Compliance-Oriented Prescribing: Simplifying Drug Regimens

Richard G. Fischer, PharmD
Jackson, Mississippi

Simplifying drug regimens is one method of improving patient compliance. Medications originally administered several times a day are now reported to maintain 24-hour effectiveness on once-daily administration. In many cases this technique of administration results in the use of less expensive medication, an improvement in compliance, and even decreased side effects. All patients may not be controlled or tolerate increased intervals between drug doses. Interpatient variation dictates that physicians closely monitor their patients when prescribing new or unapproved regimens of drug therapy.

Do you routinely write for medications to be taken three or four times a day? Do your patients tell you they frequently cannot remember to take their medications or that their dosage schedules are so complex they often get confused? If you are confronted with these problems you may not be taking full advantage of knowledge generated from recent studies attesting to the efficacy of various drugs when administered on once- or twice-a-day schedules.

A general principle of compliance oriented prescribing is to simplify the drug regimen as much as possible.[1] If several medications are to be taken on different time schedules, many patients become confused.[2] Scheduling misconceptions may be as high as 17 percent in the private practice setting.[3]

Studies have shown that the degree of compliance is related to the frequency with which a drug is administered.[4-8] Ayd[4] demonstrated a significant increase in compliance when the dosage schedule was decreased from three or four times daily to once or twice daily. Gatley[6] reported 67 percent of his patients compliant on a once-a-day dosage schedule as opposed to only 32 percent compliant on a four-times-a-day schedule, with intermediate levels of compliance observed in patients on a twice- or three-times-a-day dosage regimen. When a questionnaire concerning desirable features of anti-rheumatic medication was distributed to 200 clinic outpatients, one of the most frequently desired attributes was that of once-daily administration.[9] In general, physicians should avoid divided doses of medication when once-a-day administration would be equally effective.[1]

Possible advantages of single-daily administration include:

1. increased compliance and convenience resulting in improved control of the disease state
2. decreased cost of medication
3. decrease of some side effects
4. reduction or deletion of concomitant medications
5. patients spared the embarrassment of taking drugs in the presence of others at work or socially
6. reduced nursing and pharmacy time in institutions
7. reduced feeling of dependence on medications

From the Department of Clinical Pharmacy Practice, School of Pharmacy, The University of Mississippi Medical Center, Jackson, Mississippi. Requests for reprints should be addressed to Dr. Richard G. Fischer, Department of Clinical Pharmacy Practice, School of Pharmacy, The University of Mississippi Medical Center, Jackson, MS 39216.

0094-3509/80/030427-09$02.25

Possible disadvantages of single-daily administration include:

1. patients' objections to taking a large number of pills at one time if high strength tablets are not available
2. increase in some side effects, especially gastrointestinal upset
3. disease process possibly not controlled for 24-hour periods
4. missed medication on a once-daily regimen possibly resulting in greater potential for decreased control of disease
5. patients fearing they are not getting medication often enough to benefit them
6. toxicity, if dose is too large
7. physicians losing sight of interpatient variation and assuming all patients can be treated with increased dosage intervals

The purpose of this paper is to provide physicians with documentation which lends support to single-daily dosage with certain drugs so that dosage regimens may be tailored for specific patients in an effort to improve compliance. Complications and warnings associated with this technique are described. Some of the drugs discussed have received Food and Drug Administration (FDA) approval for increased intervals between doses, and others are currently under clinical investigation pending approval.

Anticonvulsant Drugs

Seizure patients are often noncompliant, and failure to control seizures is frequently due to missed medication.[10] Anticonvulsant drugs have traditionally been prescribed in divided daily doses, but the long plasma half-lives of several of these drugs (phenytoin—22 hours, ethosuximide—54 hours, phenobarbital—4 days) make once-daily administration feasible for many patients.[11]

Phenytoin (Dilantin)

Phenytoin received FDA approval several years ago for once-a-day administration. Efficacy of this dosage technique is supported by several clinical investigations.[12,13] In 1972 Buchanan and coworkers,[12] in a study of phenytoin kinetics (using Dilantin only), found no significant difference in absorption, steady-state plasma levels, biologic half-life, peak and trough values, or urinary recovery in patients utilizing a three-times-daily dosage schedule vs a once-daily dosage schedule. No evidence of drug toxicity was found in 13 patients receiving single-daily doses of phenytoin.[13]

There are several aspects of single-daily dosage with phenytoin of which physicians must be aware.

First, recent FDA sponsored research has found unexpected differences in dissolution and absorption among phenytoin products.[14] The significance of this finding is that only Parke-Davis' brand of phenytoin, Dilantin, has been shown to have slow release characteristics and, thus, is the only brand that is recommended for once-a-day use.

Secondly, physicians who choose a single-daily dose should first stabilize patients on divided doses, and then with careful monitoring of blood levels of the drug, change to the appropriate once-a-day dose.[14] Patients who report an increase in seizure activity, should have phenytoin serum levels drawn just prior to receiving the next dose.

Thirdly, the half-life of phenytoin varies among adults, with a reported range of 7 to 48 hours,[15] precluding some patients from being acceptable candidates for single-daily dosage. Most patients showing shorter phenytoin half-lives can be controlled on twice-a-day administration.

