Methadone dosage and retention of patients in maintenance treatment

John R M Caplehorn and James Bell

ABSTRACT **Retention of patients in methadone treatment was studied in a cohort of 238 heroin addicts who entered maintenance programmes between February 1986 and August 1987. All subjects had been assessed at a centralised unit and referred to one of two other units for maintenance. Of the ten client characteristics that we analysed, three — a history of imprisonment, a history of dependence on barbiturates or benzodiazepines and employment status at entry — were included with "clinic" and maximum dose of methadone in the Cox regression models. Allowing for the other four variables, the maximum daily dose of methadone dispensed during the study period was a highly significant predictor of retention ($P < 0.00001$). With maximum dose stratified into three levels — <60 mg, 60–79 mg, 80+ mg — and with the lowest stratum used as the baseline, the relative risk (RR) of leaving treatment was halved (RR 0.47, 95% confidence interval [CI] 0.33–0.67) for subjects receiving 60–79 mg, and halved again (RR 0.21, 95% CI 0.12–0.38) for those who received 80+ mg. Clinic dosage policies contribute significantly to retention in methadone maintenance treatment. Clinics need to develop dosage policies in negotiation with individual patients.**

(Med J Aust 1991; 154: 195-199)

Over the past five years in Australia there has been an increase in the resources allocated to the treatment of drug dependence as part of the National Campaign Against Drug Abuse (NCADA). One aspect of this campaign has been an expansion of methadone programmes, particularly in New South Wales. The principal objective of both NCADA and Australian methadone programmes is harm minimisation — an attempt to ameliorate the medical and social consequences of opioid addiction.

The potential effectiveness of methadone maintenance in reducing the harm associated with heroin addiction is well documented. Independent evaluation of the original methadone programme run by Dr Marie Nyswander and Dr Vincent Dole found that social stability (as measured by employment, and arrest and conviction rates) improved, illicit drug use decreased and survival was better than that in addicts discharged from a detoxification unit.[1] A recent authoritative review concluded that there are many reports confirming these initial findings but that there is no evidence that methadone maintenance "is a steppingstone toward permanent discontinuation of narcotic addiction".[2] Most patients who drop out of methadone maintenance return to illicit opiate abuse within a short time.[3,4] There is evidence that addicts in methadone maintenance are less likely to share syringes and, thus, less likely to become infected with the human immunodeficiency virus.[5]

As methadone maintenance is of proven benefit only to those in treatment, retention in treatment is an important measure of the effectiveness of treatment programmes.[6] However, many American,[7] British[8] and Australian methadone programmes report very low retention rates. Foy, Drinkwater and White's evaluation of the Royal Newcastle Hospital methadone clinic reported disappointing results, with a strikingly low retention of patients in treatment (median survival approximately 13 weeks).[9] Several other New South Wales methadone programmes have similarly high rates of patient turnover.[10]

To elucidate the reasons programmes fail to retain patients, we have studied the relationship between the maximum daily dose of methadone and retention in a cohort of addicts entering maintenance treatment 3–4 years ago.

Subjects and Methods

All subjects were assessed for suitability for methadone maintenance at a central assessment service in the Sydney metropolitan area. The assessment process involved a series of interviews over a period of weeks and the principal criteria of assessment were a history of opiate addiction and current illicit opiate use confirmed by urinalysis. Addicts accepted into maintenance were assigned to one of two public methadone maintenance units for treatment on the basis of their home address. The two treatment units were responsible for deciding the methadone dosage for their patient groups. The two clinics had (and have) similar budgets, facilities and staffing and serve adjacent areas of Sydney with similar (low) socioeconomic status. The cohort comprises all 238 addicts referred from the assessment unit to these two clinics between February 1986 and August 1987.

Subjects' self-reports of drug use, education, employment and family situation, addiction treatment and criminal histories were obtained from assessment records. The two clinics granted access to their records, which were inspected by the investigators to determine the maximum dose of methadone dispensed to each subject (*a*) in the first four months of treatment and (*b*) during the study period. The study period ended on January 1, 1989. Records held by the Pharmaceutical Services Section of the New South Wales Department of Health were individually inspected by the principal investigator to provide data on the duration of maintenance treatment. It is the legal responsibility of all prescribers to notify the Pharmaceutical Services Section of the details of methadone maintenance treatment. Data were collected on the subjects' dates of entry into and exit or transfer from the methadone maintenance programme to which they had been assigned.

