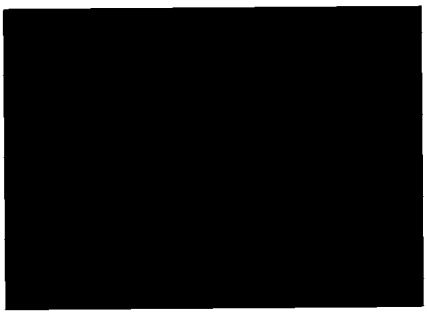
# Independent Report

# on the

# Incidence of Attempted

# Suicide in the Aropax 356 Study

# (SmithKline Beecham Protocol 29060/356)



24 March 1994

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## SYNOPSIS

The Aropax 356 Study is a double-blind multicentre trial comparing the two selective serotonin reuptake inhibiter drugs paroxetine (AROXPAX; BRL 29060) and fluoxetine (PROZAC; Eli Lilly) in daily doses of 20 mg. The aims of the study are to compare the efficacies of the two drugs in relieving depression and ameliorating anxiety, and also to compare their tolerability profiles. Of the first 100 patients enrolled in the study, nine attempted suicide; two successfully. As a consequence, this independent review of the study has been completed. The review finds that the study should be allowed to continue but that a number of changes should be made.

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TERMS OF REFERENCE

[redacted] was commissioned to conduct an independent investigation into the incidence of attempted suicide (9 attempts, 2 successful in the first 100 patients) in patients participating in a double-blind multicentre trial comparing the two selective serotonin reuptake inhibitor drugs paroxetine (AROPAX; BRL 29060) and fluoxetine (PROZAC; Eli Lilly) in daily doses of 20 mg. The specific terms of reference were:

(1) To undertake an interim analysis of the safety data to determine whether the incidence of attempted suicide was significantly greater in either the paroxetine patients or the fluoxetine patients,

(2) Given that this was not the case, to determine whether the overall incidence of attempted suicide was excessive for the particular population of patients at risk, and

(3) Depending on the results of (1) and (2), to recommend:
   (a) Whether the trial should be allowed to continue, and
   (b) If so, whether any changes should be made to the protocol.

INTERIM SAFETY DATA ANALYSIS

A sealed copy of the randomisation codes was provided from the head office of SmithKline Beecham Australia to facilitate this analysis. The information conveyed was seen by only one officer of [redacted] and remains unseen by any of the staff of [redacted] (the trial monitor) or SmithKline Beecham Australia involved in the running of the study.

The interim data analysis was conducted on all patients enrolled in the study prior to 10th February, 1994. For the purposes of this analysis the patients were followed until:

(1) The conclusion of their scheduled 8 weeks of treatment,

(2) Their withdrawal from treatment, or

(3) 10th February, 1994,

which ever came first. Two patients were lost to follow-up. Attempted suicide was treated as a terminal event.

While there are alternative ways of processing the data, this fact is considered to be of very little consequence since most of the attempted suicides occurred early in treatment; 5/9 occurred within the first week and the average time from the commencement of treatment was 12 days. In contrast, the average length of follow-up in the remaining patients was 46 days.

A summary breakdown of the characteristics of the patients enrolled in the study is given in Table I. Treatment details have been excluded so as not to compromise the study. There were 73 females and 27 males. The average age was 41 (range 19-81). There were 71 outpatients and 29 inpatients. Ten patients had HAM-D Item 3 scores greater than 2. Seventeen had a known previous history of attempted suicide.