Fourthly, children are more apt to require shorter dosage intervals than adults.[16] Curless and co-workers[17] found an average phenytoin half-life of 4.55 hours in 11 young children with seizure disorders.[17] Phenytoin should be administered to young children at least two or three times daily.[16,18,19]

Administering the total dose of phenytoin in the evening means peak plasma levels occur while the patient is asleep and the majority of unpleasant side effects should occur at that time.[12] Peak plasma levels may not be reached for up to 12 hours,[20] and some patients may complain of morning drowsiness or ataxia. This problem can be rectified by instructing patients to administer their dose in the late afternoon or early evening. Occasionally, phenytoin-induced gastrointestinal irritation will be more troublesome with the larger single doses. Administration of the drug with a full glass of water may help reduce the irritation.[21]

Even though a single-daily dose phenytoin regimen may be beneficial for selected patients, the wide individual variation in half-lives, the higher peak serum levels, and a reported average differ-

ence of 27.6 percent between peak and trough levels, lead some to recommend the twice-daily dosage regimen as the optimum dosage schedule for most patients.[16,22-24]

Phenobarbital

The half-life of phenobarbital is approximately two to four days. It has a mean elimination rate of 16 percent per 24 hours, which indicates that a single-daily dose of phenobarbital is sufficient when the serum concentration is in the therapeutic range.[18] The hourly variation is less when the drug is administered twice daily and some authors still support divided daily dosage.[16] As with phenytoin, phenobarbital elimination is more rapid in children than in adults, and therefore should be given to children in at least two doses daily.[16,22]

Ethosuximide (Zarontin)

Single-daily doses with ethosuximide may be particularly advantageous in treating children with petit mal epilepsy for whom taking medication in school is impractical. A half-life of 30 hours in children and 60 hours in adults makes this regimen feasible.[25] Buchanan et al[25] reported nine patients with petit mal epilepsy, aged 8.7 to 19.8 years, who maintained therapeutic plasma levels and control when switched from divided daily doses to single-daily doses of ethosuximide. Maintenance of therapeutic serum levels has also been reported in healthy adult volunteers after single-daily dosage with ethosuximide.[26,27]

Antihypertensive Drugs

The management of essential hypertension is often complicated because of confusing therapeutic regimens. Noncompliance with medications is the most important reason for inadequate blood pressure control.[28] While several antihypertensive agents, including thiazide diuretics, reserpine, and guanethidine, are usually prescribed for once-daily therapy, other agents are prescribed by many physicians in three or four divided daily doses.[29] Recent data in the literature document effective control of blood pressure giving methyldopa, propranolol, metoprolol, clonidine, prazosin, and hydralazine on a twice-daily schedule. The Food and Drug Administration has approved twice-daily usage of these drugs and single-daily administration is currently being studied.

Methyldopa (Aldomet)

Methyldopa provides 24-hour blood pressure control when administered twice a day.[30-32] Several investigators have studied the effectiveness of methyldopa when administered in a single-daily dose.[33,34] In a double-blind crossover study in 14 patients, Wright et al[33] found the antihypertensive effectiveness of methyldopa similar whether the drug was administered three times daily or as a single-daily dose. All patients studied were previously controlled on divided dose therapy with methyldopa. Some patients who complained of drowsiness and fatigue on a three-times-a-day schedule noted a decrease in these side effects when the drug was taken as a single total bedtime dose. The lack of further clinical trials makes it difficult to predict the efficacy of this regimen. Preliminary evidence suggests that single-dose treatment with methyldopa may be a therapeutic alternative in selected patients.

Propranolol (Inderal)

Twice-daily dosage of propranolol has been supported by the literature for several years, and this schedule has recently been approved by the Food and Drug Administration.[35,36] Reports now indicate that it is also possible to initiate and maintain hypertensive patients on a once-daily propranolol regimen.[37-39] Although not approved by the FDA for single-daily dosage in hypertension, propranolol appears to maintain 24-hour blood pressure control in the majority of patients studied.

Metoprolol (Lopressor)

Metoprolol, a more selective beta-1 blocker, has always been promoted as being effective in a twice-daily dosage schedule. Several studies now suggest that many hypertensive patients maintain 24-hour blood pressure control on single-daily dosage with metoprolol.[39-42] Like propranolol, metoprolol is not approved for single-daily dosage, but accumulating evidence supports this approach in selected hypertensive patients.

Efficacy of once-a-day dosage with the beta blockers in disease states other than hypertension is not confirmed. There is evidence that adequate beta blockade is not maintained for 24 hours,[41,42] which would preclude the use of single-daily dosage of metoprolol and propranolol in diseases other than hypertension.

Clonidine (Catapres)

Clonidine maintains 24-hour blood pressure control when administered on a twice-daily schedule.[43] Jain et al[44] reported the response to a single nighttime dose of clonidine in 12 patients with essential hypertension, but noted that blood pressure fluctuations were much wider than they were during thrice-daily therapy. However, most patients preferred the once-a-day regimen because of the lack of drowsiness during the day.