The dependent variable in the regression analyses was time in treatment (in days). Thirteen explanatory variables were tested, two treatment variables, "clinic" and the maximum dose of methadone per day dispensed to the subject in the study period ("maximum dose"); and 11 variables describing patient characteristics previously associated with retention[6,11] — sex, age, age at the time of first addiction, employment status at assessment (women caring for children were classified as employed, education level achieved ("education"), a history of previous methadone maintenance; a history of previous treatment in a therapeutic community, a history of benzodiazepine or barbiturate dependence, a history of heavy cocaine or amphetamine use, a history of alcohol dependence, and a history of imprisonment. All categorical variables were dichotomous. Both parametric (analysis of variance) and nonparametric (Wilcoxon rank-sum, Spearman rank correlation coefficient and Cox regression) tests were used to examine the relationship of

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"maximum dose" with "clinic" and the 11 patient variables.

Before data were analysed by Cox's regression, they were assessed for conformity to the proportional hazards assumption by plotting log (– log) curves of the Kaplan–Meier survival function and the p(PH) statistic (a mathematical estimate of conformity to the proportional hazards assumption; it is significant when the assumption is violated). The explanatory variable "clinic" was found to be a powerful predictor of retention but it did not satisfy the proportional hazards assumption (even when the effects of "maximum dose" were allowed for). This was probably due to one clinic having a policy of limiting the duration of methadone maintenance to two years. Consequently, two analyses were performed.

In the full-time analysis (end-point January 1, 1989) survival times were censored at that date or on transfer to another maintenance programme and a stratified (on "clinic") Cox regression was performed.[12] "Education" also failed tests for the proportional hazards assumption. When the results of a Cox regression stratified on "clinic" and "education" were compared with those from a regression stratified only on "clinic" it was concluded that exclusion of "education" from the analysis would not significantly affect the results.

As the effect of "clinic" on the outcome (retention in treatment) changed with time, an interval was chosen during which the log (– log) curves for the two clinics were parallel and over which the test of the proportional hazards assumption, p(PH), for the variable "clinic" was not significant. The longest survival time over which these two conditions were met was 450 days. Hence, in a second analysis, survival times were limited to 450 days and censor status was adjusted. This analysis made possible a numerical estimation of the effect of "clinic" and the effect of dosage over a period that should not have been affected by one clinic's attempt to limit the duration of maintenance to two years.

All explanatory variables to be used in the 450-day model were tested for conformity to the proportional hazards assumption. Three variables (age, age at the time of first addiction and "education") failed the test using the p(PH) statistic. The results of a regression stratified on the three variables were compared with a regression from which they had been excluded. The comparison indicated that all three could be excluded from the analysis.

The interaction term "clinic * maximum dose" was used in both models (full-time and 450-day) to test whether "clinic" modified the effect of "maximum dose" on time in treatment. In order to enable the construction of survival curves and the generation of a clinically meaningful measure of effect, the explanatory variable "maximum dose" was converted into a three-level, categorical variable: <60 mg; 60–79 mg; 80+mg. All analyses were repeated with "maximum dose" as a continuous variable to ensure that the conversion did not distort the analysis.

The models were developed by a stepwise elimination of variables so that the estimate of effect (relative risk) was preserved while its precision was improved. The interaction term, "clinic * maximum dose", was eliminated on the basis of the statistical significance of its estimated regression coefficient.

Additional analyses were undertaken to ensure that the observed associations between "maximum dose" and survival time were not caused by people leaving treatment within a very short time, before their starting dose could be raised to maintenance levels. Two other models (one full-time, the other 450-day) were developed using the maximum dose of methadone dispensed in the first four months of treatment as "maximum dose" (200 subjects were still in treatment at 120 days). There was no meaningful difference in the estimates of effect when maximum dose in the first 120 days was used. A separate analysis was made using only the 199 subjects who remained in treatment after 120 days and using the maximum dose of methadone dispensed in the first 120 days as the "dose" variable. Once again the result was highly significant ($P<0.0004$) and the relative risk (RR) was approximately 0.5 (0.58).

Both the full-time and 450-day analyses were repeated after all subjects who left in the first 35 days and 70 days of treatment had been excluded. Another analysis was performed with the 12 missing "maximum doses" and all values of "maximum dose" for subjects who left in the first 35 days of treatment set at 60 mg, the median and mean "maximum dose". These analyses also confirmed the results of the two principal analyses.

