RESEARCH

Informed consent for antipsychotic medication

Do family physicians document obtaining it?

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ABSTRACT

OBJECTIVE To determine family physicians' attitudes and practices regarding documentation of informed consent for antipsychotic medication.

DESIGN Pilot cross-sectional study.

SETTING Teaching and non-teaching hospitals in Toronto, Ont.

PARTICIPANTS Thirty family physicians were selected in equal numbers from teaching and non-teaching hospitals with no more than five physicians from a given hospital. Participants were treating at least 10 patients with antipsychotic medication. Participants' mean age was 44.3 years; 83% were men.

MAIN OUTCOME MEASURES Documentation of consent and of disclosure of consent for antipsychotic medication in patients' charts.

RESULTS Documentation was found in only 13% of charts. Whether it was there or not did not correlate with information disclosed, score on an attitude scale, or demographics. Physicians who found documentation time-consuming were less likely to document. Most physicians disclosed reasons for antipsychotic medication, but less than half described tardive dyskinesia, a potentially irreversible movement disorder that affects about 25% of patients on long-term treatment.

CONCLUSIONS The low rate of documentation observed in this sample was consistent with reports of similar samples and might indicate that family physicians are unaware of recommendations for documentation or simply do not have time to keep abreast of current recommendations. Many physicians thought signed consent forms unnecessary for psychotic patients, and even more believed seeking consent for antipsychotic medications would increase patient anxiety.

RÉSUMÉ

OBJECTIF Déterminer les attitudes et les comportements des médecins concernant la documentation du consentement éclairé dans le cas d'une pharmacothérapie antipsychotique.

CONCEPTION Une étude expérimentale transversale.

CONTEXTE Des hôpitaux d'enseignement et non enseignants à Toronto, en Ontario.

PARTICIPANTS Trente médecins de famille ont été choisis en nombre égal dans les hôpitaux d'enseignement et non enseignants, jusqu'à concurrence de cinq médecins par hôpital. Les participants traitaient au moins dix patients avec des antipsychotiques. L'âge moyen des participants s'élevait à 44,3 ans et 83% d'entre eux étaient des hommes.

PRINCIPALES MESURES DES RÉSULTATS La documentation concernant le consentement et la divulgation du consentement concernant les antipsychotiques versée au dossier des patients.

RÉSULTATS Seulement 13% des dossiers comportaient une documentation à cet effet. Il n'y avait pas de corrélation entre la présence ou l'absence de documentation et l'information divulguée, la note obtenue sur l'échelle d'attitude ou la démographie. Les médecins qui trouvaient la documentation onéreuse au point de vue de temps étaient moins susceptibles de documenter le consentement. La majorité des médecins indiquaient les motifs de l'ordonnance d'antipsychotiques, mais moins de la moitié décrivaient la dyskinésie tardive, un trouble de la motricité potentiellement irréversible, qui affecte environ 25% des patients qui suivent cette pharmacothérapie à long terme.

CONCLUSIONS Le faible taux de documentation observé dans cet échantillon est comparable à celui d'autres rapports sur des échantillons semblables et pourrait indiquer que les médecins de famille ne sont pas au courant des recommandations concernant la documentation ou n'ont simplement pas le temps de se tenir au fait des recommandations les plus récentes. Plusieurs médecins jugeaient inutile de faire signer un formulaire de consentement dans le cas de patients psychotiques et un plus grand nombre encore d'entre eux étaient d'avis que de chercher à obtenir la signature d'un formulaire de consentement pour des médicaments antipsychotiques ferait augmenter l'anxiété chez ces patients.

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Antipsychotic medication is the treatment of choice for psychosis and schizophrenia and is used as adjunctive therapy for aggression associated with organic brain syndromes.[1] The benefits of classic antipsychotic medications must be weighed against potential side effects, particularly tardive dyskinesia, a potentially irreversible movement disorder that affects about 25% of patients receiving long-term treatment.[2]

Older women, elderly people generally, and patients with brain damage or affective disorders are at increased risk of tardive dyskinesia.[1] Elderly people are also at increased risk of developing other side effects, such as postural hypotension, sedation, or anticholinergic effects.[1] Newer atypical antipsychotic medications, such as clozapine, risperidone, and olanzapine, are believed to pose less risk of tardive dyskinesia.[3,4]

Informed consent allows patients to make treatment decisions based on the best possible information and is particularly important for antipsychotic medications.[1,5] In Canada, the Reibl versus Hughes decision[6] raised the legal standard of disclosure to what a reasonable patient in that patient's circumstances would want disclosed. Elements of consent include that it be specific, informed, voluntary, and given by a patient capable of understanding the process. Information disclosed includes the nature, benefits, and risks of the proposed treatment and alternative treatment(s), including the option of no treatment.

