



Bibliography of Scientific Papers using the Medication Event Monitoring System (MEMS®).

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PUBLICATIONS BASED ON ELECTRONIC MEDICATION EVENT MONITORING

Following is a listing of 694 publications in which the MEMS[®] have been used, or in which data from electronic monitoring figure in the content of the publication.

Updated: February 17th, 2004.

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| TOTAL | 694 |

Peer-reviewed papers

- P89-01. Cramer JA, Mattson RH, Prevey ML, Scheyer RD, Ouellette VL. How often is medication taken as prescribed? A novel assessment technique. *JAMA* 261: 3273-3277, 1989.
Also published in the December, 1989 Italian edition of *JAMA*, vol 1 (7), pp 601-8,
- P90-01. Kruse W, Weber E. Dynamics of drug regimen compliance - its assessment by microprocessor-based monitoring. *Eur J Clin Pharmacol* 38: 561-5, 1990.
- P90-02. Kruse W, Eggert-Kruse W, Rampmaier J, Runnebaum B, Weber E. Compliance with short-term high-dose oestradiol in young patients with primary infertility - new insights from the use of electronic devices. *Agents and Actions Suppl* 29. Risk Factor for Adverse Drug Reactions: Epidemiological Approaches, pp 105-115, 1990.
- P90-03. Cramer JA, Scheyer RD, Mattson RH. Compliance declines between clinic visits. *Arch Int Med* 150: 1509-10, 1990.
- P90-04. Tritsmans L, Clincke G, Peelmans B. Does AAMI constitute a real disease entity? A placebo-controlled double-blind study with sabeluzole (R 58 735) in a patient population with real memory problems. *Drug Dev Res* 20: 473-82, 1990.
- P90-05. Averbuch M, Weintraub M, Pollack DJ. Compliance assessment in clinical trials: the MEMS device. *J Clin Res Pharmacoepidemiol* 4: 199-204, 1990.
- P90-06. Rudd P, Ahmed S, Zachary V, Barton C, Bonduelle D. Improved compliance measures: applications in an ambulatory hypertensive drug trial. *Clin Pharmacol Ther* 48: 676-85, 1990.
- P90-07. Elixhauser A, Eisen SA, Romeis JC, Homan S. The effects of monitoring and feedback on compliance. *Med Care*.28: 882-893, 1990.
- P90-08. Goetghebeur EJT, Pocock SJ. Statistical issues in allowing for noncompliance and withdrawal. *Drug Information J* 27: 837-45, 1993.
- P91-01. Lueg MC, Herron J, Zellner S. Transdermal clonidine as an adjunct to sustained release diltiazem in the treatment of mild to moderate hypertension. *Clin Ther* 13: 471-81, 1991.
- P91-02. Olivieri NF, Matsui D, Harmann C, Koren G. Compliance assessed by the medication event monitoring system. *Arch Dis Child* 66: 1399-1402, 1991.
- P91-03. Kruse W, Eggert-Kruse W, Rampmaier J, Runnebaum B, Weber E. Dosage frequency and drug-compliance behaviour - a comparative study on compliance with a medication to be taken twice or four times daily. *Eur J Clin Pharmacol* 41: 589-92, 1991.
- P91-04. Paladino JA, Sperry HE, Backes JM, Gelber JA, Serriane DJ, Cumbo TJ, Schentag JJ. Clinical and economic evaluation of oral ciprofloxacin after an abbreviated course of intravenous antibiotics. *Am J Med* 91: 462-70, 1991.
- P91-05. Efron B, Feldman D. Compliance as an explanatory variable in clinical trials. *J Am Stat Assoc* 86 (413): 9-17, 1991.
This paper was selected for the JASA Applications Lecture at the 1990 Annual Meeting of the American Statistical Society, as the best applications paper submitted to *J Am Stat Assoc* (JASA)

during the preceding year.

P91-06. Matsui D, Klein J, Hermann C, Grunau V, McClelland R, Chung D, St Louis P, Olivieri N, Koren G. Relationship between the pharmacokinetics and iron excretion pharmacodynamics of the new oral iron chelator 1,2-dimethyl-3-hydroxypyrid-4-one in patients with thalassemia. *Clin Pharmacol Ther* 50: 294-8, 1991.

P92-01. Rudd P, Ahmed S, Zachary V, Barton C, Bonduelle D. Compliance with medication timing: implications from a medication trial for drug development and clinical practice. *J Clin Res Pharmacoepidemiol* 6: 15-27, 1992.

P92-02. Rubio A, Cox C, Weintraub M. Prediction of diltiazem plasma concentration curves from limited measurements using compliance data. *Clin Pharmacokinet* 22: 238-246, 1992.

P92-03. Matsui D, Hermann C, Braudo M, Ito S, Olivieri N, Koren G. Clinical use of the Medication Event Monitoring System: A new window into pediatric compliance. *Clin Pharmacol Ther* 52: 102-3, 1992.

"The introduction of the MEMS device is a breakthrough in the ability of pediatricians to differentiate between poor compliance and other pharmacokinetic and pharmacodynamic mechanisms leading to low serum concentrations and suboptimal clinical effects."

P92-04. Kruse W, Koch-Gwinner P, Nikolaus T, Oster P, Shlierf G, Weber E. Measurement of drug compliance by continuous electronic monitoring: a pilot study in elderly patients discharged from hospital. *J Am Geriatr Soc* 40: 1151-5, 1992.

P92-05. Vander Stichele RH, Thomson M, Verkoelen K, Droussin AM. Measuring patient compliance with electronic monitoring: lisinopril versus atenolol in essential hypertension. *Post-marketing Surveillance* 6: 77-90, 1992.