In the course of the study, 9 patients attempted suicide and two of these attempts were successful. A further 26 patients withdrew or were withdrawn for other reasons. These comprised 8 for lack of efficacy (LOE), 7 for adverse

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TABLE I

SUMMARY BREAKDOWN OF CHARACTERISTICS OF THE PATIENTS ENROLLED IN THE AROPAX 356 STUDY

| | | | |
|---|---|---|---|
| Age (mean ± SD) | | | 41 ± 12 Years |
| Sex | ( | Female | 73% |
| | ( | Male | 27% |
| Source | ( | Outpatient | 71% |
| | ( | Inpatient | 29% |
| HAMD3 | ( | 0 Absent | 18% |
| | ( | 1 Life not worth living | 33% |
| | ( | 2 Wants to be dead | 39% |
| | ( | 3 Suicidal ideas, gestures | 8% |
| | ( | 4 Serious attempt at suicide | 2% |
| Previous History | ( | No known prior suicide attempt | 83% |
| | ( | Known prior suicide attempt | 17% |
| Time in study (mean ± SD) | | | 43 ± 18 Days |
| Status at 10/2/94 | ( | Completed study | 59% |
| | ( | Ongoing | 6% |
| | ( | Attempted suicide | 9% |
| | ( | Withdrawn for other reasons | 26% |

experiences (AE), a further 5 for both LOE and AE and 6 for other reasons, including the two losses to follow-up previously noted. Six of the attempted suicides involved the taking of drugs and three, including the two successful attempts, were by physical means. Neither of the two study drugs appears to have been used in any of the attempts.

**The main finding of this interim analysis is that there was no significant difference in the rate of attempted suicide between the two arms of the trial.** Specifically:

(a) Using life table analysis (Lee Desu Statistic)
$X_1 = 0.72$, $p = 0.40$,

(b) Using a 2 x 2 contingency table (Raw $X^2$)
$X^2_1 = 0.97$, $p = 0.32$, and

(c) The two successful attempts comprised one in each of the arms of the trial.

Other comparisons between the patients attempting suicide and the remaining patients are set out in Table II. One of those attempting suicide was male, the other 8 were female. The average age of those attempting suicide was 35 as against 41 for the remaining patients. Neither of these was significant. Nor was the HAM-D Item 3 score significantly different between the two groups; although the patients who attempted suicide did have a higher average score (1.78) than the remaining patients (1.40).

The two variables which did correlate significantly with attempted suicide were:

(i) Being an inpatient rather than an outpatient ($X_1 = 17.2$, $p<0.001$), and
(ii) Being known to have made a previous suicide attempt
($X_1 = 17.3$, $p<0.001$).

The incidence of attempted suicide was 27.6% among inpatients as against 1.4% among outpatients and 35.3% in patients known to have made a previous attempt as against 3.6% among those not known to have made a previous attempt. Both

TABLE II

SOME COMPARISONS BETWEEN PATIENTS
ATTEMPTING SUICIDE AND THE REMAINING PATIENTS

| Statistic | | Suicide Attempted | Not Attempted | Test | Significance |
|---|---|---|---|---|---|
| Age (Mean) | | 35 | 41 | t = - 1.58 | NS |
| Sex | Nr Females | 8 | 65 | $X_1^2$ = 1.27 (also Fishers exact test) | NS |
| | Nr Males | 1 | 26 | | |
| Source | Nr Outpatients | 1 | 70 | $X_1^2$ = 17.23 (also Fishers exact test) | p<0.001 |
| | Nr Inpatients | 8 | 21 | | |
| HAMD3 (Mean) | | 1.78 | 1.40 | t = 1.16 | NS |
| Previous History | Known prior attempt | 6 | 11 | $X_1^2$ = 17.29 (also Fishers exact test) | p<0.001 |
| | Others | 3 | 80 | | |

of the two "successful" suicides were by inpatients both of whom were known to have made a previous attempt. The relevance of both of these variables will be discussed in more detail later in this report.