For medical and legal reasons, professional associations and others recommended documenting informed consent for antipsychotic medication.[1,5,7] Some institutions have developed checklists to facilitate documentation.[8,9]

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It is unclear whether these medical-legal guidelines have translated into family physicians' practices. First, clinical guidelines are not the sole determinants of physician behaviour.[10,11] Second, most literature dealing with informed consent appears in psychiatric, medical-legal, or ethics journals rather than in general medical journals, even though many family physicians prescribe antipsychotic medication.[12]

Gurian et al[13] found no documentation of consent in charts of patients in long-term care facilities, and facilities' house staff reported documenting consent rarely or never. A study of psychiatrists' patient charts found 40% contained acceptable documentation; documentation was more complete for new prescriptions than for renewals.[8]

How family physicians feel about consent documentation is unclear. Although some attorneys favour written consent forms,[14] one survey showed that few psychiatrists did.[15] The American Psychiatric Association thought written consent forms for clinical purposes might introduce an adversarial quality to doctor-patient relationships. Physicians do not routinely endorse written consent forms for research.[16] Attitudes to research with greater disclosure requirements, however, might not hold true for clinical practice. This study determines family physicians' attitudes and practices regarding documentation of consent for antipsychotic medication.

METHOD

In 1992, 30 family physicians in Toronto, each treating at least 10 patients with antipsychotic medication, were selected. Physicians came in equal numbers from teaching and non-teaching hospitals. No more than five physicians were selected from any one hospital. Physicians provided informed consent for the study and received $100 for participating.

Procedure

Participants completed a self-report questionnaire on their behaviour and attitudes toward disclosure and documentation of informed consent for antipsychotic medication and were interviewed about their attitudes to disclosure of information. Physicians were also asked to describe discrepancies among the attitude items and between attitudes and behaviours.

Participants provided charts of the 10 patients receiving antipsychotic medication they had seen most recently. One physician provided only nine charts. Physicians and a researcher reviewed the

charts together. In the presence of the researcher, physicians looked for documentation and showed it when found. This paper examines the physicians' self-reports of disclosure regarding antipsychotic medication.

Self-report questionnaire

The questionnaire's face validity was determined by showing it to nine experienced psychiatrists and 10 experienced GPs (not including any of the 30 family physicians in the study) before the study took place. The questionnaire was divided into three sections: a section on behaviour regarding disclosure of information about benefits and risks of antipsychotic medication; a section on behaviour regarding documentation; and a section on attitudes with three subsections dealing with informed consent in general, informed consent involving antipsychotic medication, and documentation of informed consent.

Individual disclosure items were rated using a 5-point Likert scale (5—always, 4—almost always, 3—sometimes, 2—almost never, and 1—never). The overall behaviour score is a mean of the 17 items composing this scale. Self-report of documentation behaviour was derived from four questions scored using a similar Likert scale.

Questions about attitudes were answered using a 5-point Likert scale ranging from 1—strongly agree to 5—strongly disagree. The subscale on attitude to documentation consisted of nine positively or negatively keyed items. The mean of individual items provided the score. This study reports on attitudes to documentation. The questionnaire had good test-retest reliability as determined by 32 psychiatrists and family physicians not involved in the study, using the Pearson or intraclass correlation coefficient.[17] The actual documentation rate is the percentage of charts with documentation of consent.

RESULTS

Physicians' mean age was 44.3 (standard deviation [SD] ± 10); 83% were men. Average year of graduation from medical school was 1973 (SD ± 10.3). Physicians had spent a mean of 2.33 (SD ± 1.2) years in postgraduate medical training, and 70% were certificants of the College of Family Physicians of Canada (CFPC). Physicians reported they spent an average of 9.9 (SD ± 9.1) hours each month reading medical journals and 70 (SD ± 46.9) hours each year in continuing medical education (CME) activities.

