Adverse Drug Effects, Compliance, and Initial Doses of Antihypertensive Drugs Recommended by the Joint National Committee vs the Physicians’ Desk Reference

Jay S. Cohen, MD

**Background:** Compliance problems are common causes of the inadequate treatment of hypertension, with 16% to 50% of patients quitting treatment within 1 year. Dose-related adverse drug events (ADEs) frequently cause compliance problems, and many ADEs occur with the initial doses of antihypertensive drugs. Thus, it is an established tenet to initiate antihypertensive therapy at low doses to avoid ADEs that diminish patients' quality of life and reduce compliance. However, what are the lowest effective doses of antihypertensive drugs?

**Objective:** To compare the initial doses recommended in the Physicians’ Desk Reference (PDR) with those recommended by the Sixth Report of the Joint National Committee on the Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI).

**Methods:** Review of the latest JNC VI report (1997) and the 1999 and 2000 editions of the PDR and the medical literature.

**Results:** The JNC VI recommends substantially lower initial doses for 23 (58%) of 40 drugs, compared with the PDR. In addition, for 37 (82%) of 45 drugs, PDR guidelines do not suggest lower initial doses for old or frail patients than for younger adults.

**Conclusions:** Although the PDR is the drug reference most used by physicians, it does not reflect the lowest initial doses that are recommended by the JNC VI for many of the most prescribed antihypertensive drugs. Because avoidance of ADEs is essential to maintaining compliance with antihypertensive therapy, and because many antihypertensive ADEs are dose related, physicians must know the very lowest, effective, least ADE-prone doses. Patients and physicians would benefit by establishing mechanisms to make this information readily available to all practicing physicians.

**During the past quarter century, the medical profession has made a major effort to improve awareness among people who have hypertension and to start their treatment.** The result has been a significant reduction in the long-term sequelae of hypertension, including myocardial infarctions and cerebrovascular accidents. However, during the 1990s, improvements in these measures slowed, and only 29% of the 50 million Americans with hypertension had attained a blood pressure below 140/90 mm Hg. Therefore, efforts continue to be directed at (1) reaching unaware or untreated hypertensive persons and facilitating treatment; (2) improving the percentage of patients achieving treatment goals by optimizing therapeutics; and (3) improving compliance by reducing the percentage of patients quitting treatment. Optimizing therapeutics and improving compliance are the focus of this article.

**Compliance with Antihypertensive Treatment**

Compliance may be defined as the extent to which a patient’s behavior conforms to medical advice. Long-term compliance with antihypertensive medication regimens has been poor. In one study, only 49% of patients took more than 80% of their prescribed dosages during the first year of treatment. Other studies indicate that 16% to 50% of hypertensive patients quit taking their medications within the first year of treatment.

These numbers improve considerably once patients have become established in treatment regimens. A survey of 79,000 hypertensive patients in Saskatchewan found a dropout rate among new patients of 22% in the first year and 54% after 4.5 years, leaving a persistence rate that the authors deemed “remarkably poor.” Although patients with newly diagnosed hypertension frequently quit treatment, the
MATERIALS AND METHODS

The Physicians' Desk Reference (PDR)\textsuperscript{16,17} was selected because it contains the dosages that are recommended by the drugs' manufacturers and approved by the Food and Drug Administration, and the dosage recommendations of other drug references are usually very similar to those of the PDR. The PDR is the drug reference used most often among physicians\textsuperscript{16,18}; approximately 90% of physicians rely on the PDR for dosage information.\textsuperscript{19} It is also used extensively by consumers, who purchase half a million copies annually. The 1999 and 2000 editions were consulted for this analysis.

The Sixth Report of the Joint National Committee on the Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI)\textsuperscript{1} was selected because the JNC is a respected panel of experts on hypertension that issues regular reports on the status of antihypertensive therapy in America. The JNC VI, the most recent report, was published in 1997 and contains a comprehensive list of antihypertensive drugs with the panel's recommended dosages. These dosages were compared with the dosage recommendations in the PDR.