Another preliminary study of 12 outpatients receiving chlorthalidone and clonidine once-nightly reported 24-hour blood pressure control. All patients were first titrated on a twice-daily regimen.[45] This schedule is not recommended as a general measure until more data are available. Patients complaining of daytime sedation may be controlled with fewer side effects by administering two thirds of the total daily dose in the evening and one third in the morning.[44]

Prazosin (Minipress) and hydralazine (Apresoline) both maintain effectiveness on a twice-daily schedule.[46,47] Studies on once-a-day dosage with these drugs are lacking.

Simplified drug regimens with antihypertensive agents are possible. Interpatient variation to the response of once-daily or twice-daily drug administration necessitates that patients be monitored carefully for 24-hour blood pressure control. Single-dose studies alone cannot supply the physician with the answer to the optimum dosage regimen for a given patient.

Anti-Infective Drugs

Antibiotics for Urinary Tract Infections

The duration of antimicrobial therapy for simple urinary tract infections commonly ranges from 5 to 21 days with medication scheduled three or four times a day. These drug regimens are often expensive and compliance tends to decrease with the resolution of dysuria. There is now supporting evidence that single-dose therapy with certain antibiotics is effective for treating urinary tract infections in females.

Amoxicillin (Amoxil, Larotid, Polymox, Robamox)

Bailey and Abbott[48] reported success in treating 31 females with urinary tract infections with a single oral dose of amoxicillin. These patients were either asymptomatic, had cystitis, or acute pyelonephritis. A cure rate of 74 percent was reported using 3 gm of amoxicillin for adults and 100 mg/kg for children. A further controlled study in 20 women and 26 children randomly allocated to receive either a single dose of amoxicillin or a conventional five-to-seven day course of the same antibiotic reported comparable results with both treatment regimens. Failure rates in both treatment groups were highest in those patients with a radiological defect of the urinary tract.[48] The effectiveness of this dosage regimen was confirmed by Fang et al[49] when they reported a 100 percent success rate in 22 women without antibody-coated bacteria in the urine. Symptomatic monilial vulvovaginitis was also reduced with the single-dose regimen and no increase in side effects was reported. The standard ten-day drug treatment regimen can also alter periurethral flora, causing a recurrence of urinary infection. This is unlikely to occur with single-dose treatment.[50]

Sulfonamides

Sulfamethoxazole/trimethoprim (SMX/TMP) (Bactrim, Septra) is equally effective when administered in either a single dose or as a five-to-seven day course. Forty women with asymptomatic bacteriuria, cystitis, or acute pyelonephritis, and 20 children who were either asymptomatic or had cystitis, showed equal improvement on SMX/TMP whether administered in a single dose or as a five-to-seven day course.[51] Adults received a single dose of 0.48 gm of trimethoprim and 2.4 gm of sulfamethoxazole (six tablets of SMX/TMP). Dosage for children varied with age. Side effects were absent and patients preferred this regimen. A report of a lower single-daily dose of SMX/TMP (160 mg/800 mg) being effective in 9 patients and a dose twice as large being effective in 13 patients is encouraging.[52] Preliminary data suggest that sulfisoxazole (Gantrisin and others)[52,53] and similar short acting sulfonamides[54] may be effective in low, single-dose therapy.

Parenteral Drugs

Single dosage with parenteral drugs has also been effective in treating urinary tract infections. A one-time intramuscular dose of 2 gm of cephaloridine (Loridine),[55] 500 mg of kanamycin (Kantrex),[56,57] 160-200 mg of tobramycin (Nebcin),[58] and 160 mg gentamicin (Garamycin)[59] has been reported in treating urinary tract infections.

This administration schedule may allow patients to receive treatment on an ambulatory basis, eliminates the discomfort of multiple daily injections, and reduces the amount of nursing care and expensive supplies.[58]

Single-dose treatment of urinary tract infections with certain drugs appears successful in resolving most of these problems in family practice, especially those presenting as cystitis or asymptomatic bacteriuria. The cost savings with this administration schedule can be tremendous. Single-dose therapy may also assist the physician in deciding which women require further radiological and urological assessment, since the majority of patients with anatomical defects or upper urinary tract infection will relapse within three to five days following single-dose treatment.[48,49] Side effects reported in the various studies have been minimal, and treatment is well tolerated and much preferred by patients. This dosage regimen is not recommended if the patient is severely ill with acute pyelonephritis or has a known urinary tract abnormality.[51] Single-dose therapy should also not be attempted in patients with renal dysfunction, renal calculi, carcinoma, paraplegia, or obstructive uropathy.

Tetracycline for Shigellosis

Shigella is commonly treated with ampicillin, tetracycline, or chloramphenicol for five-to-seven days with multiple daily dosage. Two studies now report success with a single 2.5 gm dose of tetracycline hydrochloride, with clinical improvements and bacteriologic eradication of the organism from the stool within 48 hours.[60,61] Single dose treatment with ampicillin or cephalexin (Keflex) has not resulted in adequate bacteriologic response.[62]

Metronidazole (Flagyl) for Trichomonas Vaginalis

Metronidazole is the drug of choice for trichomonas infections. The FDA approved dose is 250 mg three times a day for seven days for both men and women.* In clinical situations cure rates with this treatment schedule are considerably less than desired.[63] This may be due to failure to take the drug as prescribed, reinfection from a sexual partner, or drug failure due to poor absorption or inactivation.