Table 1. Family physicians' disclosure practices (N = 30)

INFORMATION	ALWAYS OR ALMOST ALWAYS DISCLOSED (%)	SOMETIMES DISCLOSED (%)	NEVER OR ALMOST NEVER DISCLOSED (%)
Reasons for antipsychotic medication	84	13	3
Alternatives to antipsychotic medication	60	30	10
Whether medication is a major tranquilizer or antipsychotic	57	40	3
Brand or generic name of medication	66	27	7
Dosage of medication	64	30	6
Consequences of not receiving medication	67	33	0
Akathisia	44	43	13
Dystonic reactions	50	43	7
Rigidity	40	50	10
Tardive dyskinesia	40	40	20

Self-report of disclosure

Most physicians (84%) routinely informed patients about reasons for antipsychotic medication, and about 66% routinely informed them about alternatives, drug classification, medication name, dosage, and the consequences of not taking medication (**Table 1**). Fewer than half routinely informed patients about tardive dyskinesia. Mean score on disclosure behaviour was 3.3 (SD ± .60).

Self-reports of documentation

Physician reports of documenting informed consent ranged from always to never (**Table 2**). About 67% said they did not document informed consent for competent patients, while 50% said they did not for incompetent patients.

Actual documentation

On average, physicians had documentation in 13% (SD ± .22) of charts. There was good correlation between self-reports of documentation and actual documentation (r 0.64, n 30, P < .001).

The three physicians who reported routinely documenting consent for competent patients had documentation in 50% of charts; the six who reported sometimes documenting consent had documentation in 39% of charts; and the 18 who said they never or

Table 2. Self-reports of documentation (N = 30)

PRACTICE	ALWAYS OR ALMOST ALWAYS (%)	SOMETIMES (%)	NEVER OR ALMOST NEVER (%)
Document in chart that a competent patient was informed about risks and benefits of antipsychotic medication	10	23.3	66.6
Obtain written consent when prescribing antipsychotics to competent patients	0	0	100
Document in chart that a relative of an incompetent patient was informed about risks and benefits of antipsychotic medication	27.6	20.7	51.7
Obtain written consent from relatives when prescribing antipsychotics to incompetent patients	0	3.4	96.6

almost never documented consent had documentation in 2% of charts. When consent was obtained from relatives, the four physicians who reported routinely documenting consent had documentation in 17% of charts; the five who sometimes documented had documentation in 15% of charts; and the 14 who reported never or almost never documenting consent had documentation in 10% of charts.

Attitudes to documentation

Attitudes to documenting informed consent are shown in **Table 3**. Virtually all physicians endorsed having signed consent forms for surgery; only 23% thought they were necessary for non-surgical procedures. Only 40% thought they were necessary for medications with serious side effects; 77% thought they were not necessary for antipsychotic medication. Only 53% of participants agreed that informed consent for antipsychotic medications should be recorded, and 90% thought consent to antipsychotic medications should not be audiotaped or videotaped. Reasons physicians did not endorse signed consent forms included thinking they might increase patients' anxiety (83%), thinking they might be detrimental to physician-patient relationships (37%), and thinking that documenting informed consent took too much time (30%). Mean score on the attitude-to-documentation subscale was 2.8 (SD±0.47).

Table 3. Attitudes to documentation (N = 30)

ATTITUDE	AGREE OR STRONGLY AGREE (%)	NEUTRAL (%)	DISAGREE OR STRONGLY DISAGREE (%)
Patients should sign consent forms for surgical procedures	93	7	0
Patients should sign consent forms for non-surgical medical procedures	23	17	60
Signed consent forms for medications with serious side effects are necessary	40	20	40
Signed consent forms for antipsychotics are unnecessary	77	20	3
Informed consent process for antipsychotics should be recorded in chart	53.3	23.3	23.3
Informed consent process for antipsychotics should be audiotaped or videotaped	3	7	90
Signed consent forms could increase patient anxiety	83	14	3
Consent forms for medication might be detrimental to patient-physician relationships	36.7	26.7	36.7
It takes too much time to document that risks and benefits were explained to patient	30	23	47

Correlates of actual documentation

Actual documentation did not correlate with total information disclosed to patients (r -.10, n 30, P not significant [NS]), information about tardive dyskinesia (r -.21, n 30, P NS), or documentation attitude score (r .12, n 30, P NS). In bivariate and multivariate analyses, none of sex, hospital affiliation, CFPC certification, hours spent in formal CME, or smallest interval since either graduation significantly explained variation in actual documentation.