As noted above, of the 91 patients who did not attempt suicide, a further 26 either withdrew or were withdrawn prematurely from the trial. As with attempted suicide, premature withdrawal was not associated with treatment ($X^2_1 = 0.99$, p=0.32) or sex ($X^2_1 = 1.74$, p=0.19). The withdrawn patients were older (average age 45) than those not withdrawn (average age 40); this was also not significant (t=1.93,p=0.06). There was however a significant association between premature withdrawal and being an inpatient ($X^2_1 = 4.85$, $p<0.05$). This is set out in Table III. When these (other) premature withdrawals are pooled with the attempted suicides, we see that 18/29 (i.e. 62%) of inpatients either attempted suicide or prematurely withdrew from the trial compared to 17/71 (i.e. 24%) of the remaining patients. Viewed alternatively, as at 10/2/94, only 10/29 (34%) of inpatients had successfully completed the trial compared to 49/71 (69%) of outpatients.

TABLE III

COMPARISON OF ATTEMPTED SUICIDE AND PREMATURE WITHDRAWAL BETWEEN INPATIENTS AND OUTPATIENTS

| Patient Category | Patients Attempting Suicide | Other Withdrawals | Total Attempted Suicide or Withdrawn | Other Patients | Total Patients | % Attempting Suicide or Withdrawn |
|---|---|---|---|---|---|---|
| Outpatients | 1 | 16 | 17 | 54 | 71 | 24 |
| Inpatients | 8 | 10 | 18 | 11 | 29 | 62 |
| Total | 9 | 26 | 35 | 65 | 100 | 35 |

## THE SIGNIFICANCE OF THE OVERALL RATE OF ATTEMPTED SUICIDE

In the preceding section of this report, it was found that there was no significant difference in the rate of attempted suicide between the two arms of the trial. There can therefore be no justification in placing the blame on one of the two trial drugs and not the other.

Nevertheless, superficially at least, the incidence of attempted suicide (9 patients out of 100 at risk an average of 43 days) remains unexpectedly high; which still prompts the question as to whether patients are being placed at excessive risk by being enrolled in the trial; and whether the trial should be terminated.

A search of the literature was made, partly in an endeavour to answer this question and also to provide a background perspective against which recommendations could be made. A full list of all articles reviewed based on this search is contained in the bibliography which forms the last section of this report.

The incidence of suicide and of attempted suicide observed among patients treated for depressive illness in the most relevant of the completed prospective studies reviewed are set out in Table IV. Where there was a choice, we have taken the shortest time period available but there is still a very large difference in average exposure times (from 48 days to over 15 years). In many cases we have had to infer the exposure times. We acknowledge that the calculations are very approximate but, in our opinion the table still gives a good perspective of the possible range of the underlying frequencies.

The incidence of actual and attempted suicide is clearly dependent on the observation period. In the case of actual suicide, the study most applicable to Aropax 356 is probably that of Goldacre et al (1993) where patients were followed only up to 28 days after discharge from psychiatric hospital* In the

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* The average of 48 days exposure occurs because many patients were hospitalized and discharged a number of times.

TABLE IV

THE INCIDENCE OF ATTEMPTED SUICIDE AND OF "SUCCESSFUL" SUICIDE OBSERVED IN THE MOST RELEVANT OF THE COMPLETED PROSPECTIVE STUDIES REVIEWED.