ADVERSE DRUG EVENTS AND COMPLIANCE

There are many factors that affect compliance, such as the cost of medications and the inadequacy of physicians' explanations to patients of the importance of treating hypertension, which often is asymptomatic. A primary reason for poor compliance among patients receiving antihypertensive medications is adverse drug events (ADEs), many of which are dose related.\textsuperscript{12,14} In one study, 34% of patients reported unacceptable ADEs.\textsuperscript{13} Because of the high incidence of ADEs, physicians must consider quality-of-life issues in selecting antihypertensive drugs and doses. One difficulty is that many antihypertensive medications cause ADEs at therapeutic doses. Although physicians may consider ADEs such as dizziness, headaches, constipation, low energy, or sedation as minor, these can greatly interfere with normal functioning, which many patients find unacceptable. Not infrequently, sexual functioning is impaired, another difficult ADE for patients to accept.

These problems are compounded by the nature of hypertension, which may cause few symptoms. Treatment that provokes an ADE may make some patients feel subjectively worse than before treatment initiation. Patients who believe that they must choose between a comfortable but shortened life vs an ADE-affected but prolonged life often choose the former. Because compliance is intimately related to the avoidance of troublesome ADEs, physicians are advised to start antihypertensive therapy at the very lowest effective drug dosages. However, what are the lowest effective doses of antihypertensive drugs? And are the data on the lowest effective doses readily available to physicians? This analysis attempts to answer these questions.

The JNC VI lists 57 antihypertensive drugs, but 12 are no longer listed in the 1999 or 2000 PDR or are listed only briefly without dosage guidelines. Another 5 drugs (guanfacine hydrochloride, nifedipine, prazosin hydrochloride, terazosin hydrochloride, and valsartan) are not produced in a form that would allow the use of lower dosages. Of the remaining 40 drugs, the JNC VI recommended initial doses for 23 (58%) that were substantially lower than those recommended by the PDR (Table 1). All 23 dose disparities occurred among the 34 drugs (68%) in 5 frequently prescribed groups: angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, β-blockers, calcium antagonists, and diuretics. Except for chlorthalidone and one brand of metoprolol succinate, the PDR initial doses were at least 100% higher than the JNC VI doses. These disparities occurred with some of the most prescribed antihypertensive drugs, such as amlo-dipine besylate, atenolol, bisoprolol fumarate, diltiazem hydrochloride, lisinopril, losartan potassium, metoprolol, propranolol hydrochloride, and ramipril.\textsuperscript{21} There were no drugs for which the PDR recommended lower initial doses than JNC VI. Regarding older patients, for whom experts often recommend lower initial doses than for younger adults, the PDR guidelines recommended lower doses with only 8 (18%) of 45 drugs (Table 2).

Even when the JNC VI and PDR agree on the initial doses of 17 drugs, even lower doses of these drugs might be effective. For example, the American Hospital Formulary Service recommends an initial enalapril dose of 2.5 mg vs 5 mg by JNC VI and the PDR.\textsuperscript{22} The American Hospital Formulary Service also recommends 0.05 mg of clonidine hydrochloride twice daily initially for some patients vs 0.1 mg twice daily by the JNC VI and the PDR.

The range of manufactured doses varies considerably among antihypertensive drugs. Some drugs are produced with 16- or 20-fold dosage ranges (eg, doxazosin mesylate dosage range, 1-16 mg/d), whereas others are produced with 2- or 3-fold ranges (Table 3). The most common dosage ranges are 4- and 8-fold. Individual variation in drug response due to differences in age, weight, sex, ethnic background, state of health, concomitant medication use, and genetic polymorphisms in drug metabolism is a long-accepted pharmacological principle. Therefore, drugs offering wider ranges of dosages that allow maximum flexibility in titrating treatment may be generally preferable.
COMMENT

THERAPEUTIC GOALS DURING THE INITIAL PHASE OF THERAPY

Because of the importance of avoiding ADEs at the beginning of treatment, the JNC VI cautions physicians against trying to bring mild-to-moderate hypertension under control too quickly: “Therapy for most patients (uncomplicated hypertension, stages 1 and 2) should begin with the lowest dosage . . . to prevent adverse effects of too great or too abrupt a reduction in blood pressure.”