Among the individual documentation attitude items, only one significantly correlated with actual documentation. Physicians who agreed that documentation takes too much time were less likely to actually document (r.45, P<.013).

DISCUSSION

The low rate of documentation reported is consistent with rates observed in chronic care facilities,[13] in a survey of psychiatrists,[18] and in our findings among psychiatrists.[19] Physicians tended to overestimate their documentation activities. Documentation behaviour did not correlate with the amount of information given to patients about antipsychotic medication or about tardive dyskinesia. The data did not support the hypothesis that physicians aware of the medical-legal necessity of informing patients about tardive dyskinesia would be both more likely to inform patients about the side effects of medication and to note this in patients' charts. While most physicians disclosed some information about antipsychotic medication, less than half specifically informed patients about tardive dyskinesia.

The low rates of documentation are consistent with more than half the sample thinking that informed consent need not be recorded. Documentation behaviour did not correlate with age, sex, interval since education, CFPC certification, hours spent reading medical journals, participation in CME, or hospital affiliation. The finding that CME involvement was not related to documentation activity agrees with results of a study of quality of care among Ontario family physicians.[20,21] Randomized trials of the effects of CME, however, have shown improvement in physician performance and health care outcomes.[22] This suggests that, while CME does affect specific activities, general CME involvement might not affect a particular aspect of behaviour, such as documentation of consent for antipsychotic medication or disclosure of information about tardive dyskinesia.

This study did not find differences in documentation behaviour related to age or sex, but other studies have found younger physicians perform better than older physicians in care and documentation and that women and younger physicians keep better charts.[21,23] The fact that CFPC certification did not affect documentation behaviour differs from results of other studies where CFPC membership has been associated with better care and more careful documentation.[21] In this study, while the sample size was large enough to detect a moderate effect for age and CME involvement, it did not have enough power to detect a moderate effect for sex or CFPC membership.

Virtually no physicians thought the process of informed consent for antipsychotic medications should be audiotaped or videotaped. Most physicians thought signed consent forms were unnecessary for antipsychotic medications, but were necessary for surgical procedures. They were divided on whether signed consent forms were necessary for medications with serious side effects and on whether consent forms for medications were detrimental to patient-physician relationships.

Table 4. Risks and benefits of neuroleptic medication

Neuroleptic medication leads to rapid control of symptoms such as hearing voices, seeing visions, feeling persecuted, and confused thinking. Neuroleptic medication has also been shown to have long-term benefits in that it prevents relapses in schizophrenia. Psychotherapy and social therapy are other forms of treatment used to help patients with schizophrenia, but neither is as effective as neuroleptic medication for preventing relapse.
Neuroleptic medication sometimes has side effects. Occasionally, within the first week of treatment, patients develop muscular spasms in the head, eyes, and neck. Some patients develop other symptoms, such as stiffness, restlessness, and the shakes. All these side effects are treatable with anticholinergic medication.
There is a serious, long-term risk associated with neuroleptic medication. Certain patients develop abnormal, involuntary movements that affect the tongue, mouth, jaw, and, occasionally, the trunk and extremities. These movements are called tardive dyskinesia. This complication is serious because there is no specific treatment for it, and it might not be reversible. This means that some patients will have the unwanted movements associated with tardive dyskinesia for the rest of their lives.
It is impossible to predict exactly which patients will get tardive dyskinesia. Certain studies suggest that older patients and women are at higher risk. According to available studies, as many as 20% to 25% of patients on long-term neuroleptic medication could develop this side effect. Tardive dyskinesia can appear within several months of treatment or take years to develop.
Although there is no known treatment for tardive dyskinesia, stopping the neuroleptic medication might result in a decrease and, in some cases, complete disappearance of the involuntary movements. In stopping the medication, however, there is a risk that the involuntary movements will increase. Some patients experience no change.
The best way to have the involuntary movements of tardive dyskinesia disappear is to discover it early and stop the neuroleptic medication. It is important to realize, however, that completely stopping the medication might result in the return of the original symptoms.
One way to lessen the risk of developing tardive dyskinesia is to use the minimum necessary dose of neuroleptic medication. It is important that patients receiving this medication are closely followed by doctors who can correctly adjust the dosage of medication and watch for the earliest signs of tardive dyskinesia.