| Reference | Nr Patients | Diagnosis | Patients X Days | Attempted Suicides | "Successful" Suicides | Attempts per 1000 patient days | Suicides per 1000 patient days |
|---|---|---|---|---|---|---|---|
| Beasley et al (1991) | 3065 | Major depressive disorder | ~ 120,000 | 13 | 1 | 0.11 | 0.008 |
| Black et al (1987) | 1007 | Major depressive disorder | ~ 735,000 | N.K. | 34 | N.K. | 0.046 |
| Bronisch and Hecht (1992) | 47 | Brief or prolonged depressive reaction | ~ 83,000 | 6 | 2 | 0.07 | 0.024 |
| Buchholz-Hansen et al (1993) | 219 | Major depressive disorder | > 230,000 | N.K. | 16 | N.K. | < 0.07 |
| Coryell et al (1987) in Lester (1993) | 372 | Major affective disorder | ~ 270,000 | > 45 | N.K. | ~ 0.2 | N.K. |
| Duggan et al (1991) | 61 | Major depressive disorder | ~ 375,000 | 81 | 5 | 0.22 | 0.013 |
| Fawcett et al (1987) | 954 | Major affective disorder | ~ 174,000 | N.K. | 8 | N.K. | 0.046 |
| Goldacre et al (1993) | ~ 2315 | Depression patients < 29 days post discharge from psychiatric hospital | 112,000 | N.K. | 15 | N.K. | 0.13 |
| Keller and Shapiro (1981) in Zweig et al (1993) | N.K. | Depression | N.K. | N.K. | N.K. | 0.27 | N.K. |
| Kiloh et al (1988) | 133 | Primary depressive illness | ~ 240,000 | N.K. | 6 | N.K. | 0.025 |
| Lopez-Ibor (1992) | 3145 | Depression | ~ 130,000 | 58 | N.K. | 0.45 | N.K. |
| Paykel et al (1971) in Zweig et al (1993) | N.K. | Depression | N.K. | N.K. | N.K. | 0.26 | N.K. |
| Roy-Byrne et al (1988) in Lester (1993) | 87 | Major affective disorder | ~ 63,000 | N.K. | 3 | N.K. | 0.048 |
| Seager et al in Achte (1986) | 206 | Manic depression | ~ 145,000 | N.K. | 7 | N.K. | 0.048 |
| Zisking et al in Achte (1986) | 109 | Manic depression | ~ 120,000 | N.K. | 9 | N.K. | 0.075 |
| Zweig et al (1993) | 115 | Major depressive disorder - elderly patients | 42,000 | 11 | 0 | 0.26 | 0.0 |

Aropax 356 Study there were two suicides in 4321 days of exposure. Based on Poisson probabilities, this is not significantly high for an underlying incidence rate of 0.13 per 1000 days exposure (equivalent to an expected rate of 0.58 for 4321 days exposure). The underlying rate per 1000 days exposure would need to be 0.08 or less (one sided) or less than 0.06 (two sided) for significance at the 5% level.

Based on the papers reviewed, it is unlikely that the underlying rate of attempted suicide per 1000 days applicable to the Aropax 356 Study is greater than 0.5. Although a figure of 0.45 "appears to have been reported" by Lopez-Ibor (1992), we have reason to doubt that figure as it is in conflict with the results reported by Montgomery et al (1993) based on the same data. In the Aropax 356 Study there were 9 attempts in 4321 days. This is significantly high ($p<0.001$, Poisson probabilities) when compared to an underlying rate of 0.5 per 1000 days exposure (equivalent to an expected rate of 2.16 in 4321 days exposure).

But these are not totally fair comparisons. While it is a prospective study, the Aropax 356 Study is not a completed study. The incidence of suicides as at 10 February 1994 is very likely some kind of peak. That is largely why it was noticed. To compare this peak result with "average" values, is not strictly valid, regardless of the compatability of the patients in terms of periods of treatment, intervals of follow-up, the depth of their depression, associated anxiety or any other diagnostic criterion. Possibly a more appropriate test would be to compare the incidence of attempted suicide in Aropax 356 to 10 February 1994 with retrospectively reviewed high rates in other studies, taking cognizance of the reasons (if any) given for these high rates.

Only a small number of the studies reviewed are relevant in this regard. Taiminen et al (1992) give an example of eight suicides in one inpatient clinic within a three month period during 1985 and explain how the Werther ("copycat") effect was responsible for at least five of them. They also cite other inpatient

suicide epidemics with comparable incidences. Fernando and Storm (1984) cite a further example of 4 men suiciding at a psychiatric unit in the UK within a three month period in 1980; all were related to employment. The Werther effect could possibly be relevant to the Aropax 356 Study as four of the attempted suicides took place in a four month period in a single centre. However the referenced studies appear to be more serious.