First report of investigator fraud detected by MEMS[®] Monitoring.

P92-06. Weidler D, Wallin JD, Cook E, Dillard D, Lewin A. Transdermal clonidine as an adjunct to enalapril: an evaluation of efficacy and patient compliance. *J Clin Pharmacol* 32: 444-9, 1992.

P92-07. Park DC, Morrell RW, Frieske D, Kincaid D. Medication adherence behaviors in older adults: effects of external cognitive supports. *Psychol Aging* 1992; 7:252-6.

P92-08. Lee CR, Nicholson PW, Souhami RL, Deshmukh AA. Patient compliance with oral chemotherapy as assessed by a novel electronic technique. *J Clin Oncol* 1992 Jun;10(6):1007-13

P93-01. Waterhouse DM, Calzone KA, Mele C, Brenner DE. Adherence to oral tamoxifen: a comparison of patient self-report, pill counts, and microelectronic monitoring. *J Clin Oncology* 11: 1189-97, 1993.

P93-02. Matsuyama JR, Mason BJ, Jue SG. Pharmacists' interventions using an electronic medication-event monitoring device's adherence data versus pill counts. *Ann Pharmacother* 27: 851-5, 1993.

P93-03. Guerrero D, Rudd P, Bryant-Kosling C, Middleton BF. Antihypertensive medication-taking. Investigation of a simple regimen. *Am J Hypertension* 6:586-92, 1993.

INPHARMA summarized this paper as follows (4 Sept 93):

"Pill counts overestimate patient compliance say US researchers, and their continued use in clinical trials may be harmful. The belief that pill counts are reliable may mislead investigators, pharmaceutical industry sponsors and regulators, unless validating recording methods such as electronic monitoring are used to assess compliance. In particular, incorrect assessment of

compliance may lead to 'potentially dangerous approval of excessive dosages'.
"The researchers assessed medication taking behaviour among 19 patients with hypertension, using both pill counts and electronic monitoring. Patients took 1 pill per day for 63 weeks or more and pill taking was assessed at 1- to 4-week intervals. The study revealed that changes in medication-taking behaviour early in therapy may predict subsequent patient compliance rates and that prolonging drug action may compensate for some imperfect medication-taking behaviour."

P93-04. Levy G. A pharmacokinetic perspective on medicament noncompliance. *Clin Pharmacol Ther* 54: 242-4, 1993.

P93-05. Kruse W, Eggert-Kruse W, Rampmaier J, Runnebaum B, Weber E. Compliance and adverse drug reactions: a prospective study with ethinylestradiol using continuous compliance monitoring. *Clin Investigator* 71, 483-7, 1993.

P93-06. Kruse W, Nikolaus T, Rampmaier J, Weber E, Schlierf G. Actual versus prescribed timing of lovastatin doses assessed by electronic compliance monitoring. *Eur J Clin Pharmacol* 44: 211-15, 1993.
"Pill counts overestimated compliance, as revealed by the monitoring method. The times of actual consumption of doses by the patients often differed from that prescribed, predominantly in patients who were told to take the evening dose. Partial time compliance may have confounded the efficacy of the drugs. Electronic compliance monitoring appears to be particularly useful in chronopharmacological studies."

P93-07. Goetghebeur EJT, Pocock SJ. Statistical issues in allowing for noncompliance and withdrawal. *Drug Information J* 27: 837-45, 1993.

P93-08. Urquhart J. Variable patient compliance in ambulatory trials -- nuisance, threat, opportunity. *J Antimicrobial Chemotherapy* 32: 643-9, 1993.

P93-09. Rudd P, Ramesh J, Bryant-Kosling C, Guerrero D. Gaps in cardiovascular medication taking: the tip of the iceberg. *J Gen Int Med* 8: 659-66, 1993.

P93-10 Mengden T, Binswanger B, Spühler T, Weisser B, Vetter W. The use of self-measured blood pressure determinations in assessing dynamics of drug compliance in a study with amlodipine once a day, morning versus evening. *J Hypertension* 11: 1403-11, 1993.
"Neither causal nor ambulatory day- or night-time readings detected a significant difference between morning and evening administration. However, self-measurement documented significantly greater blood pressure reductions for morning than for evening administration. The MEMS showed different compliance on the days of ambulatory monitoring (100% with both drug regimens) compared with the whole treatment period. The number of days with missed medication was thus significantly higher for the evening dosing regimen. The difference in self-measured blood pressure between the two regimens was lost if the days with missed medication were removed from the statistical analysis."

P93-11. Lee CR, Nicholson PW, Souhami RL, Slevin ML, Hall MR, Deshmukh AA. Patient compliance with prolonged low-dose oral etoposide for small cell lung cancer. *Br J Cancer* 1993 Mar;67(3):630-4

P93-12. Erickson J. The cost of medication noncompliance. *AAPPO J* 1993 Apr-May;3(2):33-4, 38-40

P94-01. Kruse W, Rampmaier J, Ullrich G, Weber E. Patterns of drug compliance with medication to be taken once and twice daily assessed by continuous electronic monitoring in primary care. *Int J Clin Pharmacol Ther* 32: 453-7, 1994.

"Days without any dosing events were twice as often with the QD than the BID regimen. ... Episodes of 3 or more subsequent days without dosing events ... were also observed more often with the QD than the BID regimen. ... Doses were omitted more frequently on weekends than on any other day of the week ... ($p < 0.001$). ... Evening doses were omitted about twice as often as ... morning doses [in] ... patients prescribed the BID regimen ($p < 0.001$)."

P94-02. Petri H, Urquhart J. Patient compliance with beta-blocker medication in general practice. *Pharmacoepidemiology Drug Safety* 3: 251-6, 1994.

