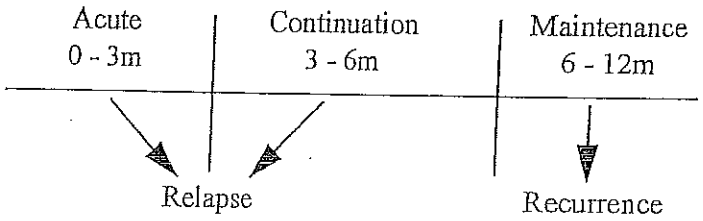
DURATION OF TREATMENT AND DEPRESSION RELAPSE and RECURRENCE RATES

INTRODUCTION

The distinction between relapse of old symptoms and recurrence of new episodes of depression is of particular importance, both in assessing antidepressant efficacy during the continuation phase of acute treatment and in the separate assessment of the prophylactic efficacy of antidepressant therapy.

Relapse is defined as the return of symptoms of the **current** depressive episode, whereas recurrence is defined as the appearance of a **new** episode of major depressive disorder. Recurrence can only occur during a recovery period (Hirschfeld, 1994) and would usually be expected to occur between 6-12 months after the initial depressive episode (See figure 1).

Figure 1 : Definitions in Treatment of Depression



Relapse

It has been estimated that between 30 and 50% of patients relapse within 4-6 months of halting antidepressant therapy. Relapse occurs most frequently after early discontinuation of therapy. Data from a number of studies suggest that it is advisable to maintain antidepressant therapy beyond the period of apparent symptomatic improvement in order to consolidate the response and prevent relapse. Lower rates of relapse have been observed in patients who received SSRIs (paroxetine, sertraline, citalopram and fluoxetine), compared with placebo in long-term studies in the treatment of depression (Montgomery and Dunbar, 1993; Montgomery et al, 1993; Bjork, 1983; Claghorn and Feighner, 1993; Doogan and Caillard, 1992; Dunbar et al; 1993, Robert & Montgomery; 1995, Dekker et al; 2000). Efficacy for paroxetine and sertraline has been demonstrated in studies with a 1 year follow-up period (Montgomery and Dunbar, 1993; Doogan and Caillard, 1992). The long-term efficacy of fluoxetine and citalopram has been demonstrated over a 5 month and 6 month period respectively (Dekker et al; 2000, Montgomery et al; 1993, Robert & Montgomery; 1995).

The current opinion is that virtually all responders should be maintained on antidepressant therapy to prevent relapse. The AHCPR guidelines recommend treatment of the depressive episode for at least 4-9 months following acute response.

Recurrence

Recurrent depression is common (1 year risk is 33%, five year risk is 50% and lifetime risk is >70%), disabling, potentially chronic and possibly life-threatening illness Risk factors are believed to include;

- number of previous episodes (0 = 50%, 1 = 70%, 2 =80% , 3=90%),
- recent remission,
- incomplete recovery (1/3 patients only experience a partial response to antidepressant therapy),
- dysthymia,
- comorbid anxiety disorders,
- gender: women may have a higher risk than men,
- Onset after age 60.

WHO guidelines (1990) recommend prophylaxis in patients who have experienced more than one severe episode or several episodes of depression within a 5 year period and advise review of the need for continued prophylaxis only after a 2 year euthymic period. Current opinion is that patients are maintained on the full therapeutic dose.

Long-term continuation studies

Maintenance therapy in depression studies with imipramine (5-year study, Prien et al, 1984) and paroxetine (Claghorn, 1991) clearly demonstrate that there is a significant difference in relapse rates between treated and untreated groups. The first study took patients who were well for 3 years on imipramine, and randomised them to imipramine or placebo. After 2 years, approximately 2/3 of those on placebo had a recurrence of depression, whereas less than 10% (n=1/11) on imipramine had a recurrence. In the case of paroxetine, a 20% relapse rate was observed at 2 years compared to a placebo group which had >50% relapse. It was observed that there was a lower failure rate in SSRI therapy due to the improved tolerability of these products. Paroxetine has also been shown to be effective in maintaining remission of depression for periods of up to 4 years (Duboff, 1993).

Table 1: Relapse rates versus placebo in continuation studies (Adapted from Keller and Boland, 1998).

Drug	Weeks treatment	Relapse (active) %	Relapse (placebo) %	Treatment difference	p value	Reference
Fluoxetine	52 28	26 27	57 47	31 20	<0.01 NS	Montgomery et a 1988 Dekker et al 200(
Paroxetine*	52	16	43	27	<0.001	Montgomery & Dunl 1993
Sertraline	44	13	46	33	<0.001	Doogan & Caillard 1992
Citalopram	24 32	11 14	31 24	20 10	<0.05 <0.05	Montgomery et al 1993 Robert & Montgomer 1995
Mirtazapine	20	4	23	19	<0.0001	Montgomery et al 1988
Nefazodone	36	17	33	16	<0.05	Feiger et al 1999

NB. The figures for paroxetine in the table shown above are calculated based on analysis of 52 weeks treatment, whereas the figures quoted below are the result of two separate analyses, i.e. analysis of the first 16 weeks and a second analysis of data for weeks 17-52.

The long-term efficacy of paroxetine in the prevention of relapse and recurrence of depression in patients with a history of 2 or more previous episodes in the preceding 4 years has been demonstrated (Montgomery and Dunbar; 1993).

Study design:

- 8 weeks open acute treatment (paroxetine 20-40mg/day)
- 12 month double-blind paroxetine (20-30mg/day or placebo)
- analysed first 16 weeks and weeks 17-52 separately to provide some indication of prevention of relapse and recurrence of depression.