Table 1. Differing Recommendations for the Initial Doses of 23 Antihypertensive Drugs

<table>
<thead>
<tr>
<th>Medication</th>
<th>JNC VI</th>
<th>PDR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretics (7/9 drugs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorthalidone</td>
<td>12.5</td>
<td>15</td>
</tr>
<tr>
<td>Ethacrynic acid</td>
<td>25</td>
<td>50</td>
</tr>
<tr>
<td>Furosemide</td>
<td>40</td>
<td>80</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>12.5</td>
<td>25</td>
</tr>
<tr>
<td>Torsemide</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>25-100</td>
<td>50-100</td>
</tr>
<tr>
<td>Triamterene</td>
<td>25-100</td>
<td>200</td>
</tr>
<tr>
<td>ACE inhibitors (4/8 drugs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Captopril</td>
<td>25</td>
<td>50-75</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Quinapril hydrochloride</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Ramipril</td>
<td>1.25</td>
<td>2.5</td>
</tr>
<tr>
<td>Angiotensin II receptor blockers (1/2 drugs, 1 drug not testable)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Losartan potassium</td>
<td>25</td>
<td>50</td>
</tr>
<tr>
<td>β-Blockers (7/10 drugs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acebutolol</td>
<td>200</td>
<td>400</td>
</tr>
<tr>
<td>Atenolol</td>
<td>25</td>
<td>50</td>
</tr>
<tr>
<td>Betaxolol hydrochloride</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Bisoprolol fumarate</td>
<td>2.5</td>
<td>5†</td>
</tr>
<tr>
<td>Metoprolol succinate, tartrate</td>
<td>50</td>
<td>50-100§</td>
</tr>
<tr>
<td>Penbutolol sulfate</td>
<td>10</td>
<td>20j</td>
</tr>
<tr>
<td>Propranolol hydrochloride</td>
<td>40</td>
<td>80</td>
</tr>
<tr>
<td>(regular and LA)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium antagonists (4/5 drugs, 1 not testable)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amlodipine</td>
<td>2.5</td>
<td>5</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>120</td>
<td>2 brands, 180; 1 brand 120</td>
</tr>
<tr>
<td>Felodipine</td>
<td>2.5</td>
<td>5</td>
</tr>
<tr>
<td>Verapamil hydrochloride</td>
<td>90</td>
<td>120-180 (different brands)</td>
</tr>
<tr>
<td>α-Receptor blockers</td>
<td>(0/1 drug, 2 not testable)†</td>
<td></td>
</tr>
<tr>
<td>Other blockers (2/2 drugs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central adrenergic agonists (0/3 drugs, 1 not testable)†</td>
<td></td>
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</tbody>
</table>

*JNC VI indicates the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; PDR, Physicians’ Desk Reference; ACE, angiotensin-converting enzyme; and LA, long-acting. Doses are given for initiating treatment in adults with mild to moderate hypertension.
†Five drugs are produced as capsules, or as coated or irregularly shaped pills that cannot be prescribed at doses lower than recommended by the PDR.
‡The PDR-recommended “usual” initial dose of bisoprolol fumarate is 5 mg/d, but adds that 2.5 mg may be sufficient for “some patients.” The JNC VI recommends 2.5 mg initially for all patients.
§One brand of metoprolol (metoprolol succinate) has recommended 100 mg/d initially, whereas another brand (metoprolol tartrate) recommends 50 to 100 mg/d initially.
jThe PDR states “A dose of 10 mg also lowers blood pressure, but the full effect is not seen for 4-8 weeks.”