## DISCUSSION

Our literature review also included a number of papers which claim a decrease in suicidal thoughts and ideation on both fluoxetine and paroxetine. We do not necessarily dispute these findings. However as pointed out in the comprehensive review by Teicher et al (1993), thoughts and ideation do not necessarily correspond with action; and in some of the studies cited, the incidence of attempted suicide actually rose even though (average) ideation fell. This is consistent with the finding of our interim analysis that the initial HAM-D Item 3 score was not significantly correlated with attempted suicide.

We are also persuaded by the evidence cited by Teicher et al, that use of fluoxetine has in some cases led to suicidal acts. For this reason, we must regard attempted suicide as an adverse experience potentially attributable to either of the two serotonin reuptake inhibitors.*

Given that some patients may be at added risk through their participation in the study, the important task is to identify which patients. Once this has been done, consideration can be given to a range of options : taking no action, taking additional precautions, excluding some or all patients.

The interim analysis identified two variables which correlated significantly with attempted suicide. These were being known to have made a previous suicide attempt ($X^2_1 = 17.3$, $p<0.001$) and being an inpatient rather than an outpatient ($X^2_1 = 17.2$, $p<0.001$).

While known previous suicide attempt is very frequently cited in the literature as being significantly associated with (later) attempt, we consider that the level

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* This is not to say that the US FDA and other authorities are wrong to sanction the drugs. In their opinion, the long term benefits clearly outweigh any possible short term problems. Surgery can also bring misadventure. No one seriously wants to ban surgery.

of significance attributed to it in the interim analysis is an overstatement of its real importance in this study. Previous suicide attempt was not recorded rigourously in a prospective manner in the case report form (CRF). Rather it seems to have been retrospectively obtained in a very large number of cases. Furthermore, several obvious errors in its recording were identified. These considerations aside, the circumstances of any known previous suicide attempt by any potential participant in the study should be given particularly serious attention.

The second of the two variables significantly associated with attempted suicide was whether the patient was an inpatient or an outpatient. There were 29 inpatients as against 71 outpatients, yet 8 of the attempted suicides were by inpatients and only one was by an outpatient. It is relevant that withdrawal from the study for other reasons was also significantly associated with being an inpatient ($X^2_1 = 4.85$, $p<0.05$). As at 10/2/94, only 34% of inpatients had successfully completed the study as compared to 69% of outpatients. A very easy option therefore is to simply restrict future enrolments to outpatients. Not only might this reduce the number of attempted suicides, it might also enhance evaluability and so improve the power of the study.

That inpatients appear to be so much more at risk than outpatients also suggests an alternative course of action. Possibly the best way to reduce the incidence of suicide is to remove the means available to those inclined to attempt it. With outpatients the psychiatrist has very little opportunity to do this; however with inpatients there is far greater scope. Patients can be denied access to guns, sharp knives, gas ovens, ropes etc and the intake of drugs (and other toxic substances) can be more strictly controlled. This fact is recognised in the protocol which contains more stringent conditions on the admission of outpatients than inpatients for this very reason. Unfortunately, the intent of the relevant clause (3.2.3f) was not observed in the case of almost if not all of the eight inpatient attempters. Four including the two "successful" cases were "let out"; one had a sharp implement in her possession and three had drugs in their possesion.

The alternative course of action has two components. First, no patient enrolled as an inpatient who would not be eligible for enrolment as an outpatient should be discharged or given leave prior to completion of the study. And second, it should be a condition of entry, to be realized at the time of signing of the consent form, that the patient yields up all of the means of attempting suicide available to him or her in his or her possession. These include drugs, polish removers, sharp scissors, nail files, mirrors etc.

Psychiatric inpatients are nearly always hospitalised because they pose a serious risk in the ex-hospital environment. If there is a possibility that the trial drugs could increase this risk, then a fortiori, patients should not be discharged nor given leave so long as the risk remains.

Several of the papers which we have reviewed, list ways of reducing the means of suicide and regard many of them as standard precautions in a psychiatric institution. In Australia, in a non-trial setting, (temporary) confiscation of a patient's possessions could be seen as a violation of his or her basic rights and thus may not be possible. This objection is very easily overcome in a trial situation. Unless the patient agrees to comply, he or she is unable to participate in the trial.