All survival analyses were performed by means of the Statistical Package for Interactive Data Analysis (SPIDA; Statistical Laboratory, Macquarie University). Other analyses were performed with the SAS statistics package (SAS Institute, Cary NC, United States).

Results

Of the 238 subjects, 163 attended Clinic 1 and 75 Clinic 2. One hundred and seventy-three (73%) were men, 70 (29%) were classified as employed and 79 (33%) had the School Certificate or trade qualifications. Fifty subjects (21%) reported receiving methadone maintenance previously, 65 (27%) reported treatment in a therapeutic community and 111 (47%) had been imprisoned. Ninety-eight members of the group (41%) were classified as having a history of dependence on benzodiazepines or barbiturates, 104 (44%) had been dependent on alcohol and 41 (17%) were classified as having been regular users of cocaine or amphetamines. The average age of the group was 27 years; the average age at the time of first addiction was 19 years. For 93 subjects the maximum dose of methadone dispensed was less than 60 mg of methadone per day, 92 received a maximum dose of 60–79 mg and 41 a maximum dose of 80+ mg of methadone. Maximum dose data were missing for 12 cases.

The average maximum dose was 60 mg, (median 60 mg, mode 60 mg, range 20–110 mg). The mean maximum dose at Clinic 1 was 59 mg (median 60 mg, mode 60 mg, range 20–80 mg); at Clinic 2 the mean dose was 64 mg, (median 65 mg, mode 40 mg, range 40-110 mg). When maximum dose and the other predictor variables used in the final Cox regression models (clinic, employment status and histories of benzodiazepine or barbiturate abuse and imprisonment) were included in an analysis of variance (with "maximum dose" the dependent variable), only "clinic" was significantly associated with maximum dose ($P<0.03$). When the variable "maximum dose" was converted to categorical form and a χ-square constructed, the association between clinic and maximum dose was again statistically significant ($P<0.005$). Only one patient variable (age) was significantly associated with "maximum dose" ($P<0.05$, Cox regression and Spearman rank correlation) and then only when Clinic 1 was considered separately.

The average time in treatment (survival time) was 405 days (range 2–1076 days); 88 cases were censored. Using stratified Cox regression and allowing for the effects of clinic, employment status, a history of benzodiazepine or barbiturate abuse and a history of imprisonment, we found a highly significant ($P<0.00001$) association between maximum dose of methadone and retention in treatment. The estimated relative risks of leaving treatment at any point during the study period for the three dose

Table: Relative risk of leaving methadone maintenance treatment

Dose per day (mg)	Relative risk	95% confidence interval
A		
<60	1.0	
60–79	0.47	0.33–0.67
80+	0.21	0.12–0.38
B		
<60	1.0	
60–79	0.40	0.21–0.62
80+	0.13	0.05–0.34

A: Relative risk of leaving maintenance treatment during the study period.
B: Relative risk of leaving maintenance during the first 450 days of treatment.

strata are shown in the Table. Using the risk for those patients who received a maximum dose of less than 60 mg of methadone as the baseline (i.e. RR = 1.0), we found the relative risk of leaving treatment to be halved (0.47) for those who received a maximum dose of 60 to 79 mg of methadone and halved again (0.21) for those who at one stage received 80 mg or more of methadone a day. The effect of maximum dose on retention is displayed in Figures 1 and 2, which show the fitted survival curves for the three dosage levels for Clinics 1 and 2, respectively

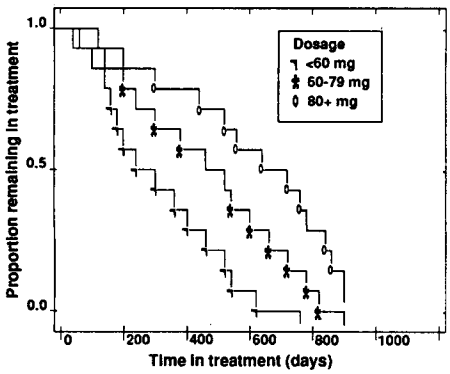

FIGURE 1: Retention of clients in methadone maintenance treatment — fitted survival curves for Clinic 1. "Dosage" indicates dose per day.