Table 2. Antihypertensive Drugs for Which the PDR Does Not Recommend Lower Initial Doses for Older Patients

<table>
<thead>
<tr>
<th>Medication</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretics (9/9 drugs)</td>
<td></td>
</tr>
<tr>
<td>Amiloride hydrochloride</td>
<td></td>
</tr>
<tr>
<td>Chlorthalidone</td>
<td></td>
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<tr>
<td>Ethacrynic acid</td>
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<tr>
<td>Furosemide</td>
<td></td>
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<tr>
<td>Hydrochlorothiazide</td>
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<tr>
<td>Metolazone</td>
<td></td>
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<tr>
<td>Spironolactone</td>
<td></td>
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<tr>
<td>Torsemide</td>
<td></td>
</tr>
<tr>
<td>Triamterene</td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors (8/8 drugs)</td>
<td></td>
</tr>
<tr>
<td>Captopril</td>
<td></td>
</tr>
<tr>
<td>Enalapril maleate</td>
<td></td>
</tr>
<tr>
<td>Fosinopril sodium</td>
<td></td>
</tr>
<tr>
<td>Lisinopril (more careful adjustments advised)</td>
<td></td>
</tr>
<tr>
<td>Moxepiril</td>
<td></td>
</tr>
<tr>
<td>Quinapril hydrochloride</td>
<td></td>
</tr>
<tr>
<td>Ramipril</td>
<td></td>
</tr>
<tr>
<td>Trandolapril</td>
<td></td>
</tr>
<tr>
<td>α-Receptor blockers (3/3 drugs)</td>
<td></td>
</tr>
<tr>
<td>Doxazosin mesylate</td>
<td></td>
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<tr>
<td>Prazosin hydrochloride</td>
<td></td>
</tr>
<tr>
<td>Terazosin hydrochloride</td>
<td></td>
</tr>
<tr>
<td>β-Blockers (7/10 drugs)</td>
<td></td>
</tr>
<tr>
<td>Acebutolol</td>
<td></td>
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<tr>
<td>Carteolol hydrochloride</td>
<td></td>
</tr>
<tr>
<td>Metoprolol succinate, tartrate</td>
<td></td>
</tr>
<tr>
<td>Nadolol</td>
<td></td>
</tr>
<tr>
<td>Penbutolol sulfate</td>
<td></td>
</tr>
<tr>
<td>Propranolol hydrochloride</td>
<td></td>
</tr>
<tr>
<td>Timolol maleate</td>
<td></td>
</tr>
<tr>
<td>Angiotensin II receptor blockers (3/3 drugs)</td>
<td></td>
</tr>
<tr>
<td>Irbesartan</td>
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<tr>
<td>Losartan potassium</td>
<td></td>
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<tr>
<td>Valsartan</td>
<td></td>
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<tr>
<td>Calcium antagonists (3/6 drugs)</td>
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<tr>
<td>Diltiazem</td>
<td></td>
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<tr>
<td>Nifedipine</td>
<td></td>
</tr>
<tr>
<td>Nisoldipine</td>
<td></td>
</tr>
<tr>
<td>Other drugs (4/6 drugs)</td>
<td></td>
</tr>
<tr>
<td>Carvedilol</td>
<td></td>
</tr>
<tr>
<td>Guanfacine hydrochloride</td>
<td></td>
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<tr>
<td>Labelol hydrochloride</td>
<td></td>
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<tr>
<td>Methyldopa</td>
<td></td>
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</tbody>
</table>

*PDR indicates Physicians’ Desk Reference; ACE, angiotensin-converting enzyme. Includes 37 (82%) of 45 antihypertensive drugs.
lated, starting with the lowest effective doses that minimize ADEs is recommended. MacConnelliche and Maclean link compliance directly to dosage: “Therefore, any measure [that] reduces the dosage requirement of an antihypertensive while maintaining therapeutic efficacy, or otherwise limits the possibility of commonly encountered ADEs, will encourage good patient compliance and so improve long-term control of hypertension.” For these reasons, some physicians subscribe to starting with a dose that may be subtherapeutic rather than a dose that is “correct” but may provoke troublesome ADEs.

FIRST-DOSE REACTIONS

First-dose reactions are ADEs that occur with the initial dose of a drug or when the dosage is increased. First-dose reactions have been described with the use of α-receptor blockers, calcium channel blockers, ACE inhibitors, and β-blockers, but clinical experience suggests that first-dose reactions may occur with any antihypertensive drug. First-dose reactions due to antihypertensive drugs are frequently dose related and may result from an abrupt lowering of blood pressure, causing postural hypotension, dizziness, syncope, headaches, lethargy, or other symptoms. First-dose reactivity explains why a large proportion of ADEs due to antihypertensive drugs occur at the beginning of treatment and may indicate that some patients are sensitive to the pharmacological effects of the standard initial doses of antihypertensive drugs that physicians are prescribing.