The most extreme options are to do nothing or to stop the trial. We do not consider doing nothing to be a responsible course of action. To find the drugs or the trial guilty of the two deaths on the evidence available would be a grave miscarriage of justice. On the other hand, given hindsight, there is no doubt that both of these deaths could have been avoided, even if only temporarily. Participating psychiatrists do have the means to reduce the incidence of such occurrences in patients they enrol in the trial, although not necessarily in other patients. Now that the trial has been put on notice, not to avail themselves of these means would be at the very least unwise.

The aims of the trial are to compare the efficacies of the two drugs in relieving depression and ameliorating anxiety, and also to compare their tolerability profiles. Treatment of depression is important to the health and wealth of the nation and any knowledge gained of the advantages and disadvantages of alternative modalities is very valuable to both. The target enrolment in the study was 160 patients. The target number of patients completing the study was 120 in order to have a 90% chance of showing a "detectable difference" in efficacy between the two groups. As at 10 Feb 1994, 60 patients had completed the study.* Were the study to be terminated at this point, there would only be a 63% chance of showing such a difference. Thus the power of the study would be considerably reduced. Most of the time and effort expended in the study could be lost and important questions could well remain unanswered. Under the circumstances, it is unlikely that the trial would be repeated so that these questions would continue to remain unanswered.

We advise against discontinuing the trial, not only for the reasons outlined above, but also because in our opinion it is not necessary. By putting in place the precautions recommended above, patients should be at no greater risk because of their participation in the study. In our experience, patients in trials generally do better than patients not in trials with the same diagnosis. We see no reason why that cannot be the case in the Aropax 356 Study.

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* This figure includes one of those attempting suicide who was allowed to continue in the study. Accordingly it differs from the data shown in Table I.

## RECOMMENDATIONS

As a result of the considerations above, our recommendations are:

(1) That the study should be continued for so long as is required to treat the target accrual of 160 patients.

(2) That the following changes should be made (to the protocol where necessary):

(2.1) In assessing the eligibility of patients to participate in the trial, more attention should be paid to whether they constitute a serious suicide risk. Specifically, past history of suicide attempts should be sought prospectively and entered in a field to be provided in the case report form (CRF). The question as to whether the patient constitutes a serious suicide risk should be answered in the CRF after the past history and screen visit information and immediately prior to the final assessment of eligibility. The question as to whether the patient would be eligible to enter the study as an outpatient should also be answered in the CRF;

(2.2) Where a patient who would not be eligible to enter the study as an outpatient is enrolled as an inpatient, that patient must remain an inpatient until completion of the study period. Otherwise he or she should not be enrolled in the study; and

(2.3) As a condition of their entry into the study, to be agreed and realized at the signing of the consent form, <u>all</u> inpatients should hand over all means of attempting suicide in their possession. These include drugs and other toxic substances and any sharp or potentially sharp objects. They should be withheld from the patient <u>at least</u> until the end of the study period. If patients cannot agree to this condition, then they should not be enrolled in the study.

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BIBLIOGRAPHY

Achte K (1986) Depression and suicide. Psychopathology. Vol 19: suppl 2, pp 210-214.

Allgulander C and Lavori PW (1991). Excess mortality among 3302 patients with 'pure' anxiety neurosis. Arch Gen Psychiatry. Vol 48: pp 559-602.

Beasley CM, Dornseif BE, Bosomworth JC, Sayler ME, Rampey AH, Heiligenstein JH, Thompson VL, Murphy DJ and Masica DN (1991). Fluoxetine and suicide : a meta-analysis of controlled trials of treatment for depression. BMJ. Vol 303: pp 685-692.

Beecham L (1992) Increases in suicide among the young and elderly. BMJ. Vol 304: pp 1332-1333.

Berglund M and Nilsson K (1987). Mortality in severe depression. Acta Psychiatr Scand. Vol 76: pp 372-380.