P94-03. Steiner TJ, Catarci T, Hering R, Whitmarsh T, Couturier EGM. If migraine prophylaxis does not work, think about compliance. *Cephalalgia* 14: 463-4, 1994.

"It is possible that all evaluations of efficacy and tolerance of migraine prophylactics reported so far have been unsoundly based [because of unrecognized variable compliance]."

P94-04. Detry J-M R, Block P, De Backer G, Degaute J-P, Six R. Patient compliance and therapeutic coverage: amlodipine versus nifedipine (slow-release) in the treatment of angina pectoris. *J Intl Med Res* 22: 278-86, 1994.

P94-05. Matsui M, Hermann C, Klein J, Berkovitch M, Olivieri N, Koren G. Critical comparison of novel and existing methods of compliance assessment during a clinical trial of an oral iron chelator. *J Clin Pharmacol* 34: 944-949, 1994.

P94-06. Brun J. Patient compliance with once-daily and twice-daily oral formulations of 5-isosorbide mononitrate: a comparative study. *J Int Med Res* 22: 266-72, 1994. (erratum published *ibid*, p 350)
"... compliance assessed using the electronic Medication Event Monitoring System (MEMS) was better with the once-daily than with the twice-daily formulation; patients on the once-daily regimen performed better with respect to the total number of bottle openings, the number of openings per day, the timing of openings and the intervals between openings. The apparently superior compliance with the once-daily regimen appeared to be reflected in better efficacy; patients on the once-daily regimen experienced fewer angina attacks (a mean of 1.7 per 7 days, compared with 3.3 per 7 days for patients on the twice-daily regimen) and used fewer nitroglycerin tablets than those on the twice-daily regimen."

P94-07. Wallen NH, Andersson A, Hjemdahl P. Effects of treatment with oral isosorbide dinitrate on platelet function in vivo; a double-blind placebo-controlled study in patients with stable angina pectoris. *Br J Clin Pharmacol.* 38: 63-70, 1994.

P94-08. Schwed-Girardin A, Darioli R. Evaluation de la compliance thérapeutique: breve revue des différentes méthodes de mesure et de leur application aux traitements hypolipémiants. *Med-Hyg* 52: 561-3, 1994.

P94-09 Erne P, Saxenhofer H, Waeber B, Heynen G. The time of intake for antihypertensive and antianginous medication. *Schweizerische Rundschau für Medizin/Praxis* 1994; 83:1079-1083.

P94-10. Kraag GR, Gordon DA, Menard HA, Russell AS, Kalish GH. Patient compliance with tenoxicam in family practice. *Clin Ther* 1994 May-Jun;16(3):581-93

P94-11. Waeber B, Erne P, Saxenhofer H, Heynen G. Use of drugs with more than a twenty-four-hour duration of action. *J Hypertens Suppl* 1994 Nov;12(8):S67-71

P94-12. Kalvik, A., Kwok, M., Tseng, A., Currie, N., Busto, U. E. and Naranjo, C. A. Variations in medication

management systems (MEMS) performance. *Clinical Pharmacology and Therapeutics*, 55, 157.

P95-01. Sheiner LB, Rubin DB. Intention to treat analysis and the goals of clinical trials. *Clin Pharmacol Ther* 57: 6-15, 1995.

ABSTRACT: Intention-to-treat analysis, where the analyst essentially discards all information about compliance to assigned treatment, is the standard analytic approach to randomised clinical trials. When non-compliance is present, however, intention-to-treat analysis estimates only so called use-effectiveness, the average outcome difference attributable to prescribing, but not necessarily taking, the alternative treatments. Method effectiveness, the expected outcome difference among patients from some clinically relevant population if they did, in fact, adhere to their assigned regimen is an important issue, and trial results should also be analysed to estimate it. After discussing the usual estimators of treatment effect, including the intention-to-treat estimator, we emphasize that model-based analyses involving at least a model for the assignment mechanism (i.e., a model for how actual, not intended treatment is "assigned"), along with data on compliance and possibly on prognostically important covariates, can sometimes provide unbiased estimates of method-effectiveness despite non-compliance.

P95-02. Detry J-M R, Block P, De Backer G, Degaute J-P, Six R. Patient compliance and therapeutic coverage: comparison of amlodipine versus nifedipine (slow-release) in the treatment of hypertension. *Eur J Clin Pharmacol* 47: 477-81, 1995.

P95-03. Cramer J, Vachon L, Desforges C, Sussman NM. Dose frequency and dose interval compliance with multiple antiepileptic medications during a controlled clinical trial. *Epilepsia* 36: 1111-7, 1995.

"The number of medications prescribed did not affect overall compliance because patients almost always took all tablets and capsules together if they took any medication."

P95-04. Mason BJ, Matsuyama JR, Jue SG. Assessment of sulfonylurea adherence and metabolic control. *Diabetes Educ.* 21: 52-7, 1995.

"Assessment of medication adherence by provider, patient, and pill counts did not explain metabolic control as closely as assessment by MEMS."

P95-05. Mallion JM, Dutrey-Dupagne C, Vaur L, Genes N, Renault M, Baguet P, Boutelant S, Elkik F. Comportement des patients ayant une hypertension artérielle légère à modérée vis-à-vis de leur traitement. Apport du pilulier électronique. *Ann Cardiol Angeiol* 44: 597-605, 1995.

"Various profiles were distinguished on the basis of the individual chronograms for the 501 patients able to be analysed in terms of compliance, and as a function of the deviations observed in relation to the treatment regimen prescribed. One hundred and two patients (20%) omitted more than 20% of the prescribed doses, either consecutive doses or scattered throughout the month of treatment; these patients were referred to as 'omitters'. The other patients were classified according to the scatter of openings in relation to the mean time of the dose: 10 'metronome' patients (2%), 126 'regular', patients (25%), 221 'irregular', patients (44%) and 42 'anarchic', patients (8%). Irregularities of dose times were more frequent on public holidays than on week days and in patients living in Paris or the Paris region."

