Evaluation of Using Dog as an Animal Model to Study the Fraction of Oral Dose Absorbed of 43 Drugs in Humans[1]

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Purpose. To conduct a retrospective evaluation of using dog as an animal model to study the fraction of oral dose absorbed (F) of 43 drugs in humans and to briefly discuss potential factors that might have contributed to the observed differences in absorption.

Methods. Mean human and dog absorption data obtained under fasted state of 43 drugs with markedly different physicochemical and pharmacological properties and with mean F values ranging from 0.015 to 1.0 were obtained from the literature. Correlation of F values between humans and dogs was studied. Based on the same references, additional F data for humans and rats were also obtained for 18 drugs.

Results. Among the 43 drugs studied, 22 drugs were virtually completely absorbed in both dogs and humans. However, the overall correlation was relatively poor ($r^2 = 0.5123$) as compared to the earlier rat vs. human study on 64 drugs ($r^2 = 0.975$). Several drugs showed much better absorption in dogs than in humans. Marked differences in the nonliner absorption profiles between the two species were found for some drugs. Also, some drugs had much longer T_{max} values and prolonged absorption in humans than in dogs that might be theoretically predicted. Data on 18 drugs further support great similarity in F between humans and rats reported earlier from our laboratory.

Conclusions. Although dog has been commonly employed as an animal model for studying oral absorption in drug discovery and development, the present study suggests that one may need to exercise caution in the interpretation of data obtained. Exact reasons for the observed interspecies differences in oral absorption remain to be explored.

KEY WORDS: oral absorption; humans; dogs; rats; interspecies scale-up; pharmacokinetics.

INTRODUCTION

Dog has been commonly employed as an animal model for oral absorption study in drug discovery and development. This is carried out assuming that the results obtained may be successfully extrapolated to humans. Literature on extensive examination of this subject matter appears quite limited to date.

Recently, it has been reported from our laboratory (1) that there is a linear correlation of the fraction (F) of oral dose absorbed between rats and humans for 64 drugs with wide physicochemical and pharmacological properties and with F values ranging from zero to unity. The absorption process for these drugs includes paracellular and/or transcellular pathway, passive and/or carrier mediated process and/or the involvement of efflux pump. It is also of interest to note that this great similarity in absorption occurred in spite of the fact that fast-release tablets and capsules were usually employed in human studies while drug solutions were commonly used in rat studies. The main purpose of this study is to extend our earlier rat-versus-human study to the dog-versus-human correlation using 43 widely different drugs as examples and to briefly discuss the potential reasons and significance of our findings that dogs may absorb drugs differently or much better than humans. As a result of literature evaluation for this study, data on fractional dose absorbed in humans and rats of additional 18 drugs, not reported earlier (1), are also obtained and reported in here.

METHODS

Initially, dog absorption data for the 64 drugs reported earlier (1) were searched using Medline® service. Reliable data based on proper pharmacokinetic design and analysis (1–3) were found or estimated for 20 drugs (Table 1). Additional dog and human absorption data for 23 drugs were mainly obtained from an extensive search of articles published from their first volume to mid 1998 in journals such as Drug Metabolism and Disposition, Journal of Pharmacology and Experimental Therapeutics, Arzneimittelforschung, Journal of Pharmacokinetics and Biopharmaceutics, Biopharmaceutics and Drug Disposition, and Xenobiotica. The human F data for acyclovir, atenolol, benazeril, and lovastatin were obtained from the Physicians' Desk Reference (2). As reported earlier (1), most of the F values were obtained from studies using radiolabeled compounds; most often being based on the ratio of the total urinary radioactivity recovery between oral and intravenous or subcutaneous (3) administration or based on standard pharmacokinetic principles for unchanged drugs (4). The dose fraction absorbed was found or assumed to be in the linear range. For acyclovir (1,2,5), chlorothiazide (1,6,7) and miglitol (8) showing dose-dependency in absorption, F values at lower doses were initially used or estimated for comparison (Table 1). It is assumed (1) that in vivo dissolution rates from dosage forms employed did not significantly affect the extent of oral absorption and the drugs were generally stable in the gut lumen. Exclusion criteria reported earlier (1) are employed in the present study. The F values for 18 drugs in rats were similarly obtained. Like the early study (1), drugs were administered under fasted conditions.