Berglund M and Smith GJW (1988). Post-diction of suicide in a group of depressive patients. Acta Psychiatr Scand. Vol 77:pp 504-510.

Black DW, Winokur G and Nasrallah A (1987). Suicide in subtypes of major affective disorder. Arch Gen Psychiatry. Vol 44:pp 878-880.

Breslau N (1992). Migraine, suicidal ideation, and suicide attempts. Neurology. Vol 42: pp 392-395.

Bronisch T and Hecht H (1992). Prospective long-term follow-up of depressed patients with and without suicide attempts. Eur Arch Psychiatry Clin Neurosci. Vol 242:pp 13-19.

Buchholtz-Hansen PE, Wang AG, Kragh-Sorensen P and the Danish University Antidepressant Group (1993). Mortality in major affective disorder: relationship to subtype of depression. Acta Psychiatr Scand. Vol 87: pp 329-335.

Buckley NA, Dawson AH, Whyte IM and Henry DA (1994). Greater toxicity in overdose of dothiepin than of other tricyclic antidepressants. Lancet. Vol 343: pp 159-162.

Cantor CH (1989). Substances involved in fatal drug overdoses in Brisbane, 1979-1987. Acta Psychiatr Scand. Vol 80: suppl 354, pp 69-71.

Coleridge J, Cameron PA, Drummer OH and McNeil JJ (1992). Survey of drug-related deaths in Victoria. MJA. Vol 157: pp 459-462.

Daly RJ (1993). Suicide in depressed patients : medico-legal issues. Brit J Psychiatry. Vol 163: suppl 20, pp 29-32.

Duggan CF, Sham P, Lee AS and Murray RM (1991). Can future suicidal behaviour in depressed patients be predicted? J Affective Disord. Vol 22: pp 111-118.

Dunbar G (1992). A double-blind, multicentre study comparing paroxetine and fluoxetine in the treatment of patients with major depressive disorder with regard to antidepressant efficacy, effects on associated anxiety, and tolerability. Protocol: 29060/356 SB Australia.

Farmer, R (1993) Prescription drugs and suicide. Abstract. Satellite Symposium ECNP. Budapest Oct 1993:pp 7-8.

Fawcett J, Scheftner W, Clark D, Hedeker D, Gibbons R and Coryell W (1987). Clinical predictors of suicide in patients with major affective disorders: a controlled prospective study. Am J Psychiatry. Vol 144: pp 35-40.

Fawcett J, Scheftner WA, Fogg L, Clark DC, Young MA, Hedeker D and Gibbons R (1990). Time-related predictors of suicide in major affective disorder. Am J Psychiatry. Vol 147: pp 1189-1194.

Fernando S and Storm V (1984). Suicide among psychiatric patients of a district general hosptial. Psychological Med. Vol 14: pp 661-672.

Goldacre M, Seagroatt V and Hawton K (1993). Suicide after discharge from psychiatric inpatient care. Lancet. Vol 342: pp 283-286.

Goldstein RB, Black DW, Nasrallah A and Winokur G (1991). The prediction of suicide. Arch Gen Psychiatry. Vol 48: pp 418-422.

Hardwicke C, Holt L, James R and Smith AJ (1986). Trends in self-poisoning with drugs in Newcastle, New South Wales, 1980-1982. MJA. Vol 144: pp 453-454.

Hawton, K (1992). By their own hand. BMJ. Vol 304: p 1000.

Henderson S (1992). Evaluating suicide risk. Patient Management. August 1992: pp 23-27.

Henriksson MM, Aro HM, Marttunen MJ, Heikkinen ME, Isometsa ET, Kuoppasalmi KI and Lonnqvist JK (1993). Mental disorders and comorbidity in suicide. Am J Psychiatry. Vol 150: pp 935-940.

Isometsa E, Henriksson M, Heikkinen M and Lonnqvist J (1993). Suicide after discharge from psychiatric inpatient care (letter). Lancet. Vol 342:pp 1055-1056.