**Reprinted with permission from Kleinman et al.[24]*

Limitations

This study has some methodologic limitations. First, the sample was not a representative sample of family physicians so the results might not be generalizable to other family physicians. Also, sample selection excluded physicians with no hospital affiliation and those with fewer than 10 patients receiving antipsychotic medication (it could be assumed that family physicians working with many psychotic patients would be a more informed group than other physicians). The sample also included some physicians who reported spending considerably more time in formal CME activities than the CFPC recommends. Finally, this study did not have sufficient power to detect small effect sizes for the continuous variables or moderate effect sizes for the categorical variables. Thus, the results reported here can be best described as pilot data requiring replication with larger, more representative samples.

Conclusion

This pilot study reports family physicians' rates of disclosure about and documentation of consent for antipsychotic medication and their attitudes to documentation. The low rates of disclosure of tardive dyskinesia and documentation are consistent with the literature and suggest a gap between recommended documentation practices and actual attitudes and practice. The gap might reflect limited awareness of recommendations, due to dissemination problems, or lack of time to keep abreast of recommendations. Information forms (eg, **Table 4**[24]) might facilitate disclosure and documentation by reminding physicians of these activities. To facilitate adoption of recommendations, specialists and family physicians need to collaborate in development and dissemination of guidelines and practical tools that will help family physicians adhere to recommendations.

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Key points

- Antipsychotic medications can cause tardive dyskinesia, a potentially irreversible movement disorder, in up to 25% of patients on long-term treatment.
- This survey found that less than half the family physicians routinely informed patients about tardive dyskinesia, and only 13% documented such disclosure on their charts. Studies of psychiatrists had similar findings.
- Many (77%) family physicians thought signed consent forms unnecessary for psychotic patients; 83% believed they would increase patient anxiety; 30% thought explaining the process and getting the forms signed would take too much time.

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P ONCE • A • DAY **Plendil**

FELODIPINE EXTENDED RELEASE TABLETS

2.5 mg, 5 mg and 10 mg

Antihypertensive Agent/Dihydropyridine Calcium Channel Blocker

INDICATIONS AND CLINICAL USE PLENDIL (felodipine) is indicated in the treatment of mild to moderate essential hypertension. PLENDIL should normally be used in those patients in whom treatment with a diuretic or a beta-blocker was found ineffective or has been associated with unacceptable adverse effects. PLENDIL can be tried as an initial agent in those patients in whom the use of diuretics and/or beta-blockers is contraindicated or in patients with medical conditions in which these drugs frequently cause serious adverse effects. Combination of PLENDIL with a thiazide diuretic or a beta-blocker has been found to be compatible and showed an additive antihypertensive effect. Safety and efficacy of concurrent use of PLENDIL with other antihypertensive agents has not been established.

CONTRAINDICATIONS PLENDIL (felodipine) is contraindicated in:

1) Patients with a known hypersensitivity to felodipine or other dihydropyridines.

2) In women of childbearing potential, in pregnancy, and during lactation. Fetal malformations and adverse effects on pregnancy have been reported in animals. **Teratogenic Effects.** Studies in pregnant rabbits administered doses of 0.46, 1.2, 2.3 and 4.6 mg/kg/day (from 0.4 to 4 times the maximum recommended human dose on a mg/m^2 basis) showed digital anomalies consisting of reduction in size and degree of ossification of the terminal phalanges in the fetuses. The frequency and severity of the changes appeared dose-related and were noted even at the lowest dose. These changes have been shown to occur with other members of the dihydropyridine class. Similar fetal anomalies were not observed in rats given felodipine. In a teratology study in cynomologus monkeys, no reduction in the size of the terminal phalanges was observed but an abnormal position of the distal phalanges was noted in about 40 percent of the fetuses. **Non-teratogenic Effects.** In a study on fertility and general reproductive performance in rats, prolongation of parturition with difficult labour and an increased frequency of fetal and early postnatal deaths were observed in the groups treated with doses of 9.6 mg/kg/day and above. Significant enlargement of the mammary glands in excess of the normal enlargement for pregnant rabbits was found with doses greater than or equal to 1.2 mg/kg/day. This effect occurred only in pregnant rabbits and regressed during lactation. Similar changes in the mammary glands were not observed in rats or monkeys.

