table 1).

Challenge 3: Heterogeneity in Types of Control Groups

Heterogeneity in the type of control group also poses a challenge for comparing intervention dosing parameters. In our data set of ART adherence interventions, there were three types of control groups: usual care, enhanced usual care, and attention control. For usual care control groups, ascertaining between-group differences in dosing parameters may be difficult because authors rarely report on the resources used by usual care participants during the study period. When synthesizing findings, one could assume that usual care participants receive no additional care, as we did here, so that between-group differences in dosing parameters represent the amount incurred by the intervention group.

In the case of an enhanced usual care group (i.e., participants receive some level of intervention but not a comparison intervention), the *duration, frequency*, and *amount* of care received by the control group is assumed to be greater than zero. As with usual care groups, however, assigning values for each parameter may be challenging given the lack of detail on the intervention provided to enhance usual care.

Finally, in studies that include an attention control group, *duration, frequency*, and *amount* of contact may or may not be equal to those of the intervention group (i.e., the difference between groups is zero). If they are assumed to be equal, then the treatment and control groups differ only on intervention content. However, the extent to which equivalence was achieved is often difficult to evaluate given the absence of dosing data on the control group.

Discussion

Dose is often examined in systematic reviews and reports of primary research studies directed toward identifying why some interventions are efficacious or effective and others are not. Yet, dose may be misconstrued as a unidimensional parameter (e.g., number of

intervention contacts) while other aspects of intervention dose are ignored. We propose standardized terminology for intervention dosing—*duration*, *frequency*, and *amount*—that should be reported consistently to facilitate the use of dosing data in systematic examinations of dose-response relationships for the purpose of intervention development and refinement for dissemination.

One aspect of dosing that has been promoted but that we did not operationalize is *purity*, which has been defined as the "concentration of active elements of a treatment" (p. 312).[2] *Purity* is an aspect of dosing that differentiates an intervention group from an attention control group matched for *duration*, *frequency*, and *amount*. In a concept analysis conducted to yield aspects of nurse dose, purity was operationalized as the nurse's knowledge, which was indicated by education, experience, and skill mix.[2] The authors suggested that purity of behavior therapy is "information or instructions given to address the presenting clinical problem." Deriving values for *purity* of behavioral interventions may be challenging because the active ingredient may relate not only to interventionist knowledge and experience, as proposed for nurse dose, but also to intervention content or approach (e.g., education, training, social support).[5] Future work is needed to operationalize this concept in the context of behavioral interventions.

Although the approach to dosing outlined in this paper was illustrated with a review of behavioral interventions for ART adherence, they are not limited to such interventions. Previous literature has underscored a general tendency to under-report information on interventions across different therapeutic areas.[6] Lack of reporting of dosing information also challenges efforts to synthesize literature on the relationship between medications and patient outcomes. For example, in a Cochrane review comparing paracetemol to nonsteroidal anti-inflammatory agents for rheumatoid arthritis, it was noted that the reports did not include justification for the doses examined and therefore it was unclear whether equipotent doses were examined.[7]

Conclusions

On the basis of the challenges we identified, we make several specific recommendations that will facilitate the examination of dosing in systematic reviews of the literature, which is critical to assessing the comparative effectiveness of different intervention options and for translating existing interventions into clinical practice. To build the evidence base on dosing, investigators, when planning studies, should develop a plan to assess intervention fidelity that includes an assessment of how many intervention contacts are actually made and how long each contact lasts. This information will allow comparison of values for actual and intended *duration, frequency* and *amount* of intervention delivered, which will inform whether deviation in fidelity to the intervention protocol is a source of variation in outcomes within the treatment arm and across similar interventions from different studies. Investigators should also standardize training across interventionists to improve the likelihood of an equal level of skill, which may enhance the correspondence between intended and actual delivery. Finally, sufficient detail on intended and actual *duration*, *frequency*, and *amount* should be included in reports of intervention studies so that the relationship between dosing and patient outcomes can be investigated more fully in systematic reviews. To complement these efforts, intervention banks can be created whereby intervention detail, including manuals, videos, written materials can be stored and accessed by individuals designing studies or conducting systematic reviews.[8]

We hope that, by conceptualizing and operationalizing intervention dose, investigators will be poised to collect this information in their trials and include it in published reports. The use of standardized dosing terminology and consistent detailed reporting on intervention dose along these parameters will allow investigators and reviewers alike better to design

new interventions, to translate efficacious interventions in clinical practice, and to systematically review dose-response relationships.