P95-06. Magometschnigg D. Compliance von hypertonikern in der ärztlichen praxis. *Wien Med Wochenschr.* 145 360-364, 1995.

P95-07. Olivieri NF, Brittenham GM, Matsui D, et al. Iron-chelation therapy with oral deferiprone in patients with thalassemia major. *N Engl J Med* 332: 918-22, 1995.

P95-08. Wall TL, Sorensen JL, Batki SL, Delucchi KL, London JA, Chesney MA. Adherence to zidovudine

(AZT) among HIV-infected methadone patients: A pilot study of supervised therapy and dispensing compared to usual care. *Drug Alcohol Depend.* 37: 261-9, 1995.

"Results suggest supervised therapy and dispensing may be an effective strategy for improving AZT adherence, but only while provided."

P95-09. Carney RM, Freedland KE, Eisen SA, Rich MW, Jaffe AS. Major depression and medication adherence in elderly patients with coronary artery disease. *Health Psychology*; 14:88-90, 1995.

P95-10. Detry JM, Block P, De Backer G, Degaute JP. Patient compliance and therapeutic coverage: comparison of amlodipine and slow release nifedipine in the treatment of hypertension. The Belgian Collaborative Study Group. *Eur J Clin Pharmacol* 1995;47(6):477-81

P95-11. al-Refaie FN, Hershko C, Hoffbrand AV, Kosaryan M, Olivieri NF, Tondury P, Wonke B. Results of long-term deferiprone (L1) therapy: a report by the International Study Group on Oral Iron Chelators. *Br J Haematol* 1995 Sep;91(1):224-9

P96-01. de Klerk E, van der Linden Sj. Compliance monitoring of NSAID drug-therapy in ankylosing spondylitis, experiences with an electronic monitoring device. *Br J Rheumatol* 35: 60-5, 1996.

P96-02. Mallion J-M, Dutry-Dupagne C, Vaur L, Genes N, Renault M, Elkik F, Baguet P, Boutelant S. Benefits of electronic pillboxes in evaluating treatment compliance of patients with mild to moderate hypertension. *J Hypertens* 14: 137-44, 1996.

"... the prescription of an antihypertensive medication with an action span greater than 24h would allow sufficient therapeutic coverage while respecting difference in patient's lifestyle."

P96-03. Lee JY, Kusek JW, Greene PG, Bernhard S, Norris K, Smith D, Wilkening B, Wright JT Jr, for the AASK Pilot Study Investigators. Assessing medication adherence by pill count and electronic monitoring in the African American study of kidney disease and hypertension (AASK) pilot study. *Am J Hypertens* 9: 719-25, 1996.

P96-04. Geletko, SM, Segarra M, Mayer KH, Figre TC., Bettencourt FA, Flanigan TP, Dudley MN. Electronic compliance assessment of antifungal prophylaxis for human immunodeficiency virus-infected women. *Antimicrobial Agents and Chemotherapy* 40: 1338-41, 1996.

"Many women were very enthusiastic about seeing the computer display of compliance. Patients often wanted to know their medication compliance rates over the previous 3-month period, and many were encouraged when they saw that they had been compliant. In addition, during refill appointments with MEMS readings, the patients would often explain why the medication dosages were missed on certain days, which was helpful in gathering accurate dosing histories."

P96-05. Barter LS, Watson ADJ, Maddison JE. Owner compliance with short term antimicrobial medication in dogs. *Aust Vet J* 74: 277-280, 1996

P96-06. Ekstom E-C, Kavishe FP, Habicht J-P, Frongillo EA Jr, Rasmussen KM, Hemed L. Adherence to iron supplementation during pregnancy in Tanzania: determinants and hematologic consequences. *Am J Clin Nutr* 64: 368-74, 1996.

P96-07. Girard P, Sheiner LB, Kastrissios H, Blaschke TF. Do we need full compliance data for population pharmacokinetic analysis? *J Pharmacokinetics Biopharm* 24: 265-82, 1996.

Abstract of paper follows:

“For population pharmacokinetic analysis of multiple oral doses one of the key issues is knowing as precisely as possible the dose inputs in order to fit a model to the input-output (dose-concentration) relationship. Recently developed electronic monitoring devices, placed on pill containers, permit precise records to be obtained over months, of the time/date opening of the container. Such records are reported to be the most reliable measurement of drug taking behavior for ambulatory patients. To investigate strategies for using and summarizing this new abundant information, a Markov chain process model was developed, that simulates compliance data from real data from electronically monitored patients, and data simulations and analyses were conducted. Results indicate that traditional population pharmacokinetic analysis methods that ignore actual dosing information tend to estimate biased clearance and volume and markedly overestimate random interindividual variability. The best dosing information summarization strategies consist of initial estimating population pharmacokinetic parameters, using no covariates and only a limited number of dose records, the latter chosen based on an a priori estimate of the half-life of the drug in the compartment of interest; then resummarizing the dose records using either population or individual posterior Bayes parameter estimates from the first population fit; and finally reestimating the population parameters using the newly summarized dose records. Such summarization strategies yield the same parameter estimates as using full dosing information records while reducing by at least 75% the CPU time needed for a population pharmacokinetic analysis.”

P96-08. Potter L, Oakley D, de Leon-Wong E, Canamar R. Measuring compliance among oral contraceptive users. *Family Planning Perspectives* 28:154-158, 1996.

See also the detailed statistical report listed as E95-4.