*Recently, the FDA approved a single 2 gm dose of metronidazole for trichomonas vaginalis.

In the past several years studies attesting to the efficacy of a single 2 gm dose of metronidazole have been reported.[63-68] One large investigation of 203 females with symptomatic trichomonas, treated with a single 2 gm dose of metronidazole along with 2 gm to each of their sexual partners, reported a 95 percent adjusted cure rate.[64] Side effects reported were no more frequent than those reported in studies utilizing a three-times-a-day schedule for ten days. The most common complaints were of bad taste and nausea. However, side effects have been reported to occur in as many as 80 percent of patients ingesting a single 2 gm dose.[65]

The use of a single 2 gm dose of metronidazole has been proven safe, effective, and fairly well tolerated. Whenever possible, it is advantageous to treat sexually transmitted diseases with one dose treatment under medical supervision. This ensures compliance with the medication in the correct dose, enables treatment of both partners (especially the partner who is asymptomatic and reluctant to take the drug), and renders the patient non-infective in the shortest possible time.[65] The cost savings of this regimen is tremendous, since the cost of Flagyl to the pharmacist is approximately 27 cents per tablet.[69] Therefore, the standard regimen for two people (42 tablets) is over $11 wholesale cost compared to the single dose regimen for two people (16 tablets) of a little over $4. The cost of this medication is prohibitive for many patients and the single dose regimen may be one method to improve compliance. Patients receiving this therapy should be warned to abstain from alcohol for 48 hours after administration due to the possibility of an antabuse-like reaction.[64] The most common side effects consisting of nausea, abdominal discomfort, and bad taste should be better tolerated with the decreased length of treatment.**

Psychotherapeutic Drugs

Phenothiazines

Patients with psychiatric problems are often noncompliant to prescribed drug regimens.[70] One method to improve compliance is to administer the drug less often. Ayd[4] studied the compliance of

**The primary contraindication to the single-dose regimen is in pregnant patients in the second and third trimester, because this results in higher serum levels which reach the fetal circulation. The seven-day regimen may be preferred in women with several sexual partners since this may minimize reinfection long enough to treat all contacts.

psychiatric and medical patients on a variety of dosage schedules. He reported a 70 percent noncompliance rate with four-times-a-day dosage, a 60 percent noncompliance rate with three-times-a-day dosage, a 30 percent noncompliance rate with twice-daily dosage, and only a 7 percent noncompliance rate with once-a-day dosage. Long-term noncompliance rates may not always be this striking, but this study documents improved compliance with decreased dosage frequency.

The use of phenothiazine spansule formulations is generally inappropriate since these drugs are intrinsically long acting. Slow release formulations do not have many advantages over an equivalent single-daily dose of tablets and may even result in lower blood levels.[71] These dosage forms are also more expensive, costing approximately twice as much. Spansules may be used advantageously if there is a question regarding the safety of giving the entire daily dose in a single administration of a conventional dosage form.[72]

Phenothiazine drugs are frequently prescribed on a three-to-five-times-a-day schedule with treatment lasting for many years.[73] Studies now support single-daily administration of most antipsychotics. Initial treatment, however, should be with divided doses in order to minimize many of the initial side effects (sedation and alpha adrenergic blocking activity) and allow better titration of the dose.[74]

Unique advantages of daily dosage one hour before bedtime are[73-77]:

1. The sedative activity of the psychotherapeutic drugs may be beneficial in helping the patient to sleep and may avoid the need for a sedative-hypnotic.

2. Pharmacological side effects occur when the patient is asleep and therefore patients have fewer complaints of lethargy, dry mouth, blurred vision, and tremor.

3. A reduction in the need for anti-parkinsonian drugs has been reported.

4. Administration of a single-daily dose allows for the use of proportionately less expensively sized tablets. For example: the Thorazine wholesale cost per 100 tablets is: 50 mg - $4.75, 100 mg - $5.86, 200 mg - $7.00.[69] Annual savings in the thousands of dollars may be seen by merely switching patients to daily doses.[76,78,79]

Cautions and exceptions to a single-daily dosage schedule include the elderly, with compromised metabolism, who may not be able to tolerate once-daily dosing and thus require smaller doses and more frequent administration. Patients who require the daytime sedative properties of neuroleptics would also not be candidates for this dosing technique. If very large amounts of drugs are required, some physicians may prefer to divide the total daily dose, prescribing one third in the late afternoon and the remainder at bedtime. The occasional patient who paradoxically reacts with restlessness or insomnia (usually with phenothiazines in the piperazine group) should receive the bulk of the daily drug dosage in the morning instead of at bedtime.[73]

Tricyclic Antidepressants

When the tricyclic antidepressants were first introduced on the market they were commonly prescribed in three to four divided daily doses. The plasma half-life of these drugs is generally greater than 24 hours, and their metabolism and excretion proceed at a very slow rate, making once-daily administration feasible in most patients.[75,80-82]

The initial dosage regimen for the tricyclics should be with divided doses. This regimen increases flexibility in determining the optimum dose and may also lessen side effects.[83] Kales et al[83] evaluated the effects of a single 75 mg dose of doxepine hydrochloride (Sinequan, Adapin) administered at bedtime. Patients experienced a marked hangover on awakening in the morning and were extremely drowsy and uncoordinated for several hours. A number of patients complaining of terrifying nightmares has also been reported when single bedtime doses of tricyclic antidepressants were administered.[84] The nightmares disappeared when the drug regimen was changed to divided doses. Thus, while it may be advantageous to administer the tricyclic antidepressants as a single bedtime dose, it is safer and generally better tolerated when one gradually titrates to the larger bedtime dose.