WARNINGS Congestive Heart Failure. The safety and efficacy of PLENDIL (felodipine) in patients with heart failure has not been established. Caution should, therefore, be exercised when using PLENDIL in hypertensive patients with compromised ventricular function, particularly in combination with a beta-blocker. Acute hemodynamic studies in a small number of patients with New York Heart Association Class II or III heart failure treated with felodipine have not demonstrated negative inotropic effects. **Hypotension, Myocardial Ischemia.** PLENDIL may, occasionally, precipitate symptomatic hypotension and rarely syncope. It may lead to reflex tachycardia which, particularly in patients with severe obstructive coronary artery disease, may result in myocardial ischemia. Careful monitoring of blood pressure during the initial administration and titration of felodipine is recommended. Care should be taken to avoid hypotension especially in patients with a history of cerebrovascular insufficiency, and in those taking medications known to lower blood pressure. **Beta-Blocker Withdrawal.** PLENDIL gives no protection against the dangers of abrupt beta-blocker withdrawal; any such withdrawal should be a gradual reduction of the dose of beta-blockers. **Outflow Obstruction.** PLENDIL should be used with caution in the presence of fixed left ventricular outflow obstruction.

PRECAUTIONS Peripheral Edema. Mild to moderate peripheral edema was the most common adverse event in the clinical trials. The incidence of peripheral edema was dose-dependent. Frequency of peripheral edema ranged from about 10 percent in patients under 50 years of age taking 5 mg daily to about 30 percent in those over 60 years of age taking 20 mg daily. This adverse effect generally occurs within 2-3 weeks of the initiation of treatment. Care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction. **Use in Elderly Patients.** Patients over 65 years of age may have elevated plasma concentrations of felodipine and, therefore, may require lower doses of PLENDIL (see ACTION AND CLINICAL PHARMACOLOGY – Pharmacokinetics'). These patients should have their blood pressure monitored closely during initial administration and after dosage adjustment of PLENDIL. A dosage of 10 mg daily should not be exceeded (see DOSAGE AND ADMINISTRATION - Use in the Elderly). **Use in Patients with Impaired Liver Function.** Patients with impaired liver function may have elevated plasma concentrations of felodipine and, therefore, may require lower doses of PLENDIL (see ACTION AND CLINICAL PHARMACOLOGY– Pharmacokinetics'). These patients should have their blood pressure monitored closely during initial administration and after dosage adjustment of PLENDIL. A dosage of 10 mg daily should not be exceeded (see DOSAGE AND ADMINISTRATION – Use in Patients with Impaired Liver Function). **Gingival Hyperplasia.** PLENDIL can induce gingival enlargement in patients with pronounced gingivitis and parodontitis. However, such changes may be reversed by measures of good oral hygiene and mechanical debridement of the teeth. **Pregnancy and Lactation.** See CONTRAINDICATIONS. **Use in Children.** PLENDIL is not recommended in children since the safety and efficacy in children have not been established. **Interaction with Grapefruit Juice.** Published data shows that through inhibition of cytochrome P-450, grapefruit juice can increase plasma levels and augment pharmacodynamic effects of dihydropyridine calcium channel blockers. In view of the absolute bioavailability of PLENDIL, the potential for a significant increase in pharmacodynamic effects exists (see ACTION AND CLINICAL PHARMACOLOGY – Pharmacokinetics'). Therefore, the consumption of grapefruit juice prior to or during treatment with PLENDIL should be avoided. **Drug Interactions.** As with all drugs, care should be exercised when treating patients with multiple medications. Dihydropyridine calcium channel blockers undergo biotransformation by the cytochrome P-450 system, mainly via the CYP 3A4 isoenzyme. Coadministration of felodipine with other drugs which follow the same route of biotransformation may result in altered bioavailability of felodipine or these drugs. Dosages of similarly metabolized drugs, particularly those of low therapeutic ratio, and especially in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered felodipine to maintain optimum therapeutic blood levels. Drugs known to be inhibitors of the cytochrome P-450 system include: azole antifungals, cimetidine, cyclosporine, erythromycin, quinidine, warfarin. Drugs known to be inducers of the cytochrome P-450 system include: phenobarbital, phenytoin, rifampin. Drugs known to be biotransformed via P-450 include: benzodiazepines, flecainide, imipramine, propafenone, terfenadine, theophylline. **Enzyme Inhibitors.** *Cimetidine:* In healthy volunteers pharmacokinetic studies showed an approximately 50 percent increase in the area under the plasma concentration time curve (AUC) as well as the C_{max} of felodipine when given concomitantly with cimetidine. It is anticipated that a clinically significant interaction may occur in some hypertensive patients. Therefore, it is recommended that low doses of PLENDIL be used when given concomitantly with cimetidine. *Erythromycin:* Concomitant treatment with erythromycin has been shown to cause an increase in felodipine plasma levels. **Enzyme Inducers.** *Phenytoin, Carbamazepine and Phenobarbital:* In a pharmacokinetic study maximum plasma concentrations of felodipine were considerably lower in epileptic patients on long-term anticonvulsant therapy (phenytoin, carbamazepine, phenobarbital) than in healthy volunteers. The mean area under the felodipine plasma concentration-time curve was also reduced in epileptic patients to approximately 6% of that observed in healthy volunteers. Since a clinically significant interaction may be anticipated, alternative antihypertensive therapy should be considered in these patients. *Alcohol:* Alcohol can enhance the hemodynamic effects of felodipine. *Beta-Adrenoceptor Blocking Agents:* A pharmacokinetic study of felodipine in conjunction with metoprolol demonstrated no significant effects on the pharmacokinetics of felodipine. The AUC and C_{max} of metoprolol, however, were increased approximately 31 and 36 percent, respectively. In controlled clinical trials, however, beta-blockers including metoprolol were concurrently administered with felodipine and were well tolerated. *Digoxin:* When given concomitantly with felodipine as conventional tablets the peak plasma concentration of digoxin was significantly increased. With the extended release formulation of felodipine there was no significant change in peak plasma levels or AUC of digoxin. *Other Concomitant Therapy:* In healthy subjects there were no clinically significant interactions when felodipine was given concomitantly with indomethacin or spironolactone.