P96-09. Milgrom H, Bender B, Ackerson L, Bowry P, Smith B, Rand C. Noncompliance and treatment failure in children with asthma. *J Allergy Clin Immunol* 98: 1051-7, 1996.

“The children failed to comply with inhaled corticosteroid therapy, they misrepresented their steroid use, and they did so with the tacit approval of their parents. Failure to comply was linked with exacerbation of disease and the resultant need for administration of systemic steroids and hospitalization. Both the human toll and the financial burden may have been reduced by more conscientious adherence and reliable reporting. Inadequate control of asthma should alert the physician to the possibility of noncompliance, a behavior that is widespread and clearly not limited to those who are poorly informed or overtly uncooperative. A compelling need exists for objective means of assessing adherence because patient reports are unreliable and physicians do not judge compliance accurately. As clinicians, we must find ways that will encourage patients to comply with their therapy. It is evident that providing them with accurate information, though necessary, is not sufficient. Our responsibility extends beyond accurate diagnosis and appropriate recommendations. It is essential that we acknowledge and accept the responsibility for patient compliance, a direction more likely to result in better control of asthma than efforts to seek out more aggressive or innovative therapies.”

P96-10. Straka RJ, Fish JT, Benson SR, Suh JT. Magnitude and nature of noncompliance with treatment using isosorbide dinitrate in patients with ischemic heart disease. *J Clin Pharmacol* 36: 587-594, 1996.

P96-11. Barter LS, Maddison JE, Watson ADJ. Comparison of methods to assess dog owners' therapeutic compliance. *Aust Vet J* 74: 443-446, 1996.

P96-12. Lee CR, Nicholson PW, Ledermann JA, Rustin GJS. Patient compliance with prolonged oral

altretamine treatment in relapsed ovarian cancer. *Eur J Gyneac Oncol* 17: 99-103, 1996

P96-13. Burney KD, Krishnan K, Ruffin MT, Zhang D, Brenner DE. Adherence to single daily dose of aspirin in a chemoprevention trial: An evaluation of self-report and microelectronic monitoring. *Arch Family Med*. 5:297-300, 1996.

An editor's note was added to the publication:

'Only 35% compliance by the monitoring system and self-report! I agree with the author. If an educated group of individuals, who volunteer to take a once-daily medicine, agreed to undergo sigmoidoscopic biopsies, and are paid, cannot be compliant for 2 weeks, who is? This makes me rethink some of my patients who swear they are compliant but with other data (such as protimes) suggesting otherwise. Marjorie A. Bowman, MD, MPA.

P96-14. Kastrissios H, Flowers NT, Blaschke TF. Introducing medical students to medication noncompliance. *Clin Pharmacol Ther* 59: 577-82, 1996.

P96-15. Geletko SM, Segarra M, Ravin DS, Babich MP. Zidovudine compliance as measured by different methods in an HIV ambulatory clinic. *J PHARM TECHNOL. Journal of Pharmacy Technology* 1996; 12:105-108.

P96-16. Mason BJ, Matsuyama JR, Jue SG. Use of a medication event monitoring system to assess sulfonylurea timing and dosing intervals. *Journal of Geriatric Drug Therapy* 1996; 11, 53-59.

P96-17. Mason BJ. Anticoagulant clinic warfarin adherence rates and assessment. *Journal of Pharmacy Technology* 1996 12, 97-101.

P96-18. Dutrey-Dupagne C, Vaur L, Genes N, Mallion JM, Meredith P, Elkik F. Errors in trough: peak ratio determinations induced by patient behaviour. *Blood Press Monit* 1996 Jun;1(3):273-277

P96-19. Mallion JM, Asmar R, Ambrosioni E, MacMahon M, Coupeze JM, de Cordoue A, Barrandon S, Brault Y, Guez D, Safar M. Evaluation of trough/peak ratio of indapamide 1.5 mg sustained-release form assessed by ambulatory blood pressure monitoring [Article in French]. *Arch Mal Coeur Vaiss* 1996 Sep;89 Spec No 4:27-38

P96-20. Mason BL, Matsuyama JR, Jue SG. Microprocessor-assessed adherence with once- or twice-a-day dosing with Sulfonylurea--no difference. *West J Med* 1996 Feb;164(2):182

P97-01. de Klerk E, van der Linden S, van der Heijden D, Urquhart J. Facilitated analysis of data on drug regimen compliance. *Stat Med* 16: 1653-64, 1997.

P97-02. Leenen FH, Wilson TW, Bolli P, Larochelle P, Myers M, Handa SP, Boileau G, Tanner J. Patterns of compliance with once versus twice daily antihypertensive drug therapy in primary care: a randomized clinical trial using electronic monitoring. *Can J Cardiol*. 13: 914-20, 1997.

"The results suggest that the negative consequences of partial compliance for blood pressure control can be offset by choosing agents with a duration of action well beyond the dosing interval."

P97-03. Vrijens B, Goetghebeur E. Comparing compliance patterns between randomized treatments. *Controlled Clin Trials* 18: 187-203, 1997.

P97-04. Paes AH, Bakker A, Soe-Agnie CJ. Impact of dosage frequency on patient compliance. *Diabetes Care* 20: 1512-1517, 1997.