Specific advantages of single evening dosage are similar to those seen with the phenothiazine drugs.[75,82-85] This includes avoiding both the need in many cases for a sedative-hypnotic and major pharmacological side effects when the patient is asleep.

Cautions with single-daily dosage include the use of divided doses when more than 150 mg of

imipramine (Tofranil and others) or its equivalent is required, since single doses above 200 mg approach the level of toxicity in selected patients.[84] The tricyclic antidepressants may also have a stimulatory effect in a few patients[86]—usually seen with desipramine (Norpramin, Pertofrane) or protriptyline (Vivactil)—and therefore should not be prescribed for those individuals as a single bedtime dose.

Benzodiazepines

Single-daily dosage of the benzodiazepine drugs after the daily requirement is determined has been successful.[87-91] The accumulation of major active metabolites of these drugs which have plasma half-lives in the range of one to three days make this dosage technique possible.[91,92] Oxazepam (Serax) and lorazepam (Ativan) have one-step elimination pathways without active metabolites, and thus will not maintain therapeutic plasma levels for 24 hours if administered once-a-day.

Single bedtime doses of a benzodiazepine drug should help the anxious patient troubled by insomnia since peak plasma levels occur during sleep.[89] Single doses should be used cautiously in the elderly, in patients with respiratory disorders, and in others who may be susceptible to hypnotic doses of these agents.[92] A five-to-ten day equilibrating period should ensue before single-daily dosage is started.[87]

Miscellaneous Drugs

Allopurinol (Zyloprim)

When allopurinol was first marketed in the mid 1960s it was recommended for administration in divided daily doses. Subsequent research discovered that a large portion of allopurinol was metabolized to an active metabolite, oxypurinol, which has a half-life of 18 to 30 hours.[93] Studies supporting the effectiveness of once-daily dosage[93-95] led to the recommendation in the 1974 allopurinol package insert that appropriate dosage may be administered in divided doses or as a single equivalent with the 300 mg tablet. Occasionally, gastrointestinal problems are seen on the single-daily dosage schedule and may necessitate a divided dose schedule.

Antithyroid Drugs

Greer et al[96] in 1965 stimulated interest in the possibility that propylthiouracil and methimazole (Tapazole) are effective in inducing and maintaining remission in thyrotoxic patients when administered in a single-daily dose. They reported 18 patients successfully treated with a single average dose of 300 mg of propylthiouracil and 2 patients successfully treated and 1 maintained on a single-daily dose of 30 mg of methimazole. Other studies in 1969 and 1977 reported success with single-daily dosage with propylthiouracil and methimazole in inducing and maintaining remission in hyperthyroid patients.[97-99] Gwinup[99] randomly divided 49 patients into two groups; one group received 150 mg of propylthiouracil every eight hours, and the other group, 450 mg of propylthiouracil as a single-daily dose. The divided dosage regimen was significantly superior in achieving remission, as only slightly more than half of the single-dose group had evidence of remission within ten weeks.

Some patients do respond to the single-daily dose of propylthiouracil and methimazole. However, divided doses seem more effective and it may be wise to initiate conventional therapy in a critically ill patient and change to a single-daily dose only when the patient is considerably improved or euthyroid. This dosage regimen is not approved by the Food and Drug Administration.

Topical Corticosteroids

Topical corticosteroids are expensive[100] and are customarily applied three or four times a day. Few pharmacokinetic studies have been reported on the efficacy of longer dosage intervals. Topical steroids are held in a reservoir underneath the horny layer, and if the area is re-occluded, more steroid is released into the underlying dermis.[101] Fluorinated steroids may remain underneath the horny layer for up to 41 days.[102] One multi-clinic study of 409 patients with eczematous dermatoses reported comparable efficacy between once-daily application of diflorasone diacetate (Florone) and three-times-a-day application of betamethasone valerate (Valisone).[103] Once-daily treatment with betamethasone was not studied. Once-a-day application appears adequate when occlusive therapy with plastic or corticosteroid tape is prescribed.[104] Pruritis ani may be relieved by as little as once-weekly application of a corticosteroid cream.[105] Currently, it is recommended that as the patients' lesions respond, the frequency of application should be decreased to the least number that will control the disease process.[104]

Conclusion

New data concerning the efficacy of single and twice-daily dosages with specific drugs are accumulating. Physicians who are aware of information supporting simplified therapeutic regimens will be in a better position to improve compliance and decrease drug costs for many patients. Generalizations concerning single-daily dosage are difficult to make; some patients respond and others do not. Whenever employing a new or unapproved dosage technique, careful patient selection and follow-up is a necessity.