RESULTS AND DISCUSSION

Molecular weights, basic physical properties (acid, base, neutral compound or zwitterionic compound), the dosage form used in the study, and the mean F values in humans, dogs and rats are summarized in Table 1. The molecular weights range from 151 for acetaminophen to 646 for acarbose. Among the drugs studied 25 are bases, 8 acids, 5 neutrals and 5 zwitterions. These drugs include a wide range of lipophilicity. For example, the log $P_{oct\text{-}water}$ for acylovir is −1.8 and for propranolol 3.4

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Table 1. Summary of Data[a] on the Mean Fraction of Oral Dose of Drugs Absorbed in Humans, Dogs, and Rats

Drug	Mol. wt.[b]	Property[c]	Absorption (% dose)[d]		
			Humans	Dogs	Rats
Acarbose	646	B	1.5 (1–2)^{sol}	4^{cap}	1.5 (1–2)^{sol}
Acetaminophen	151	A	100^{tab}	94^{sol}	
Acyclovir	225	Z	20^{cap}	100 ± 7.1^{cap}	
Atenolol	266	B	50^{tab}	100^{cap}	
Benazepril	425	B	37	39 ± 6.1^{cap}	
Bisoprolol	325	B	100^{sol}	98	96
Camazepam	372	N	100	100^{susp}	
Chlorothiazide	296	A	56^{tab}	100^{tab}	
Cimetidine	252	B	100^{sol}	98 ± 2.3^{cap}	
Doxazosin	451	B	100^{cap}	81	100
Enalapril maleate	376	B	60^{cap}	61^{sol}	
Ethnylestradiol	296	N	100	100^{cap}	
Famotidine	337	B	45	44	
Fenoterol	303	B	60	70	57
Fluvastatin	411	A	98^{sol}	100^{cap}	100^{susp}
Fosinopril	564	A	30	25	
Furosemide	331	Z	61 ± 17^{tab}	54 (50–60)^{sol}	
Granisetron	312	B	97 ± 6.2^{sol}	100^{cap}	
Iothalamate	613	A	1.9 ± 0.5^{cap}	10 ± 2.9^{sol}	
Isoxepac	332	A	98 ± 0.4^{sol}	100^{sol}	99^{sol}
Ketanserin	389	B	100	100^{sol}	100 ± 18^{sol}
Lovastatin	405	N	31^{sol}	23 ± 11^{sol}	29 ± 9^{sol}
Methyldopa	211	Z	43^{cap}	100^{powder}	
Miglitol	207	B	100^{e,tab}	100 ± 6.5^{e,cap}	100^{sol}
Nadolol	309	B	20 ± 2.1^{cap}	98 (88–104)^{cap}	
Nimodipine	418	N	100	100^{cap}	100^{sol}
Nitrendipine	360	A	88 ± 16^{sol}	73^{cap}	90 ± 5^{sol}
Nizatidine	332	B	100	99 ± 5.1^{sol}	
Olanzapine	312	N	75	97^{sol}	
Omeprazole	345	N	97^{sol}	100^{susp}	100
Pelrinone	241	B	98 ± 3.5^{cap}	96 ± 2.6^{cap}	71 ± 3.4^{sol}
Prenalterol	229	B	97 ± 1.8^{sol}	94 ± 0.6^{sol}	
Propranolol	259	B	100^{tab}	100^{cap}	
Ramipril	417	Z	60^{sol}	43^{susp}	56^{susp}
Ranitidine	314	B	61 ± 13^{tab}	100^{f,sol}	
Remoxipride	371	A	100^{cap}	99^{cap}	100^{sol}
Sultopride	354	B	100^{tab}	92 ± 13^{cap}	
Sumatriptan	295	B	62^{sol}	97^{sol}	
Tamsulosin	372	B	100^{cap}	90	100^{sol}
Terbutaline	225	Z	60^{tab}	78^{sol}	
Tolmesoxide	214	B	100^{cap}	100^{sol}	100^{sol}
Xamoterol	339	B	8.6 ± 4.7^{cap}*	36 ± 8.5^{cap}	19 ± 3.5^{sol}
Zopiclone	389	B	100	100	

[a] The sources of references are available upon request.
[b] Molecular weight.
[c] N: neutral compound; A: weak acid; B: weak base; Z: zwitterionic compound.
[d] Parenthesis indicating range.
[e] Absorption at lower dose (Fig. 2).
[f] Bioavailability being about 75% and estimated hepatic first-pass extraction being about 25%.
* Superscripts to F data refer to formulation information: cap for capsule; sol for solution; tab for tablet; and susp for suspension.