ADVERSE REACTIONS In 861 essential hypertensive patients treated once daily with 2.5 mg to 10 mg PLENDIL (felodipine) as monotherapy in controlled clinical trials, the most common clinical adverse events were peripheral edema and headache. Adverse events that occurred with an incidence of 1.5% or greater at any of the recommended doses of 2.5 mg to 10 mg once a day, without regard to causality, are listed by dose in Table 1 below. These events are reported from controlled clinical trials with patients who were randomized to either a fixed dose of PLENDIL or titrated from an initial dose of 2.5 mg or 5 mg once a day. **A dose of 20 mg once a day has been evaluated in some clinical studies. Although the antihypertensive effect of PLENDIL is increased at 20 mg once a day, there is a disproportionate increase in adverse events, especially those associated with vasodilatory effects** (see DOSAGE AND ADMINISTRATION).

Table 1. Percent of patients with adverse events in controlled trials of PLENDIL (N=861)* as monotherapy without regard to causality (incidence of discontinuations shown in parentheses).

Body System Adverse Events	Placebo N=334	2.5 mg N=255	5 mg N=581	10 mg N=408
Body as a Whole				
Peripheral Edema	3.3 (0.0)	2.0 (0.0)	8.8 (2.2)	17.4 (2.5)
Asthenia	3.3 (0.0)	3.9 (0.0)	3.3 (0.0)	2.2 (0.0)
Cardiovascular				
Palpitation	2.4 (0.0)	0.4 (0.0)	1.4 (0.3)	2.5 (0.5)
Warm Sensation/Flushing	0.9 (0.3)	3.9 (0.0)	6.2 (0.9)	8.4 (1.2)
Digestive				
Nausea	1.5 (0.9)	1.2 (0.0)	1.7 (0.3)	1.0(0.7)
Dyspepsia	1.2 (0.0)	3.9 (0.0)	0.7 (0.0)	0.5 (0.0)
Constipation	0.9 (0.0)	1.2 (0.0)	0.3 (0.0)	1.5 (0.2)
Nervous				
Headache	10.2 (0.9)	10.6 (0.4)	11.0 (1.7)	14.7 (2.0)
Dizziness	2.7 (0.3)	2.7 (0.0)	3.6 (0.5)	3.7 (0.5)
Paresthesia	1.5 (0.3)	1.6 (0.0)	1.2 (0.0)	1.2 (0.2)
Respiratory				
Upper Respiratory Infection	1.8 (0.0)	3.9 (0.0)	1.9 (0.0)	0.7 (0.0)
Cough	0.3 (0.0)	0.8 (0.0)	1.2 (0.0)	1.7 (0.0)
Skin				
Rash	0.9 (0.0)	2.0 (0.0)	0.2 (0.0)	0.2 (0.0)

* Some patients have been exposed to more than one dose level of PLENDIL.