- P97-05. Straka RJ, Fish JT, Benson SR, Suh JT. Patient self-reporting of compliance does not correspond with electronic monitoring: an evaluation using isosorbide dinitrate as a model drug. *Pharmacotherapy* 17: 126-132, 1997.
- P97-06. Roache JD, Stanley MA, Creson DR, Shah NN, Meisch RA. Alprazolam-reinforced medication use in outpatients with anxiety. *Drug Alcohol Depend* 45: 143-155, 1997.
- P97-07. Favre O, Delacretaz E, Badan M, Glauser M, Waeber B. Relationship between the prescriber's instructions and compliance with antibiotherapy in outpatients treated for an acute infectious disease. *J Clin Pharmacol* 37: 175-178, 1997.
- P97-08. Insull W. The problem of compliance to cholesterol altering therapy. *J Intern Med* 241: 317-325, 1997.
- P97-09. Jonsson EN, Wade JR, Almqvist G, Karlsson MO. Discrimination between rival dosing histories. *Pharm Res* 14: 984-991, 1997.
- P97-10. Blowey DL, Hebert D, Arbus GS, Pool R, Korus M, Koren G. Compliance with cyclosporine in adolescent renal transplant recipients. *Pediatr Nephrol* 11 (5): 547-551, 1997.
- P97-11. Curtin RB, Svarstad BL, Andress D, Keller T, Sacksteder P. Differences in older versus younger hemodialysis patients' noncompliance with oral medications. *Geriatr Nephrol Urol* 7 (1): 35-44, 1997.
- P97-12. Grabowski J, Roache JD, Schmitz JM, Rhoades H, Cheson D, Korszun A. Replacement medication for cocaine dependence: methylphenidate. *J Clin Psychopharmacol* 17: 485-488, 1997.
- P97-13. Oakley D, Potter L, de Leon-Wong E, Visness C. Oral contraceptive use and protective behavior after missed pills. *Fam Planning Perspect* 29: 277-9, 1997.
- P97-14. Curtin RB; Svarstad BL; Andress D; Keller T; Sacksteder P. Differences in older versus younger hemodialysis patients' noncompliance with oral medications. *Geriatr Nephrol Urol* 7:35-44, 1997.
- P97-15. van der Meer JM, Briet E, Vandenbroucke JP, Sramek DI, Versluis MHPM, Rosendaal FR. The role of compliance as a cause of instability in oral anticoagulant therapy. *Br J Haematol* 1997;98:893-900
- P97-16. DeMyttenaere K. Compliance during treatment with antidepressants. *J Affect Disord* 43: 27-39, 1997.
- P97-17. Burnier M, Schneider M.P, Waeber B. L'observance thérapeutique dans le traitement de l'hypertension artérielle: un facteur important à évaluer. *Méd. Hyg* 1997; 2175: 1591-1594.
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In discussion of the papers, of which this was one, from the Limburg Compliance Symposium, Sir David Cox commented: "It is excellent, however, that the first paper, by Drs. Urquhart and de Klerk, gives a fascinating account of measurement and definitional questions connected to compliance. The ideas and new methods outlined in that paper surely have major implications for design and statistical analysis." *Stat Med* 17: 387, 1998.

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This paper described the effect of simple medication usage skills on compliance among patients with bipolar and psychotic disorders. Patients were randomized to either a control group with usual care or an intervention group that received special instructions on life skills and reinforcing techniques on

how to develop cues to remember doses. Compliance rates were significantly higher for patients who received the intervention. These preliminary data demonstrate the potential applicability of a simple, focused intervention technique to enhance medication-taking behavior.

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ABSTRACT: Nonadherence to treatment is a common problem in the clinical management of hypercholesterolemic patients. This study was carried out with the aim of monitoring the daily compliance to a 6-month course of lipid-lowering therapy, using a microelectronic device, the Medication Event Monitoring System (MEMS™), versus pill count. Forty men with primary hypercholesterolemia were prescribed fluvastatin 1 x 40 mg daily, provided in a MEMS package to record the date and time of each opening of the pillbox. Thirty-nine of 40 patients (98%) completed the study. Total cholesterol and LDL cholesterol levels decreased significantly (18% and 25%, $p < 0.01$) during the 6-month therapy period. A high mean rate of compliance was achieved by MEMS(TM) using the following three indexes-compliance to total prescribed dose (88.8% +/- 13.5%), compliance to prescribed days (82.4% ± 19.5%), and compliance to prescribed time of day (81.86% +/- 19.5%)-and by pill count (93.4% ± 9.5%). In addition, the MEMS(TM) provided some patterns of nonadherence to medication, undetectable by pill count alone, such as a drug holiday in 38% of cases, a drug omission for more than 7 consecutive days in 9% of cases, and, conversely, use of more than the one prescribed daily dose in 47% of cases. A significant correlation between the rate of compliance and the decrease in LDL cholesterol was observed only when the compliance was assessed by MEMS. The results indicate that MEMS is a useful tool for monitoring compliance in clinical practice and may possibly increase adherence to long-term lipid-lowering therapy.

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Comment: the findings in this paper illustrate how the compliance-correlates of observed therapeutic effectiveness can reveal the degree of forgiveness provided by the pharmaceutical in question, when prescribed at its recommended dose. Patients' actual dosing histories are almost invariably skewed downwards, towards varying degrees of under-dosing, relative to the prescribed regimen. It is important for good outcomes of treatment that the recommended regimen provide some degree of forgiveness for delayed and omitted doses. If, however, the degree of forgiveness seems excessive, as the Bachmann paper suggests may be the case for doxycycline treatment of *C. trachomatis* infections, then the results can be interpreted as support for the hypothesis that the recommended dose is set higher than necessary, and might beneficially be reduced. Indeed, the recommended doses of many pharmaceuticals have been discovered in the marketplace during the past two decades to be higher than necessary – see the papers by Cross et al. & by Heerdink et al. in *Pharmacoepidemiology & Drug Safety* 11: 439-446, and 447-453, 2002. In the editorial (E-99-5) that accompanies the Bachmann paper, the editorialist worries about potential biases, which may or may not be present, but which can, in any case, be resolved by treating the results in the Bachmann paper as “learning” (or hypothesis-generating) and then proceeding to test their validity in a suitably controlled “confirming” study, as described by Sheiner in his now-classic paper on the learn-confirm

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Following is the article's conclusion (emphasis added):

"The literature is replete with reports of counselling patients to improve compliance. Unfortunately, most studies used inadequate methodology to assess compliance (i.e., performed before the 'gold standard' microelectronic monitoring methods were developed). Such studies have not documented the cost effectiveness of counselling programmes, apart from research settings, because of the time required for a professional counsellor. In clinical practice, few healthcare providers have the luxury of spending half an hour with a patient to discuss health beliefs or attempt to modify patient behaviour.