INITIAL DOSES FOR OLDER PATIENTS

Hypertension is most prevalent among people older than 60 years, and treatment can be especially challenging because of altered pharmacokinetics (eg, reduced liver and kidney function, and increased receptor sensitivity), which can produce even greater extremes in individual drug response than in younger adults. In addition, treatment is further complicated because two thirds of people older than 65 years take at least 1 medication daily, with the average being 3 prescription and/or nonprescription drugs daily. Thus, the overall incidence of ADEs is 2 to 3 times greater in elderly than in young adults. These ADEs in older patients are typically dose related and may result from an abrupt lowering of blood pressure, causing postural hypotension, dizziness, syncope, headaches, lethargy, or other symptoms. First-dose reactivity explains why a large proportion of ADEs due to antihypertensive drugs occur at the beginning of treatment and may indicate that some patients are sensitive to the pharmacological effects of the standard initial doses of antihypertensive drugs that physicians are prescribing.

RECOMMENDATIONS FOR CLINICAL PRACTICE

Hypertension is the most common indication for visits to US physicians, and it is a leading cardiovascular risk factor. Because of considerable variation among patients, the optimal pharmacological treatment of hypertension requires a flexible approach. Such flexibility involves the use of the lowest effective initial doses to facilitate a positive therapeutic alliance and to avoid ADEs that may affect compliance. Low-dose therapy allows patients time to adjust psychologically to the fact they have hypertension and to begin making lifestyle changes recommended by the physician—no small undertaking for most patients. Some patients experience distress about having hypertension and possibly requiring lifelong drug therapy, and they develop anxiety symptoms that may be mistaken for ADEs, which may lead to skipping doses or quitting treatment. Drug therapy commencing with minimal doses is generally more acceptable to patients, allays fears about unpleasant side effects, and minimizes possible confusion between drug-related ADEs vs anxiety-related symptoms or coincidental factors.

The danger in commencing treatment with the lowest recommended doses is, of course, undermedication, which also is a problem in antihypertensive management today. However, undermedication is usually a result of inadequate follow-up rather than a low initial dose. The stepwise approach to treating hypertension presupposes that proper titration will lead to higher doses in some patients or to the addition of 1 or 2 more antihypertensive drugs.

Table 3. Range of Dosages Provided by the Manufacturers of 45 Commonly Prescribed Antihypertensive Drugs

<table>
<thead>
<tr>
<th>Range of Dosages</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-Fold</td>
<td>Hydrochlorothiazide, metolazone (1 brand), torsemide, triamterene</td>
</tr>
<tr>
<td>2.5-Fold</td>
<td>Diluizem (2 brands)</td>
</tr>
<tr>
<td>3-Fold</td>
<td>Atenolol, captopril, chlorothalidone, guanfacine hydrochloride, nisoldipine, timolol maleate</td>
</tr>
<tr>
<td>4-Fold</td>
<td>Amlodipine hydrochloride, amiodipine, bisoprolol fumarate, carteolol hydrochloride, carvedilol, ethacrynic acid, felodipine, irbesartan, lisinopril, losartan potassium, metolazone (1 brand), nifedipine, penbutolol sulfate, verapamil hydrochloride, valsartan</td>
</tr>
<tr>
<td>5-Fold</td>
<td>Diluizem (1 brand), metoprolol tartrate</td>
</tr>
<tr>
<td>6-Fold</td>
<td>Acebutolol, methyldopa</td>
</tr>
<tr>
<td>7.5-Fold</td>
<td>Furosemide, guanadrel sulfate</td>
</tr>
<tr>
<td>8-Fold</td>
<td>Betaxolol hydrochloride, enalapril hydrochloride, fosinopril sodium, moexipril, nadolol, propranolol hydrochloride, quinapril hydrochloride, ramipril, spironolactone, trandolapril, metoprolol succinate</td>
</tr>
<tr>
<td>12-Fold</td>
<td>Clonidine hydrochloride, labetalol hydrochloride</td>
</tr>
<tr>
<td>15-Fold</td>
<td>Prazosin hydrochloride</td>
</tr>
<tr>
<td>16-Fold</td>
<td>Doxazosin mesylate</td>
</tr>
<tr>
<td>20-Fold</td>
<td>Terazosin hydrochloride</td>
</tr>
</tbody>
</table>