(9). The absorption in humans varied from negligibility (such as acarbose and iothalamate with F being about 0.02) to about unity (22 drugs).

The correlation of extent of oral absorption of the 43 drugs between humans and dogs is shown in Fig. 1. The correlation coefficient (r^2) is 0.5123 that is much lower than 0.971 reported earlier (1) for 64 drugs between humans and rats. As shown for 16 polyethylene glycol oligomers (1,10), dogs absorbed many drugs better than humans in the present study. For example, in 12 out of the 43 drugs studied (i.e., 28%), dogs absorbed either more than 15% of the dose or two-fold (such as acarbose and iothalamate) higher than humans. The drugs showing most dramatic differences are acyclovir (2,5) and nadolol (11); F in dogs being about unity while F in humans being only about 0.20. Great differences are also found for atenolol (0.50 vs. 1.0), methyldopa (0.43 vs. 1.0), ranitidine (0.63 vs. 1.0), sumatriptan

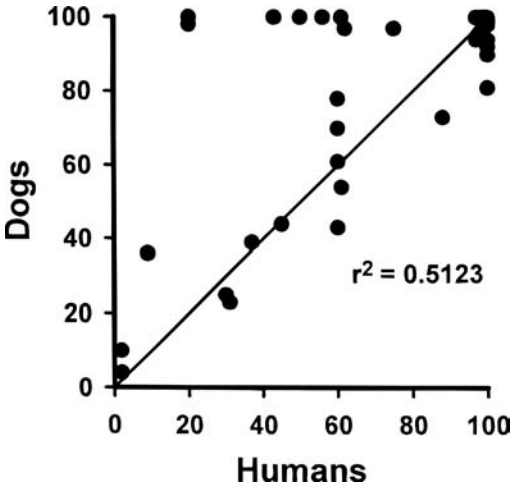

Fig. 1. Correlation of percent of oral dose absorbed between humans and dogs for the 43 drugs with a regression equation of $F_{dog} = 0.6341 F_{human} + 35.29$ ($p < 0.0001$). The straight line has a slope of one.

(0.60 vs. 0.97) and xamoterol (0.086 vs. 0.36). Only 4 drugs (doxazosin: 0.81 vs. 1.0; nitrendipine: 0.73 vs. 0.88; ramipril: 0.43 vs. 0.60; tamsulosin: 0.90 vs. 1.0) seem to be absorbed less in dogs than in humans. However, these differences are not very large and probably not practically very significant. The above results suggest that when a drug is found to be well absorbed in humans, this may also be most likely the case in dogs. However, the reverse may not be always true and the magnitude of overprediction from the dog study may be sometimes substantial. This is very much different from the consistent similarity in oral absorption between humans and rats (1).

For chlorothiazide, its oral absorption in humans, rats and dogs has been all shown to be quite dose-dependent. In humans, F values ranged from about 0.56 at 0.70 mg/kg to only 0.09 at 14 mg/kg (6). In a limited study in dogs (7), they were 0.70 at 7.3 mg/kg, 0.37 at 29 mg/kg and 0.27 at 44 mg/kg. Based on the empirical linear F vs. log dose/kg of body weight plot (Fig. 2, top), one may reasonably predict the F for this drug to be close to unity at doses around 1 mg/kg (a 100% is assumed in Table 1 and Fig. 1 for comparison purpose). At about 7 mg/kg dose, dogs absorbed chlorothiazide about 5 times better than humans (Fig. 2). Potential reasons for causing dose-dependency in the absorption of chlorothiazide in rats have been discussed earlier (6); saturable, carrier-mediated transport was postulated as a major reason for causing the observed phenomenon. Similar dose-dependent plots for acyclovir and miglitol are also shown in Fig. 2. Although miglitol was almost completely absorbed at the lowest doses studied (Table 1 and Fig. 2), dogs absorbed this drug much better than humans at other doses based on unit body weight. The above three examples clearly demonstrate a potential pronounced interspecies difference in dose-dependent absorption profiles of drugs.