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Table 1

Dosing Parameters of Antiretroviral Therapy Adherence Interventions (n=31)

Report	Analysis N	Duration (weeks)	Intervention		Control		Fixed or Variable	Tailored or Untailored
			Frequency (per week)[+]	Amount (min)[†]	Frequency (per week)[+]	Amount (min)[†]		
Altice et al., 2007	141	26	5	5	UC (=0)	UC (=0)	Fixed	Untailored
Collier et al., 2005	282	96	.17	NR	UC (=0)	UC (=0)	Variable	Untailored
DiIorio et al., 2003	17	6	.5	NR	UC (=0)	UC (=0)	Fixed	Untailored
DiIorio et al., 2008	213	13	.42	37	UC (=0)	UC (=0)	Fixed	Untailored
Golin et al., 2006	155	10	.33	NR	10	.33	Fixed	Untailored
Gross et al., 2009	243	24	5	NR	UC (=0)	UC (=0)	Fixed	Untailored
Holzemer et al., 2006[*]	240	13	.5	22	UC (=0)	UC (=0)	Variable	Untailored
Johnson et al., 2007	204	65	.25	90	UC (=0)	UC (=0)	Fixed	Untailored
Jones et al., 2007	237	22	.73	136	.73	136	Variable	Untailored
Koenig et al., 2008	226	26	.54	34	0	0	Variable	Untailored
Mann 2001	44	4	2	10	UC (=0)	UC (=0)	Fixed	Untailored
Margolin et al., 2003	90	26	2	120	0	0	Fixed	Untailored
Milam et al., 2005	437	1	1	NR	1	NR	Fixed	Untailored
Murphy et al., 2002	33	7	.71	NR	UC (=0)	UC (=0)	Fixed	Untailored
Murphy et al., 2007	141	24	.375	29	UC (=0)	UC (=0)	Fixed	Untailored
Parsons et al., 2007	130	8	1	60	1	60	Fixed	Untailored
Purcell et al., 2007	966	5	2	NR	1.6	NR	Fixed	Untailored

Report	Analysis N	Duration (weeks)	Intervention		Control		Fixed or Variable	Tailored or Untailored
			Frequency (per week)[+]	Amount (min)[†]	Frequency (per week)[+]	Amount (min)[†]		
Rathbun et al., 2005	33	12	NR	NR	UC (=0)	UC (=0)	Variable	Tailored
Rawlings et al., 2003	195	4	1	NR	UC (=0)	UC (=0)	Fixed	Untailored
Remien et al., 2005	215	5	.83	53	UC (=0)	UC (=0)	Fixed	Untailored
Reynolds et al., 2008 [*]	109	16	.83	7.9±2.5	UC (=0)	UC (=0)	Variable	Untailored
Safren et al., 2009	45	12	.92	50	.08	50	Fixed	Untailored
Samet et al., 2005	151	13	.33	36	UC (=0)	UC (=0)	Variable	Untailored
Simoni et al., 2007	136	13	1.5	35	UC (=0)	UC (=0)	Variable	Untailored
Smith et al., 2003	43	13	.5	NR	UC (=0)	UC (=0)	Fixed	Untailored
van Servellen et al., 2005	85	26	NR	NR	UC (=0)	UC (=0)	NR	NR
Wagner et al., 2006	230	6	.83	38	UC (=0)	UC (=0)	Fixed	Untailored
Westling et al., 2007	41	4	2	10	2	10	Fixed	Untailored
Williams et al., 2006	171	52	.5	NR	UC (=0)	UC (=0)	Variable	Untailored
Wohl et al., 2009 [*]	250	26	1	20	UC (=0)	UC (=0)	Fixed	Untailored
Wyatt et al., 2004	147	11	1	150	.09	NR	Fixed	Untailored

NR=not reported. UC=usual care.

[+] Weekly frequency averaged across all encounters and intervention components, reported as intended.

[†] Per encounter, reported as actually delivered.

[*] Reported only as delivered for all three dosing parameters.