logical data on the response of older patients, so the physician’s ability to make educated judgments about dosage is limited. With some drugs, physicians wanting to use half doses are stymied because the pills do not facilitate this (capsules or irregular or coated tablets).
The optimal pharmacotherapy of hypertension depends on

the availability of information on the full range of effective
dosages of antihypertensive drugs. This includes effective
dosages that may be lower than those recommended by
drug manufacturers. The PDR is the most used source of
drug information among physicians, and it is heavily relied on by hospital staff who may lack the clinical experience to know that PDR dosage recommendations are general guidelines based on limited prerelease research, not on hard and fast rules of optimal therapeutics. This analysis reveals that, compared with the PDR, the initial doses of antihypertensive drugs recommended by JNC VI are substantially lower for 23 (58%) of 40 drugs for which the use of lower doses was possible. Moreover, although experts generally suggest reduced initial doses for older patients, the PDR does not recommend such reductions for old or even very old patients with 37 of 45 drugs. If the JNC VI recommendations, which represent prerelease and postrelease data, are considered the state of the art, mechanisms need to be implemented by which these recommendations are incorporated into the PDR and the corresponding package inserts, where physicians are most likely to see and use them. If such mechanisms cannot be established for the PDR, another source of current, readily available drug information should be created so that physicians' methods will keep pace with evolving standards of optimal pharmacotherapy for patients with hypertension.

CONCLUSIONS

The findings of this article raise many questions. What initial doses of antihypertensive drugs are physicians actually prescribing? Studies have shown that the recommendations of the JNC VI have had little impact on the types of antihypertensive drugs that physicians prescribe, but this has not been examined in regard to doses. Furthermore, the implementation of optimal pharmacotherapeutic methods ultimately depends on physicians. If physicians were better informed about the JNC VI–recommended initial doses of antihypertensive drugs, would they alter their methods? What would best motivate them to do so? What would motivate drug manufacturers to define the lowest, safest doses of new drugs in their prerelease research, to provide pills that allow for flexible dosing, to provide rational guidelines for older patients, and to reverse the trend that seems apparent in drug advertising toward 1-size-fits-all and other simplistic methods of dosing?

With a perennial high incidence of ADEs, most of which are dose related, and with well-defined problems with ADEs and compliance in treating hypertensive patients, these questions need to be answered and solutions need to be found and implemented.