Differences in oral dosage forms or formulations employed are known to be able to change the rate and/or extent of absorption of drugs. In our earlier study (1), it was assumed that the in vivo dissolution from fast-release dosage forms, such as tablets or capsules, would not significantly affect the extent of absorption or F. This appears to be true as judged by the great similarity in F between human and rat for all of the 64 drugs studied as well as by the often reported similarity in F between

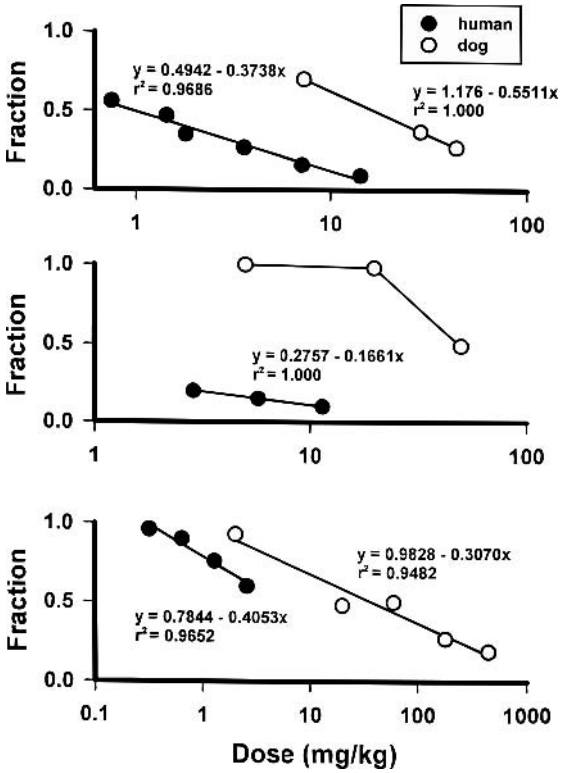

Fig. 2. Comparison of the fraction of oral dose absorbed as a function of dose per kilogram of body weight of chlorothiazide (top), acyclovir (middle), and miglitol (bottom) between humans (-●-) and dogs (-○-). Data were obtained from published studies (ref. 1–6).

solid dosage form and solution in humans (6,12). Although different dosage forms (Table 1) and formulations were employed in the oral study in humans and dogs, this factor is unlikely to play a significant or major role in accounting for the substantial differences in F observed for many drugs reported in Table 1 and Fig. 2. It is of interest to note that for acylovir, capsules were used in both humans (2) and dogs (5); for atenolol tablets in humans (2) and capsules in dogs (13); for chlorothiazide, tablets in both species (6,7); for nadolol (11) and xamoterol (14), capsules in both species. The above drugs all showed marked differences in F between humans and dogs. The fact that 16 very water-soluble polyethylene oligomers (in vivo dissolution should not be a factor) were absorbed very differently between humans and dogs (1,10) is consistent with our reasoning that the observed major differences in F between dogs and humans (Table 1 and Fig. 1) are probably mainly attributed to the interspecies difference in "intrinsic" oral absorption. In this regard, information obtained from an in vivo intestinal perfusion study in both species (15) may provide some valuable insights.

Excellent reviews and discussions on the similarities and differences in physiology, anatomy and biochemistry of the gastrointestinal tract between humans and dogs and their potential effects on drug absorption have been published (16–18). The present and previous (1,10) findings of greater extent of absorption in dogs than in humans seem contrary to the expectation from the much shorter intestinal transit time in dogs (111 ± 17 min) than in humans (4 hours; range 3–5 hours) as being pointed out earlier (17). However, it is also known that dog

Table 2. Plasma Level Peak Times (T_{max}) of Several Drugs after Oral Administration to Fasted Humans and Dogs[a]

	Dogs		Humans	
Drug	F	T_{max} (hours)	F	T_{max} (hours)
Atenolol	1.0	1.0	0.50	4.0
Famotidine	0.44	1.5	0.45	3.0
Methyldopa	1.0	1.8	0.43	3.0
Ranitidine	1.0	<0.5–1.0	0.61	3.0
Sumatriptan	0.97	0.50	0.62	1.3 (0.75–5)
Tamsulosin	0.90	0.13	1.0	1.6
Zopiclone	1.0	0.75	1.0	1.3