References

1. Matthews D, Hingson R: Improving patient compliance: A guide for physicians. Med Clin North Am 61: 879, 1977
2. Podell RN: Noncompliance and Strategies for Improvement. Nutley, NJ, Roche Laboratories, 1975
3. Hulka BS, Cassel JC, Kupper LL: Disparities between medications prescribed and consumed among chronic disease patients. In Lasagna L (ed): Patient Compliance. Mount Kisco, NY, Futura Publishing, 1976, p 148
4. Ayd FJ: Rational pharmacotherapy: Once-a-day drug dosage. Dis Nerv Syst 34:371, 1973
5. Porter AMW: Drug defaulting in general practice. Br Med J 1:218, 1969
6. Gatley MS: To be taken as directed. J R Coll Gen Pract 16:39, 1968
7. Jenkins BW: Are patients true to TID and QID doses? Gen Pract 9(6):66, 1954
8. General practitioner clinical trials: Dosage schedules in general practice. Practitioner 204:719, 1970
9. Wright V, Hopkins R: Administration of antirheumatic drugs. Ann Rheum Dis 35:174, 1976
10. Gibberd FB, Dunne JF, Handley AJ, et al: Supervision of epileptic patients taking phenytoin. Br Med J 1:147, 1970
11. Atkinson AJ: Individualization of anticonvulsant therapy. Med Clin North Am 58:1037, 1974
12. Buchanan RA, Kinkel AW, Goulet JR, et al: The metabolism of diphenylhydantoin (Dilantin®) following once-daily administration. Neurology 22:126, 1972
13. Haerer AF, Buchanan RA: Effectiveness of single daily doses of diphenylhydantoin. Neurology 22:1021, 1972
14. New prescribing directions for phenytoin. FDA Drug Bull 8(4):27, 1978
15. Arnold K, Gerber N: Rate of decline of phenytoin in plasma. Clin Pharmacol Ther 11:121, 1970
16. Livingston S: Medical treatment of epilepsy: Part 1. South Med J 71:298, 1978
17. Curless RG, Walson PD, Carter DE: Phenytoin kinetics in children. Neurology 26:715, 1976
18. Buchthal F, Lennox-Buchthal MA: Diphenylhydantoin: Relation of anticonvulsant effect to concentration in serum. In Woodbury DM, Penry JK, Schmidt RP (eds): Antiepileptic Drugs. New York, Raven Press, 1972
19. Svensmark O, Buchthal F: Diphenylhydantoin and phenobarbital: Serum levels in children. Am J Dis Child 108:82, 1964
20. Dill WA, Kazenko A, Wolf LM, et al: Studies on 5, 5-diphenylhydantoin (Dilantin®) in animals and man. J Pharmacol Exp Ther 118:270, 1956
21. Ginn PD: Epilepsy. In Young LY, Kimble MA (eds): Applied Therapeutics for Clinical Pharmacists. San Francisco, Applied Therapeutics, 1975, p 300
22. Svensmark O, Buchthal F: Dosage of phenytoin and phenobarbital in children. Dan Med Bull 10:234, 1963
23. Jellett LB: Plasma concentrations in the control of drug therapy. Drugs 11:412, 1976
24. Parsonage M: Epilepsy. Practitioner 213:552, 1974
25. Buchanan RA, Kinkel AW, Turner JL, et al: Ethosuximide dosage regimens. Clin Pharmacol Ther 19:143, 1976
26. Goulet JR, Kinkel AW, Smith TC: Metabolism of ethosuximide. Clin Pharmacol Ther 20:213, 1976
27. Colburn WA, Gibaldi M: Use of multdos for pharmacokinetic analysis of ethosuximide data during repetitive administration of single or divided doses. J Pharm Sci 67:574, 1978
28. Gifford RW: Managing hypertension. Postgrad Med 61:153, 1977
29. Miller WA, Self TH, Miller ST: Simplified regimens for hypertension. Drug Intell Clin Pharm 12:424, 1978
30. Sheps SG, Kirkpatrick RA: Hypertension. Mayo Clin Proc 50:709, 1975
31. Hannsen J: Alpha-methyldopa (Aldomet) in the treatment of hypertension. Acta Med Scand 183:323, 1968
32. McMahon F: Efficacy of an antihypertensive agent: Comparison of methyldopa and hydrochlorothiazide in combination or singly. JAMA 231:155, 1975
33. Wright JM, McLeod PJ, McCullough W: Antihypertensive efficacy of a single bedtime dose of methyldopa. Clin Pharmacol Ther 20:733, 1976
34. Jain AK, Ryan JR, McMahon FG: The effect of single morning doses of alpha methyldopa (MD) on blood pressure. Clin Pharmacol Ther 14:137, 1973
35. MacLeod SM, Hamet P, Kalplan H, et al: Antihypertensive efficacy of propranolol given twice daily. Can Med Assoc J 121:737, 1979
36. Hansson L, Olander R, Aberg H: Twice daily propranolol in the treatment of hypertension. Lancet 2:713, 1971
37. Wilson M, Morgan G, Morgan T: The effect of blood pressure on B-adrenoreceptor blocking drugs administered once-daily and their duration of action when therapy is ceased. Br J Clin Pharmacol 3:857, 1976
38. Wilson M, Morgan G, Morgan T: The effect on blood pressure of beta-adrenoreceptor-blocking drugs administered once-daily. Clin Sci Mol Med 51:527s, 1976
39. Gordon RD: Initial treatment of the young hypertensive: Thiazide diuretic or B-adrenoreceptor-blocking agent in a single daily dose? Clin Sci Mol Med 51:631s, 1976
40. Watson RDS, Stallard TJ, Littler WA: Influence of once-daily administration of B-adrenoceptor antagonists on arterial pressure and its variability. Lancet 1:1210, 1979
41. Reybrouck T, Amery A, Fagard R, et al: Beta-blockers: Once or three times a day. Br Med J 1:1286, 1978
42. Karlberg BE, Nilsson O, Tolagen K: Once-daily metoprolol in primary hypertension. Clin Pharmacol Ther 25:399, 1979
43. Lilja M, Jounela A, Juustila H, et al: Antihypertensive effects of clonidine. Clin Pharmacol Ther 25:864, 1979
44. Jain AK, Ryan JR, Vargas R, et al: Efficacy and acceptability of different dosage schedules of clonidine. Clin Pharmacol Ther 21:382, 1977
45. Paschal J: ASCPT roundup: New drugs, new doses, new side-effects. Current Prescribing 5(7):69, 1979
46. LeSher DA, Harris L, Hawkinson RW: Comparison of BID vs QID hydralazine dosage regimens in hypertensive patients on multiple drug therapy. Clin Pharmacol Ther 19:110, 1976
47. Okun R: Dosage schedule routine for prazosin: Two cross-over trials comparing TID with QID administration and TID with BID administration. In Proceedings of a Symposium on Prazosin-Evaluation of a New Anti-Hypertensive Agent. Amsterdam, Excerpta Medica, 1974, pp 82-91
48. Bailey RR, Abbott GD: Treatment of urinary tract infection with a single dose of amoxycillin. Nephron 18:316, 1977
49. Fang LS, Tolkoff-Rubin NE, Rubin RH: Efficacy of single-dose and conventional amoxicillin therapy in urinary-tract infection localized by the antibody-coated bac-