REFERENCES


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23. Sorrentino MJ. Turning up the heat on hypertension: it's time to be more ag-
18. Cohen JS, Insel PA. The Physicians' Desk Reference: problems and possible im-
14. Flack JM, Yunis C, Preisser J, et al, for the ATIME Research Group. The rapidity
16. Physicians' Desk Reference. 54th ed. Montvale, NJ: Medical Economics Co,
17. Lip GY, Beevers DG. Doctors, nurses, pharmacists and patients: the Rational
19. Connelly DP, Rich EC, Curley SP, Kelly JT. Knowledge resource preferences of
20. Ely JW, Burch RJ, Vinson DC. The information needs of family physicians: case-
15. Lip GY, Beevers DG. Doctors, nurses, pharmacists and patients: the Rational
16. Physicians' Desk Reference. 53rd ed. Montvale, NJ: Medical Economics Com-
18. Cohen JS, Insel PA. The Physicians' Desk Reference: problems and possible im-
23. Sorrentino MJ. Turning up the heat on hypertension: it's time to be more ag-
14. Flack JM, Yunis C, Preisser J, et al, for the ATIME Research Group. The rapidity
16. Physicians' Desk Reference.53rd ed. Montvale, NJ: Medical Economics Com-
11. Caro JJ, Salas M, Speckman JL, et al. Persistence with treatment for hyperten-
12. MacConnachie AM, Maclean D. Low dose combination antihypertensive therapy:
19. Connelly DP, Rich EC, Curley SP, Kelly JT. Knowledge resource preferences of
10. Flack JM, Novikov SV, Ferrario CM. Benefits of adherence to anti-hypertensive
11. Caro JJ, Salas M, Speckman JL, et al. Persistence with treatment for hyperten-
12. MacConnaiche AM, Maclean D. Low dose combination antihypertensive therapy:
dose-response relationship in mild to moderate hypertension. J Cardiovasc
14. Flack JM, Yunis C, Preisser J, et al, for the ATIME Research Group. The rapidity
of drug dose escalation influences blood pressure response and adverse effects
burden in patients with hypertension: the Quinapril Titration Interval Manage-
15. Lip GY, Beevers DG. Doctors, nurses, pharmacists and patients: the Rational
Evaluation and Choice in Hypertension (REACH) survey of hypertension care
16. Physicians’ Desk Reference. 53rd ed. Montvale, NJ: Medical Economics Com-
pany; 1999.
18. Cohen JS, Insel PA. The Physicians’ Desk Reference: problems and possible im-
19. Connelly DP, Rich EC, Curley SP, Kelly JT. Knowledge resource preferences of
20. Ely JW, Burch RJ, Vinson DG. The information needs of family physicians: case-
American Society of Hospital Pharmacists; 1999.
23. Sorrentino MJ. Turning up the heat on hypertension: it’s time to be more ag-
gressive in finding and treating this silent killer. Postgrad Med. 1999;105:82-84, 89-93.
24. Curzen N, Purcell H. Matching the treatment to the patient in hypertension. Prac-
titioner. 1997;241:152-156.
26. Liebson PR, Grandits GA, Dianzumba S, et al. Comparison of five antihyperten-
sive monotherapies and placebo for change in left ventricular mass in patients
receiving nutritional-hygienic therapy in the Treatment of Mild Hypertension Study
27. Gran B. Non-pharmacological methods reduce drug use in the treatment of hy-
9:121-128.
28. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hos-
pitalized patients: a meta-analysis of prospective studies. JAMA. 1998;279:1200-
1205.
29. Melmon KL, Morrelli HF, Hoffman BB, Nierenberg DW. Melmon and Morrelli’s
Clinical Pharmacology: Basic Principles in Therapeutics. 3rd ed. New York, NY:
30. Insinna F, Zarcone P, Cimino R. Hypotensive drugs and first-dose syndrome:
considerations on 5 cases observed during treatment with ACE inhibitors [in Itali-
31. Mullen PJ. Unexpected first dose hypotensive reaction to enalapril. Postgrad Med
32. Montolivio J, Botev A, Darnell A, Revert L. Prolonged hypotension after the first
34. Monane M, Bohn RL, Gurwitz JH, et al. The effects of initial drug choice and co-
morbidity on antihypertensive therapy compliance: results from a population-
35. Reynolds E, Baron RB. Hypertension in women and the elderly: some puzzling
and some expected findings of treatment studies. Postgrad Med. 1996;100:58-63,
67-70.
36. Montamat SC, Cusack BJ, Vestal RE. Management of drug therapy in the el-
37. Williams RD. Medications and older adults. FDA Consumer. September-
October 1997 [Food and Drug Administration Web site]. Available at: http:
38. Brawn LA, Castleden CM. Adverse drug reactions: an overview of special con-
siderations in the management of the elderly patient. Drug Safety. 1990;5:421-
435.
39. Rochon PA, Anderson GM, Tu JV, et al. Age- and gender-related use of low-
dose therapy: the need to manufacture low-dose therapy and evaluate the mini-
J Hypertens. 1997;10(suppl pt 2):300S-305S.
42. Frohlich ED. Continuing advances in hypertension: the Joint National Commit-
43. Ray WA, Griffin MR, Avorn J. Evaluating drugs after their approval for clinical
the JNC V recommendations affect prescribing? JAMA. 1997;278:1745-1748.
45. Lent cant. JNC guidelines: is the message getting through? JAMA. 1997;278:
1778-1779.