[a] Uncited references are available upon request.

has longer villi than man (16) which could offset the shorter intestinal transit time. In addition, dog seems to have higher bile salt secretion rate and higher bile salt concentration than human (16); this could potentially modify the intestianl membrane structure and make it more permeable for drug transport. Furthermore, the presence of higher bile salt concentrations might also facilitate the absorption of poorly water-soluble drugs due to their potential solubilizing effect. Since many water-soluble neutral compounds (10; Table 1) are absorbed better in dogs, it is possible that the size and frequency of the tight junction for paracellular transport may be greater in dogs than in humans as proposed earlier (10) for similar observation for polyethylene glycol oligomers between dogs and rats. The higher (about one unit) intestinal pH in fasted (as being the case in the studies cited here) dogs than in humans (17) may also partly account for more efficient absorption of many weak bases in dogs in light of the classical pH partition hypothesis. Differences in drug binding to the intestinal mucosa between humans and dogs may also play an important role for the species difference in absorption. This factor has been postulated for rationalizing higher absorption of iothalamate in dogs than in rats due to greater binding in dogs (19). The absorbabilities or absorption rates of various compounds such as dyes, β-lactam antibiotics and barbiturates have been shown to be more closely related to the binding to intestinal mucosa in rats than to lipoidal-aqueous partition coefficients (19). It is possible that greater binding in dogs than in humans may occur for weak acids due to stronger ionic or electrostatic interaction between the ionic drug and the mucosa, which in turn may facilitate absorption in dogs. This aspect seems to deserve further investigation. A clear understanding of mechanisms responsible for more efficient absorption in dogs may lead to a new approach to improve drug absorption (intestinal permeability or intestinal absorptive clearance, ref. 20) in humans. It is of interest to note that in spite of marked differences in intestinal permeability or absorptive clearance (20) between humans and rats (mean value of several compounds being 3.6-fold higher in humans), these two species can still have the same or similar F values for a variety of drugs (1).

A potential implication of the present findings is that the apparent intestinal first-order absorption rate constant of drugs might be, theoretically speaking, higher in dogs than in humans because of higher F values and shorter intestinal transit time in dogs (this may be true even if F between humans and dogs is the same). Although 22 drugs are shown to be virtually completely absorbed in both species, there may still exist a difference in absorption rate constants. In view of similar stomach emptying times of solutions between fasted humans and dogs (17), one may, therefore, expect shorter plasma-level peak times (T_{max}) and/or slower absorption after oral dosing of solution or fast-release dosage form to fasted dogs than to humans for many drugs. A limited review of the literature seems to support such a hypothesis as shown for several drugs (Table 2); plasma profiles for ranitidine (25,26), sumatriptan (3,27) and atenolol (13,28) are shown in Fig. 3. Among the examples