Adverse events that occurred in 0.5 up to 1.5 percent of patients who received PLENDIL in all controlled clinical trials at the recommended dosage range of 2.5 mg to 10 mg once a day are listed below. These events are listed in order of decreasing severity within each category regardless of relationship to PLENDIL therapy: *Body as a Whole:* Chest pain, facial edema, flu-like illness; *Cardiovascular:* Tachycardia, premature beats, postural hypotension, bradycardia; *Gastrointestinal:* Abdominal pain, diarrhea, vomiting, dry mouth, flatulence, acid regurgitation, cholestatic hepatitis, gingival hyperplasia, salivary gland enlargement; *Metabolic:* ALT (SGPT) increased; *Musculoskeletal:* Arthralgia, muscle cramps, myalgia; *Nervous/Psychiatric:* Insomnia, depression, anxiety disorders, irritability, nervousness, somnolence, decrease in libido, tremor, confusion; *Respiratory:* Dyspnea, epistaxis; *Dermatologic:* Pruritis, erythema multiforme, erythema nodosum, urticaria, photosensitivity reactions; *Special Senses:* Visual disturbances; *Urogenital:* Impotence, urinary frequency, urinary urgency, dysuria, polyuria. Serious adverse events reported from controlled clinical trials and during marketing experience (incidence <0.5 percent) were myocardial infarction, hypotension, syncope, angina pectoris, arrhythmia and anemia. Isolated cases of angioedema have been reported. Angioedema may be accompanied by breathing difficulty. *Laboratory tests:* For the following laboratory values statistically significant decreases were observed; bilirubin, red blood count, hemoglobin, and urate. Statistically significant increases were found in erythrocyte sedimentation rate and thrombocyte count. In isolated cases, there were increased liver enzymes. None of these changes were considered to be of clinical significance.

DOSAGE AND ADMINISTRATION PLENDIL should be swallowed whole and not crushed or chewed. The usual recommended initial dose is 5 mg once daily (see DOSAGE AND ADMINISTRATION – Use in the Elderly, and – Use in Patients with Impaired Liver Function). Depending on the patient's response, the dosage should be adjusted accordingly. Dose adjustment, if necessary, should be done at intervals of not less than two weeks. The maintenance dosage range is 2.5 mg to 10 mg once daily. In clinical trials, doses above 10 mg daily showed an increased blood pressure response but a disproportionately higher incidence of peripheral edema and other vasodilatory adverse events. Modification of the recommended dosage is usually not required in patients with renal impairment. **Use in the Elderly** Patients over 65 years of age may develop elevated plasma concentrations of felodipine. A starting dose no higher than 2.5 mg once daily is recommended. A dosage of 10 mg daily should not be exceeded (see PRECAUTIONS – Use in Elderly Patients). **Use in Patients with Impaired Liver Function** Patients with impaired liver function may develop elevated plasma concentrations of felodipine. A starting dose no higher than 2.5 mg once daily is recommended. A dosage of 10 mg daily should not be exceeded (see PRECAUTIONS – Use in Patients with Impaired Liver Function).

AVAILABILITY PLENDIL tablets are extended release, film-coated tablets, containing felodipine in strengths of 2.5 mg, 5 mg and 10 mg.

PLENDIL 2.5 mg Tablet: A yellow, circular, biconvex film-coated tablet, engraved A|R on one side and 2.5 on the other. PLENDIL 5 mg Tablet: A pink, circular, biconvex film-coated tablet, engraved A|M on one side and 5 on the other. PLENDIL 10 mg Tablet: A red-brown, circular, biconvex film-coated tablet, engraved A|E on one side and 10 on the other.

Each tablet strength is available in blister packages (30's) and in 10 x 10 unit dose blister packages.

NOTE: These extended release tablets must not be divided, crushed or chewed.

† Full Product Monograph available on request.

PLENDIL® is a registered trademark of Astra Pharma Inc., Mississauga, Ontario L4Y 1M4.

References: 1. Hansson L, Zanchetti A, Carruthers SG, *et al*, for the HOT Study Group. *Lancet* 1998;351:1755-62. 2. Hansson L. and Zanchetti A. for the HOT Study Group. *Blood Pressure* 1997;6:313-317. 3. PLENDIL Product Monograph, Astra Pharma Inc.

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