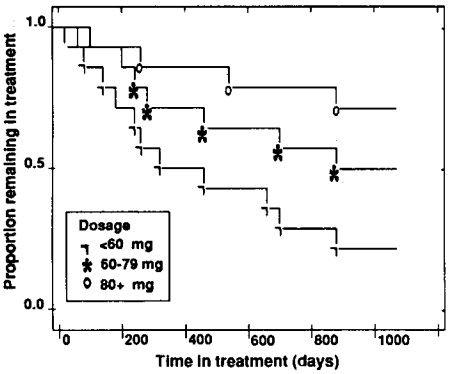

FIGURE 2: Retention of clients in methadone maintenance treatment — fitted survival curves for Clinic 2. "Dosage" indicates dose per day.

The second major analysis showed that there was also a highly significant ($P<0.00001$) relationship between the maximum dose of methadone dispensed to a patient and the risk of leaving during the first 450 days of treatment. The estimated relative risks of leaving treatment for the three dose strata (if clinic, employment status, and histories of benzodiazepine or barbiturate dependence and imprisonment are allowed for), are similar to those generated by the first analysis and are also

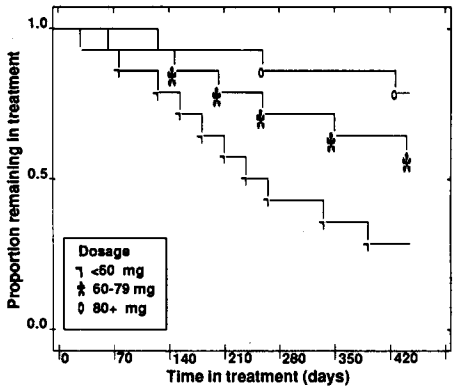

FIGURE 3: Retention of clients in methadone maintenance treatment — fitted survival curves for first 450 days for all subjects. "Dosage" indicates dose per day.

shown in the Table. The relationship of maximum dose and survival in the first 450 days of treatment is displayed in Figure 3, which shows the fitted survival curves for the three dosage levels for the whole cohort.

Three patient descriptors were found to be predictors of retention in treatment: a history of imprisonment; a history of barbiturate or benzodiazepine dependence; and, employment status at the time of entry into treatment. However, of these three patient variables, only a history of imprisonment was a statistically significant predictor of retention in the final or any other model which included all three patient variables. If the effects of "clinic", "maximum dose", employment status on entry to treatment and a history of benzodiazepine or barbiturate abuse are allowed for, the relative risk of someone with a history of imprisonment leaving treatment at any point during the study period was 1.43, (95% confidence interval, 1.01–2.04, $P<0,05$, Cox regression).

Discussion

The results of this study indicate that the relative risk of termination of treatment decreased by a factor of approximately two across each of three increasing dose strata (<60 mg, 60–79 mg, 80+ mg). Patient variables which have been shown to be associated with retention in previous studies (e.g. employment status, education level, criminality)[6,11] appear to have a minimal impact on retention compared with maximum dose of methadone dispensed.

While previous published reports have not included measures of effect (relative risks or odds ratios) they support the present finding that higher doses are associated with longer retention. A seven-year follow-up study found that two high-dose methadone maintenance programmes in California had a significantly greater retention than a low dose programme ($P<0.0001$).[13] Data were analysed by means of a Kaplan–Meier life table. No attempt was made to allow for differences in the patient groups and no measurement of effect was provided. The study's findings are supported by several other American[14-16] and Australian[17] studies. Patients at a Sydney maintenance programme who received 80 mg or more of methadone a day were more likely than patients maintained on lower doses to remain in treatment for two or more years.[17] Reports from other Australian programmes indicate that high-dose programmes have long retention times [18] whereas low-dose programmes are unable to retain patients in treatment.[9]

There is evidence from blind, randomised, controlled trials that part of the effectiveness of higher doses is pharmacological. A double-blind, randomised, controlled trial of different maintenance regimes found that 58% of patients maintained on 50 mg of methadone terminated treatment in the first 40 weeks of treatment compared with 48% of those maintained on 100 mg.[19] Most of those in the 100 mg group who terminated treatment did so before their doses had been raised to 100 mg (groups were originally defined with regard to the intended maintenance dose). One randomised trial showed that the strict enforcement of the clinic staff's "high expectation" (that their patients would abstain from illicit drugs and obtain employment) caused equally rapid (median survival approximately 13 weeks) loss from treatment of both high-dose and low-dose patients.[7]