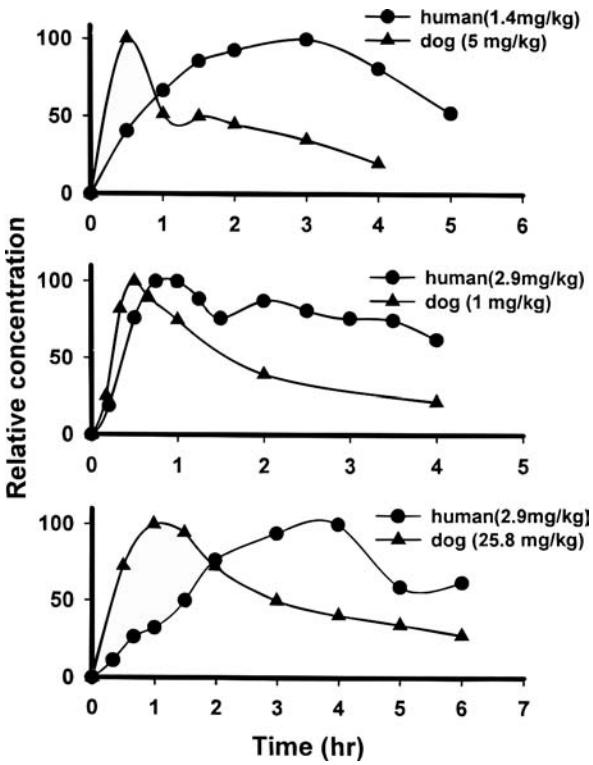

Fig. 3. Comparison of earlier mean plasma level profiles of ranitidine (top), sumatriptan (middle), and atenolol (bottom) administered to fasted humans (-●-) and dogs (-▲-). Data were obtained from published studies (ranitidine: references 25 and 26; sumatriptan: references 3 and 27; atenolol: references 13 and 28). Dosage forms employed in the studies were either solution or fast-release formulation. In the above figures, the C_{max} from each study was considered 100 unit. The fractions absorbed were 0.61 vs. 1.0, 0.62 vs. 0.97, and 0.5 vs. 1.0 in humans and dogs for the above 3 drugs, respectively.

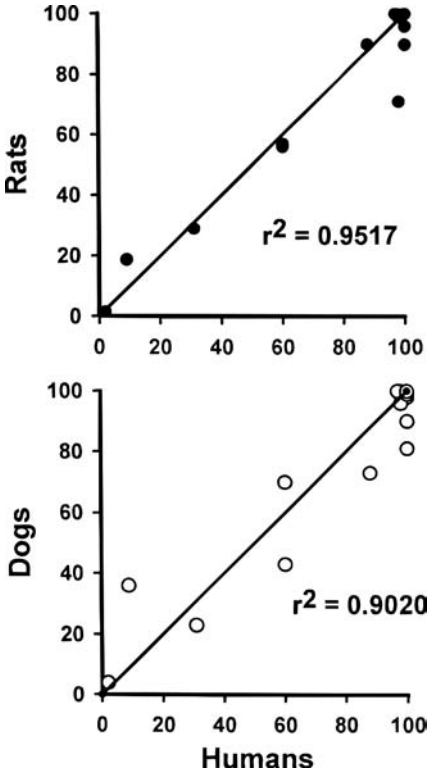

Fig. 4. Correlation of percent of oral dose absorbed between humans and rats (top) for the 18 drugs with a regression equation of $F_{rat} = 0.9469\ F_{human} + 2.578$ ($p < 0.0001$). Correlation for the same 18 drugs between humans and dogs is shown at the bottom with a regression equation of $F_{dog} = 0.8826\ F_{human} + 7.840$ ($p < 0.0001$). The straight line has a slope of one.

shown (Table 2), the extents of absorption for famotidine, tamsulosin, or zopiclone were essentially the same between humans and dogs. Potential differences in absorption rate and/or absorption extent for drugs between dog and human may partly offer a rationale as to why some preliminary bioequivalence, formulation, and drug-interaction studies conducted in dogs did not produce similar results in humans as sometimes reported in the literature. It should be noted that a shorter T_{max} in dogs might also be partly caused by a possibly faster elimination rate of drugs in dogs. This aspect may warrant a comprehensive examination.

The absorption correlation between humans and rats of 18 drugs is shown in Fig. 4. The nearly linear correlation ($r^2 = 0.9517$) without any drastic discrepancy for any drug between the two species further supports the conclusion that rat may generally serve as a reliable animal model to predict or study drug absorption in humans. The only significant discrepancy found is pelrinone with an F of 0.71 in rats (Table 1). Based on the total urinary radioactivity excretion between oral and intravenous administration, this drug was found to be almost completely absorbed in humans, dogs and mice (21). It is possible that the total radioactivity method used may underestimate the fraction of absorption in rats if the metabolites formed during the first pass in gut and liver were more extensively excreted into feces compared to intravenous administration, a known potential limitation of the method (22). In the early study (1), it was reported that enalapril (maleate) was less absorbed in rats (about 34%) than in humans (about 66%). This may be most likely attributed to the higher dose used in the rat study (23) since the drug solution administered was in the reported (24) nonlinear absorption range. For comparative purpose, the F correlation between humans and dogs for the 18 drugs is also shown in Fig. 4. It is clear that for these 18 drugs, the r^2 for correlation is much better than that for the entire 43 drugs (0.9020 vs. 0.5123), but lower than that for the rat vs. human correlation (r^2 being 0.9517 in Fig. 4). The above results indicate that caution needs to be taken in evaluating similarity or difference in oral absorption between dog and human, especially when only few compounds are examined. More in-depth studies using a larger number of drugs seem warranted.

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