"The availability of microelectronic monitoring and feedback systems could change the cost equation. Computer-generated reports are instantly available and require less than 5 minutes for a complete review and discussion because most of the data are self-explanatory. For example, a patient who sees that their calendar shows no doses on weekends clearly comprehends the need for a better reminder plan for Saturday and Sunday doses. The frequent missing of bedtime doses demonstrates the need for an evening cue. Spending a few minutes to show patients how to tailor their medication regimens to fit into their schedules could greatly enhance overall compliance with medications. Currently available microelectronic monitoring systems allow clinicians to better understand patient dose-taking behaviours, and to utilise those data to help patients develop schedules that meet the individual's lifestyle.

"Microelectronic monitoring systems allow healthcare providers a better understanding of whether a medication (or dosage) has failed because of lack of efficacy, or failure of the patient to take the medication as prescribed. These issues are important in considering the cost of medical care as well as outcomes for individual patients. If available, dose frequency calendars and dose interval lists could be used as easily as results of blood tests. The data are not presented as a mark of a malingerer, but as evidence that the reason why less-than-expected efficacy is found is because the prescribed regimen is not being followed. Many people who take medications long term have neither any concept of how poorly they comply nor thoughts about how to enhance compliance by developing special tactics to remember dose times. It may be easier and more cost effective to monitor patients and use the electronically generated reports to help the physician and patient to see both the dose pattern and impact of partial compliance on outcome than to attempt behaviour modification for a population.

"In conclusion, the potential gains in improved self-care of individual patients, as well as clinical trial efficiency, are well worth the cost of monitoring units, particularly within the cost equation of managed care systems."

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With the use of electronic monitoring, the temporal relationship between an individual's pattern of dosing and the prescribed regimen may be examined, and individual drug exposure may be estimated based on the actual history of dosing. As a result, accurate estimation of exposure-response relationships (or surrogate markers of response) can be obtained. Considerations in the design of clinical trials must therefore be expanded to include appropriate methods to measure

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Background: The explanatory power of measured antiretroviral drug exposure on virologic response in human immunodeficiency virus (HIV) infections is of great interest. Past studies showed the impact of aggregate intake of protease inhibitors (see, e.g., 1-3), but the impact of variations in dose-timing is still unclear. Substantial errors in dose timing occur in some patients who take all, or almost all, of the pre-scribed number of doses. Timing errors are incompletely characterized by the sometimes-used para-meter 'percentage of treatment days during which the correct number of doses were taken'. Here we look directly at the explanatory power of variations in interdose intervals. For reasons of taxonomic coherence (cf. 4), we use the term 'patient compliance' to mean 'the extent to which the patient's recorded dosing history corresponds to the prescribed regimen of drug administration'. This definition includes information on the timing of doses, and intervals between doses, as well as the amount of drug ingested.

Methods: From electronically compiled dosing histories (MEMS®, AARDEX Ltd) of naïve patients taking various protease inhibitors (5), we derived the usual parameters of patient compliance, i.e., percentage of prescribed doses taken, percentage of treatment days during which the correct number of doses were taken. We also derived a new parameter: Timing Error, which is related to the 3rd moment of the distribution of interdose intervals (6). We modeled viral load as a series of 4 ranges from <50 to >2000 copies/ml and examined analysis-derived probabilities for transitions between ranges. We compared the goodness of fit results from the analysis based on Timing Error vs other parameters of compliance, to predict rises or falls in viral load.

Results: Timing Errors were superior predictors of changes in viral load, compared to analyses based on the usual parameters of patient compliance. This result suggests that a few substantially prolonged inter-dose intervals have greater impact on viral load than do many marginally prolonged interdose intervals. Plots of Timing Error on the probabilities of change in viral load differ among protease inhibitors, suggesting that drugs of this class have differing degrees of forgiveness for longer interdose intervals.

Conclusion: Dose-timing data increase the explanatory power of data on patient compliance for antiretroviral treatment outcomes. The results suggest that avoidance of long interdose intervals should be a priority in efforts to improve patient compliance. We expect that the explanatory power of dose-timing data will vary from one drug and treatment situation to another. Further work is obviously needed.

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First description of the parameter, Therapeutic Coverage. Text follows:

"Partial compliance signifies sub-optimal dosing. Its consequences can be analyzed by jointly considering (a) the drug's pharmacodynamics and (b) data on dose timing from electronic compliance monitoring. Ideally, dose timing data would be input to a dynamic model of dose-dependent drug actions, projecting intervals of subtherapeutic drug action (ISDA). Duration and incidence of ISDA are pharmacodynamically logical correlates for analyzing dose-dependent bases for therapeutic failure, such as "breakthrough" events (e.g., seizures during anti-epileptic treatment), not achieving an endpoint (e.g., reversing cardiac hypertrophy during hypertension treatment), etc. Data often are insufficient for dynamic modeling, but one can estimate duration and incidence of ISDA by noting when and for how long interdose intervals exceeded the drug's duration of action -- routinely measured, when feasible, for regimen optimization. Therapeutic Coverage (%TC) lumps computed ISDA as: $100 \times [\text{Duration of Treatment} - \Sigma \text{ISDA}] \div [\text{Duration of Treatment}]$. %TC puts compliance data on a pharmacodynamic basis that "% of prescribed doses taken", which ignores dose timing, cannot."