Avram Goldstein, the principal author of a series of blind, randomised, controlled trials of methadone dosage (reviewed by Siassi et al.[16]) has subsequently acknowledged that such studies are likely to be flawed.[20] His unit conducted an uncontrolled study wherein maintenance patients were given the opportunity to adjust their dose of methadone. While the median dose increased by only 10 mg, those patients who increased their dose significantly ($P<0.01$) reduced their rate of illicit opiate use (measured by random urinalysis).[20] Those who reduced their dose showed continuing high rates of illicit opiate use. These results have been confirmed in a subsequent independent, randomised controlled trial.[21]

Goldstein et al. concluded that these results were due to a psychological rather

than a pharmacological effect.[20] They suggested that blind studies probably underestimate the clinical effectiveness of higher doses of methadone because they artificially exclude the psychological effect of patients' knowledge of their dose. Szapocznik and Ladner reached a similar conclusion in their review of the double-blind studies.[11] Goldstein et al. went on to propose that this "psychological effect" is probably caused by the patients' perceived control over their dose.[20]

Maintenance programmes with a low-dose policy generally have abstinence as their principal objective. Patients are maintained on the minimum dosage in order to discourage continuing reliance on chemicals and facilitate eventual withdrawal. However there is no evidence that methadone maintenance, or any other addiction treatment, leads to long-term abstinence.[2] Reports from the largest, longest and best independent evaluation of modes of addiction treatment indicate that neither methadone maintenance nor treatment in a therapeutic community or drug-free outpatient programmes promotes abstinence in the long term (six to twelve years after entry into treatment).[22,23] The available Australian evidence supports the proposition that abstinence-oriented methadone maintenance programmes have not been able to achieve their principal objective, abstinence.[9,17]

The continuing failure of abstinence-oriented programmes to achieve their goal would not be a problem if they were able to attract and retain patients in an effective programme of harm minimisation. However American[13] and Australian evidence indicates that they have failed not only to retain patients but also to attract addicts into treatment. At the time of writing (May 1990) the patient population of Clinic 1 (an abstinence-oriented programme) has fallen to 62 (from a high of 155 in May 1987) while that of Clinic 2 has increased to 250 (from 119 in May 1987).[10] Both clinics have had sole responsibility for their assessments and admissions since August 1987. During the last 10 months of the 14-month study period (four months being allowed to build patient numbers), the Royal Newcastle Hospital programme was able to attract and retain a monthly average of only 13.2 patients.[10] During this period, two private harm minimisation programmes in the Newcastle area maintained over 200 patients on methadone.[10] These data indicate that, once the addict community becomes aware of clinics' policies and procedures, addicts avoid entering abstinence-oriented programmes and either seek out programmes that do not set rigid goals and rules or remain outside the treatment network.

The present study provides strong evidence that one reason abstinence-oriented programmes are unable to retain patients in treatment is because the dosages employed are inadequate. However the problem is unlikely to be simply pharmacological. The measure of dosage used in this study, "maximum dose", can only have had a direct pharmacological effect on retention for the period during which it was dispensed. Although no quantitative data were collected, the authors gained the impression that most subjects who received 80 mg or more of methadone a day were dispensed the maximum dose for a limited period only.

Furthermore, the maximum dose of methadone dispensed in the first 120 days of treatment was a highly significant predictor of subsequent retention. It is likely, therefore, that "maximum dose" is, in part, acting as a proxy for some other dose-related variable or variables. As exhaustive statistical analysis revealed only one weak and limited relationship between "maximum dose" and the eleven patient variables (and a twelfth, compound variable — duration of addiction), "maximum dose" was unlikely to be acting as a proxy for a patient variable. Evidence from both the United States[24] and Britain[25] indicates that "maximum dose" reflects the quality of the patient's interaction with the clinic staff.

The authors of the present study concur with the suggestion of Goldstein et al. that "maximum dose" probably acts as a measure of the degree of control an individual patient exerts over his or her treatment.[20] The clinically and statistically significant association of "maximum dose" with retention demonstrated by this study should be interpreted as evidence: (i) that higher doses of methadone act directly (pharmacologically) to improve retention in methadone treatment; and (ii) that those patients who have a degree of control over their treatment are more likely to comply with and benefit from that treatment.

The latter conclusion is in agreement with the literature on patient compliance.[26] A corollary, that involvement of the target (addict) population in the planning and operation of a health promotion (harm minimisation) campaign will increase the campaign's effectiveness, is the basis of most modern health promotion activity.