teria technic. N Engl J Med 298:413, 1978
50. Ronald AR, Jagdis FA, Harding GKM, et al: Amoxicillin therapy of acute urinary infections in adults. Antimicrob Agents Chemother 11:780, 1977
51. Bailey RR, Abbott GD: Treatment of urinary tract infection with a single dose of trimethoprim-sulfamethoxazole. Can Med Assoc J 188:551, 1978
52. Single-dose treatment of urinary tract infections. JAMA 241:1226, 1979
53. Rubinoff H, Benner D: Urinary tract infection in children. Mayo Clin Proc 54:413, 1979
54. Kallenius G, Winberg J: Urinary tract infections treated with single dose of short-acting sulphonamide. Br Med J 1:1175, 1979
55. Brunfitt W, Faiers MC, Franklin IN: The treatment of urinary infection by means of a single dose of cephaloridine. Postgrad Med J 46:65s, 1970
56. Ronald AR, Bourtros P, Mourtada H: Bacteria localization and response to single-dose therapy in women. JAMA 235:1854, 1976
57. Fairley KF, Whitworth JA, Kincaid-Smith P, et al: Single-dose therapy in management of urinary tract infection. Med J Aust 2:75, 1978
58. Landes RR: Single daily doses of tobramycin in therapy of urinary tract infections. J Infect Dis 134:142s, 1976
59. Mosegaard A, Smith DI, Madsen PO: Single daily dosage treatment of urinary tract infections with gentamicin. In Proceedings of the Eighth International Congress of Chemotherapy, Athens, September 8-14, 1973. Athens, Hellenic Society of Chemotherapy, 1974, vol 2, pp 476-481
60. Pickering LK, Dupont HL, Olarte J: Single-dose tetracycline for shigellosis in adults. JAMA 239:853, 1978
61. Lionel NDS, Goonewardena CV, Abeyaserkera FJB, et al: A comparison of a single dose and a five-day course of tetracycline therapy in bacillary dysentery. J Trop Med Hyg 72:170, 1969
62. DuPont HL, Hornick RB: Clinical approach to infectious diarrheas. Medicine 52:265, 1973
63. Underhill RA, Peck JE: Causes of therapeutic failure after treatment of trichomonal vaginitis with metronidazole: Comparison of single-dose treatment with standard regimen. Br J Clin Pract 28:134, 1974
64. Fleury FJ, Van Bergen WS, Prentice RL, et al: Single-dose of two grams of metronidazole for trichomonas vaginalis infection. Am J Obstet Gynecol 128:320, 1977
65. Rao HTM, Shenoy DR: Single-dose oral treatment of vaginal trichomoniasis with tinidazole and metronidazole. J Intern Med Res 6:46, 1978
66. Woodcock KR: Treatment of trichomonal vaginitis with a single oral dose of metronidazole. Br J Vener Dis 48:65, 1972
67. Morton RS: Metronidazole in the single-dose treatment of trichomoniasis in men and women. Br J Vener Dis 48:525, 1972
68. Dykers JR: Single-dose metronidazole for trichomonal vaginitis. N Engl J Med 293:23, 1975
69. Drug Topics Red Book. Oradell, NJ, Litton Industries, 1979
70. Wilcox PRC, Gillan R, Hare EH: Do psychiatric patients take their drugs. Br Med J 2:790, 1965
71. Hollister LE, Curry SH, Derr JE, et al: Studies of delayed-action medication vs plasma levels and urinary excretion of four different dosage forms of chlorpromazine. Clin Pharmacol Ther 11:49, 1970
72. Gibaldi M: Biopharmaceutics and Clinical pharmacokinetics. Philadelphia, Lea and Febiger, 1977, p 51
73. Mason AS: Toward rational antipsychotic drug therapy: Avoidance of multiple dose schedules. J Ky Med Assoc 74:453, 1976
74. Hollister LE: Clinical use of psychotherapeutic drugs. Part 1: Antipsychotic and antimanic drugs. Drugs 4:321, 1972
75. Ayd FJ: Once-a-day neuroleptic and tricyclic antidepressant therapy. Int Drug Ther Newsletter 7:33, 1972