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Text of abstract follows:

Since the development in 1986-7 of reliable chemical markers (CM) and electronic monitoring (EM), the variability of dosing in ambulatory trials and practice has been shown to be far greater than indicated by older methods -- pill counts, spot checks of drug levels, histories (1-4). CM and EM show predominant skew towards dose omission, with widely variable intervals between doses, though dosing in the day or two prior to scheduled visits is usually correct (1). The indelibly time/date-stamped record of EM has many uses.

EM is a primary source document of the patient's progress through a treatment protocol, sturdy enough to reveal instances of investigator fraud (5,6). Clinical correlates of variable dosing in nominally fixed-dose drug trials provide pragmatic information on dose-dependent drug action (7-9). Levy showed how dose-response parameters modulate consequences of variable dosing (10). "Compliance" can now be seen in PK/PD terms as the degree of correspondence between actual and prescribed time histories of dosing. EM data were used with a PK model to project the entire time history of drug concentrations in plasma during a multi-week study (11). If the drug's post-dose duration of action (D_a) is known, Therapeutic Coverage (TC) can be computed thus: a segment, S_i , of the i^{th} inter-dose interval, that exceeds D_a , is considered a period of sub-optimal or absent drug action. TC is computed by summing the S_i , subtracting the sum from the EM period, and expressing the result as % of the EM period. Thus, 100% TC signifies no interdose interval $>D_a$; when TC is $<100\%$, the circadian timing of S_i is informative. Long S_i (drug "holidays") mark periods of long-lapsed efficacy, useful if prior knowledge specifies a critical S_i , as with oral contraceptives (12); if not, efficacy correlates of S_i help to develop such information. S_i mark times of likely rebound effects, as with non-ISA beta blockers (13). Correlates of abruptly resumed dosing after long S_i may reveal transient toxicity. Monte Carlo or bootstrap projections of dosing histories from trials may suggest pro-

active steps to prevent hazardous dosing in market-sized populations.

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Assessing the robustness of competing dose regimens to incomplete compliance
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In drug development, non-compliance to the prescribed regimen is the Cinderella of pharmacotherapy. However, instead of being an ignored beauty, its consequences are ugly: poor characterisation of the dose response relationship, improper selection of the optimal dosage regimen and overall increased risk to patients. The clinical pharmacology of interrupted dosing ("pharmacolapsy") is a mostly unwritten book about a frequently recurring event. One of the key decisions in drug development beyond the actual dose strength is the choice of the dose interval. Nowadays it has become almost an imperative to develop drugs that can be taken once daily. One of

the reasons commonly touted for this is that patients are more compliant on QD regimens. While there seems to be a relationship between noncompliance and increased frequency of dosing, there is much evidence to support the fact that the impact of QD vs BID dosing with respect noncompliance is minor (approx. 73 vs 70%)[1]. The impact of noncompliance on a particular pharmacotherapy depends on the PK/PD properties of the drug or more precisely the pharmaceutical formulation. Drugs which have long duration of action relative to their dosage interval are more robust to noncompliance. This robustness has been coined forgiveness and is specifically defined as the difference between the drugs post-dose duration of action and the prescribed dosage interval. In order to optimise a therapy the dosing regimen should reflect the forgiveness potential of a formulation so as to minimise the effects of non-compliance. Given the pressure for QD dosing, it is often essential to provide a clear rationale for recommendations beyond this mode of administration. Against this background, a method for demonstrating the robustness of competing regimens is presented. A naïve model for noncompliance. A naïve model of noncompliance tries to capture typical patient compliance behaviour. Several studies have demonstrated that the distribution of overall fraction of doses taken is skewed toward a median in the range of 70-90%, while median compliance with prescribed intervals is in the range of 20-40%. However these figures were subject to large interindividual variability. Urquhart [1] has come up with the following rule of thumb to summarise average noncompliance behaviour: one in six patients:

- * Remedicates punctually
- * Takes prescribed doses, but with somewhat erratic timing
- * Skips an occasional dose, but never more than one
- * Skips three or more sequential days' doses (a 'drug holiday') 3-4 times per year
- * Has one or more drug holidays per month
- * Takes few or no doses, but creates the illusion of good compliance

This rule provides the basis for assigning types of behaviour to portions of a population. Under the assumption that an individual's pattern of dosing should correspond to a prescribed frequency of dose taking, and assuming that any one dosing event depends only on the occurrence of the previous dosing event, given the individual's probability density function of dosing frequencies, a Markov process can be used to describe the time series of dosing events. A probability is assigned for missing (P_{miss}) a dose; if a dose is missed then a probability is assigned for taking (P_{take}) the subsequent doses conditional on having missed the previous dose. P_{miss} controls the frequency at which doses are missed; P_{take} controls the duration of drug holidays. The average duration of a drug holiday is given by: $1/P_{take}-1$. The drug taking behaviour as described above by the rule of sixes can then be roughly characterised by the setting appropriate values for the above probabilities. The timing of dosing can also be appropriately perturbed from the nominal dosing times. This naïve compliance model can then be linked as the input to a population PK (/PD) model for the compound in question. The effect of incomplete compliance can be assessed through simulation by counting the number of days or dosing intervals in which adequate concentrations or target effects are achieved or maintained over the treatment period. The latter can thus be used as an index for the performance of competing regimens in the presence of noncompliance. An anonymous worked example of the model will be presented and possible extensions to the basic model will be discussed.

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