The evidence from this and other studies[7,9] suggests that premature discharge from abstinence-oriented maintenance programmes is caused by both the direct pharmacological effects of inadequate doses of methadone and by deteriorating staff–patient and clinic–subculture relationships (caused by recurring conflict over methadone dosage and patients' use of illicit opiates). Poor clinic–subculture relations prevent abstinence-oriented maintenance programmes from attracting addicts into treatment. In failing to attract and hold addicts in treatment, abstinence-oriented programmes also fail to slow the spread of the human immunodeficiency virus.

Rather than impose decisions on patients, we believe methadone prescribers and clinic staff should negotiate with individual patients over treatment objectives and dosage. However, it must be recognised that many of the addicts entering methadone maintenance programmes are lacking in social skills and will be severely disadvantaged in any such negotiations.[24,25] Furthermore, the results of a previous Australian study show that many addicts have quite unrealistic expectations of methadone treatment and are likely to set themselves unattainable goals.[17] These difficulties can be best overcome if treatment staff conduct negotiations with patients in an ideologically neutral environment — where the clinic's ideology is neither "abstinence good, methadone bad" nor "methadone good, more methadone better" and where patients are not blamed for "failure". Realistic, individualised, negotiated treatment goals are the best criteria for the clinical evaluation of methadone dosage. Taken as a group, these individual treatment goals provide the objectives for an effective programme of harm minimisation.

Acknowledgements

The staff at the central assessment unit, the two treatment units, the Pharmaceutical Services Section of the Department of Health and the Directorate of the Drug Offensive kindly gave permission either to use previously collected data or to collect data. The Directorate also paid the cost of data entry. Professor David Kleinbaum, NHMRC Trials Centre, University of Sydney, gave advice on the use of Cox's regression and Professor Les Irwig, Department of Public Health, University of Sydney, undertook a detailed review of the draft report. ABC Computers Pty Ltd, Annandale, and the Department of Public Health, University of Sydney, provided access to computer hardware and software.

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(Received June 21; accepted Sep 24, 1990)

THERAPEUTICS

Anticonvulsants in pregnancy*

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Objective: To review the potential problems and their management associated with the use of anticonvulsant drugs during pregnancy.

Data sources: Studies published between 1968 and 1990 assessing the effect of pregnancy on the pharmacokinetics of anticonvulsant drugs, the teratogenicity of anticonvulsants, breast feeding and anticonvulsants and use of the oral contraceptive pill in patients taking anticonvulsant medication, were reviewed.

Results of data synthesis: In general, plasma levels fall during pregnancy and rise during the puerperium. A number of factors including possible reduced absorption, increased volume of distribution, reduced protein binding, increased clearance and noncompliance, contribute to this fall in plasma concentration. All anticonvulsants are potentially teratogenic. The incidence of fetal malformations is higher in patients treated with multiple anticonvulsant drugs and on higher dosages with higher plasma levels. Anticonvulsants are excreted in low concentrations in breast milk. All anticonvulsants except valproic acid have been associated with failure of the oral contraceptive pill. This is due to liver enzyme induction of these drugs.

Conclusion: As plasma levels of anticonvulsants fall during pregnancy, concentrations should be monitored regularly. Due to the fall in protein binding, marginally low total plasma levels of highly protein bound drugs may not reflect reduced unbound levels, and hence an increase in dosage may not be required. In order to reduce teratogenicity, one should aim to use a single anticonvulsant drug and the lowest dosage able to achieve seizure control. In general, breast feeding is not contraindicated.

(Med J Aust 1991; 154: 199-202)

Epilepsy is a common neurological disorder, with an estimated prevalence of 1%. Women with epilepsy, many of whom will be taking anticonvulsant drugs, account for approximately one of every 200 pregnancies.[1] The major problems in the management of these patients arise from the anticonvulsant drugs, their potential teratogenic effects and the altered pharmacokinetics associated with pregnancy. The objectives of treatment of the pregnant woman with epilepsy are to maintain the patient in a seizure-free state while minimising, when possible, the adverse effects of the seizure disorder on the course of the pregnancy and the possible teratogenic effect of the anticonvulsant drugs on the fetus.

When managing a patient who is pregnant or is planning a pregnancy the

*Sixth article in an occasional series on the use of drugs in pregnancy.

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