Jablensky A (1987). Prediction of the course and outcome of depression (editorial). Psychological Med. Vol 17: pp 1-9.

Johnson J, Horwath E and Weissman MM (1991). The validity of major depression with psychotic features based on a community study. Arch Gen Psychiatry. Vol 48: pp 1075-1081.

Kiloh LG, Andrews G and Neilson M (1988). The long-term outcome of depressive illness. Brit J Psychiatry. Vol 153: pp 752-757.

Lehmann HE, Fenton FR, Deutsch M, Feldman S and Englesmann F (1988). An 11 year follow-up study of 110 depressed patients. Acta Psychiatr Scand. Vol 78: pp57-65.

Lester D (1993). Suicidal behaviour in bipolar and unipolar affective disorders: a meta-analysis. J Affective Disord. Vol 27: pp 117-121.

Litman RE (1991). Predicting and preventing hospital and clinic suicides. Suicide and Life-Threat Behav. Vol 21: pp 56-73.

Lopez-Ibor JJ (1992).Reduced suicidality/anxiogenesis with paroxetine. Satellite Symposium 6th AEP, Barcelona Nov 1992: pp 11-12.

McGrath J (1989). A survey of deliberate self poisoning. MJA. Vol 150: pp 317-324.

Montgomery SA, Dunner DL and Dunbar GC (1993). Reduction of suicidal thoughts with paroxetine in comparison with reference antidepressants and placebo. Submitted to European Psychopharmacology.

Newman SC and Bland RC (1991). Suicide risk varies by subtype of affective disorder. Acta Psychiatr Scand. Vol 83: pp 420-426.

Pounder DJ (1992). Classifying suicide (letter). BMJ. Vol 305: p 472.

Ray JE, Reilly DK and Day RO (1986). Drugs involved in self-poisoning: verification by toxocological analysis. MJA. Vol 144: pp 455-457.

Read DA, Thomas CS and Mellsop GW (1993). Suicide among psychiatric in-patients in the Wellington region. ANZ J Psychiatry. Vol 27: pp 392-398.

Retterstol N (1989). Norwegian data on death due to overdose of antidepressants. Acta Psychiatr Scand. Vol 80: suppl 354, pp 61-68.

Stephens JH and McHugh PR (1991). Characteristics and long-term follow-up of patients hospitalized for mood disorders in the Phipps clinic, 1913-1940. J Nerv Ment Dis. Vol 179: pp 64-73.

Taiminen T, Salmenpera T and Lehtinen K (1992). A suicide epidemic in a psychiatric hospital. Suicide and Life-Threat Behav. Vol 22: pp 350-363.

Taiminen T (1993). Effect of psychopharmacotherapy on suicide risk in psychiatric inpatients. Acta Psychiatr Scand. Vol 87: pp 45-47.

Teicher MH, Glod CA and Cole JO (1993). Antidepressant drugs and the emergence of suicidal tendancies. Drug Safety. Vol 8: pp 186-212.

Thomas CS, Read DA and Mellsop GW (1992). New Zealand suicides 1984-8. NZMJ Vol 105: pp 231-233.

Weeke A and Vaeth M (1986). Excess mortality of bipolar and unipolar manic-depressive patients. J Affective Disord. Vol 11: pp 227-234.

Westermeyer JF, Harrow M and Marengo JT (1991). Risk for suicide in schizophrenia and other psychotic and nonpsychotic disorders. J Nerv Ment Dis. Vol 179: pp 259-266.

Wolfersdorf M, Vogel R, Keller F and Hole G (1991). The increase in suicides in psychiatric hospitals in southwestern Germany according to diagnostic subgroups. Crisis. Vol 12: pp 34-47.

Zweig RA and Hinrichsen GA (1993). Factors associated with suicide attempts by depressed older patients: a prospective study. Am J Psychiatry. Vol 150: pp 1687-1692.