76. Inoue F: Implementation of clinical pharmacy services. Hosp Form 13:278, 1978
77. Abuzzahab FS, Davis JM, Burrell CD, et al: Higher unit dose of psychotropic drugs. Pharmakopsychiatr Neuropsychopharmakol 8:331, 1975
78. Marder JE, DiMascio A: Outpatient psychotropic drug scheduling and costs. Hosp Community Psychiatry 24:556, 1973
79. Cohen M, Gordon R, Morlowe H, et al: A single-bedtime dose self-medication system. Hosp Community Psychiatry 30:30, 1979
80. Mendels J, Schless AP: A controlled comparison of doxepin HS and doxepin QID. J Clin Pharmacol 15:534, 1975
81. Marshall B: The treatment of depression in general practice by a single-dose schedule. Practitioner 206:806, 1971
82. Mendels J, Schless AP: Antidepressant effects of desipramine administered in two dosage schedules. Dis Nerv Syst 38:249, 1977
83. Kales A, Kales JD, Martin ED: Rational help with insomnia. Drug Therapy 5:31, 1975
84. Flemenbaum A: Pavor nocturnus: A complication of single daily tricyclic or neuroleptic dosage. Am J Psychiatry 133:570, 1973
85. Ayd FJ: Once a day dosage tricyclic antidepressant drug therapy: A survey. Dis Nerv Syst 35:475, 1974
86. Mendels J, DiGiacomo J: The treatment of depression with a single daily dose of imipramine pamoate. Am J Psychiatry 130:1022, 1973
87. Greenblatt DJ, Shader RI: Drug therapy: Benzodiazepines: Part 1. N Engl J Med 291:1011, 1974
88. Magnus RV: Once-a-day potassium chlorazepate in anxiety. Br J Clin Pract 27:449, 1973
89. Kaplan SA, Alexander J, Weinfeld RE: Pharmacokinetic profile of diazepam in man following single intravenous and oral and chronic oral administrations. J Pharm Sci 62:1789, 1973
90. Boxenbaum HG, Geitner KA, Jack ML, et al: Pharmacokinetic and biopharmaceutic profile of chlordiazepoxide HCl in healthy subjects: Multiple-dose oral administration. J Pharmacokinet Biopharm 5:25, 1977
91. Choice of a benzodiazepine for treatment of anxiety of insomnia. Med Lett Drugs Ther 19(481):49, 1977
92. Jinks M: Contemporary drugs in the management of anxiety. J Am Pharm Assoc 17:287, 1977
93. Rodnan GP, Robin JA, Tolchin SF, et al: Allopurinol and gouty hyperuricemia: Efficacy of a single dose. JAMA 231:1143, 1975
94. Yu TJ: Milestones in the treatment of gout. Am J Med 56:676, 1974
95. Rodnan GP, Robin J, Tolchin JF: Efficacy of single daily dose allopurinol in gouty hyperuricemia. Adv Exp Med Biol 41:571, 1974
96. Greer MA, Meihoff WC, Studer H: Treatment of hyperthyroidism with a single daily dose of propylthiouracil. N Engl J Med 272:888, 1965
97. Kammer H, Srinivasan K: The use of antithyroid drugs in a single daily dose. JAMA 209:1325, 1969
98. Greer MA, Kammer H, Bouma DJ: Short-term antithyroid drug therapy for the thyrotoxicosis of Graves's disease. N Engl J Med 297:173, 1977
99. Gwinup G: Prospective randomized comparison of propylthiouracil. JAMA 239:2457, 1978
100. Desoximetasone (Topicort) and other topical corticosteroids. Med Lett Drugs Ther 19(481):85, 1977
101. Vickers CFH: Existence of reservoirs in the stratum corneum. Arch Dermatol 88:20, 1963
102. Vickers CFH: Dam, reservoir, or filter. Trans St John Hosp Derm Soc 59:10, 1973
103. Cahn MM, Hall JH, Kirschenbaum MB, et al: Comparative topical efficacy of once-daily diflorasone diacetate and TID betamethasone valerate ointment applications. Curr Ther Res 22:297, 1977
104. Maibach HI, Stoughton RB: Topical corticosteroids. Med Clin North Am 57:1253, 1973
105. Sneddon IB: Clinical use of topical corticosteroids. Drugs 11:193, 1976