In the first 16 weeks 2/68 (2.9%) paroxetine treated patients and 13/67 (19.4%) placebo-treated patients had a relapse of their depression. Between weeks 17 and 52, 9/66 (13.6%) of paroxetine and 16/54 (29.6%) of placebo recipients experienced a recurrence of depression. In both periods, the advantages for paroxetine over placebo were

statistically significant ($p<0.05$). Kaplan Meier survival analysis also demonstrated superiority in favour of paroxetine in terms of time to relapse and recurrence compared with placebo ($p<0.005$).

Sertraline was also assessed in a 1 year study in patients responding to acute treatment, who were then randomly assigned to sertraline or placebo (Doogan and Caillard, 1992).

Study design:

- 8 weeks open label acute treatment (sertraline 50-200mg/day; n=480)
- 44 week double-blind maintenance phase (n=300)

The definition of relapse was based on CGI severity rating. Success in relapse prevention was assessed in the analysis of the first 4 months of the study and in recurrence prevention in the later period of the study. 24/184 (13%) of sertraline treated and 48/105 (45.7%) of placebo treated patients relapsed (week 44). Sertraline was more effective than placebo in preventing relapse and recurrence of depression (Doogan and Caillard, 1992).

Two placebo controlled studies have demonstrated the efficacy of citalopram as a continuation therapy for prevention of depression relapse (Montgomery et al 1993, Robert & Montgomery 1995).

In the first study (Montgomery et al 1993), 147 patients who responded to citalopram (20mg or 40mg) during an acute six week treatment period, were randomly assigned to either placebo or citalopram (fixed daily dose of either 20mg or 40mg) and continued to receive therapy at the same dose level for 24 weeks. At 12 weeks, 3/48 of citalopram 20mg (6%), 5/57 of citalopram 40mg (9%) and 10/42 (24%) of placebo treated patients experienced a relapsed of their depression. At the end of the trial (24 weeks), relapse rate (defined by threshold MADRS score of 22) were 8% and 12% with citalopram 20mg and 40mg respectively and 31% with placebo ($p<0.05$). Kaplan-Meier analysis demonstrated a significant advantage for both doses of citalopram ($p<0.05$) compared with placebo, although there were no significant differences between the two doses of citalopram.

In the second continuation study (Robert & Montgomery 1995), 226 patients who responded to citalopram (flexible daily doses of 20-60mg) during an 8 week acute treatment phase were randomly assigned to citalopram or placebo (in a ratio of 2:1) for an additional 24 week period of therapy. At the end of the study, 21/152 (14%) in the citalopram group and 18/74 (24%) in the placebo treated group experienced a relapse (defined as threshold MADRS score of 25) of their depression. Kaplan-Meier analysis demonstrated superiority in favour of citalopram in terms of time to relapse compared with placebo ($p<0.05$). Highest risk of relapse occurred in the first 8 weeks of continuation period in both groups. The relapse hazard was seen to be three times

higher in the placebo group compared with the citalopram group in the second half of the study (weeks 12-24).

Fluoxetine was also assessed in a 5 month study in patients responding to acute treatment, who were then randomly assigned to fluoxetine or placebo (Dekker et al 2000).

Study design:

- 8 weeks open label acute treatment (fluoxetine 20mg/day; n=147)
- 20 week double-blind continuation phase (n=30)

4/15 (27%) of fluoxetine treated and 7/15 (47%) of placebo treated patients relapsed (week 20). Although relapse rate was lower in the fluoxetine treated patients, the difference was not statistically significant (Dekker et al 2000).

Specific prophylactic studies designed to assess prevention of recurrence

Paroxetine, fluoxetine, fluvoxamine, citalopram, venlafaxine and milnacipran have been demonstrated to be effective prophylactic agents in prospective, placebo-controlled studies, designed specifically to test prevention of recurrence of depression. These studies require to demonstrate successful treatment of the acute depressive episode, followed by a symptom-free period of at least 18 weeks to make a clear distinction between relapse of the original episode and recurrence of a new episode

Seroxat/Paxil

Data from 2 specific studies are available::

1. Study 190 (Pitts et al; 1997)- not published as a full manuscript.

Study design:

- Acute phase: 12 weeks open label treatment with paroxetine (20-50mg/day) (n= 225 enrolled)
- Continuation phase: Responders continued on paroxetine (open label) for a further 5 months
- Double-blind, maintenance phase: Those with sustained therapeutic response were randomised to double-blind treatment with paroxetine or placebo for a further 18 months (n=125)

Patients who had experienced at least 2 previous episodes of major depression within past 5 years with the most recent episode occurring not more than 2.5 years prior to

study start were included in the study. Patients also had to have a remission period of at least 10 weeks between the current episode and most recent previous episode.

Responders:

- HAMD ≤ 7 for 3 consecutive visits (acute phase)
- HAMD ≤10 (maintenance phase)

Recurrence:

- HAMD ≥15 over 2 consecutive visits

Analysis of the data using the protocol defined recurrence criteria showed a numerical difference between the two treatment groups (5 [8.3%]) paroxetine treated patients vs 12 [19.7%] placebo patients , p=0.186). The median time to recurrence for patients meeting protocol defined criteria was longer for patients on paroxetine (140 days) compared to those receiving placebo (86 days). In addition, statistically significant differences in favour of paroxetine were observed for the majority of secondary efficacy parameters ie HAMD (first 17 and first 21 items), CGI (severity of illness) and Raskin Depression scale. In the paroxetine group the secondary efficacy variables did not show major changes from the baseline scores, indicating maintenance. In contrast, notable changes occurred in the placebo patients, indicative of further depressive deterioration.

When the number of patients who fulfilled the per-protocol definition of recurrence were combined with those who withdrew due to lack of efficacy there was a statistically significant difference between the groups in favour of paroxetine treated patients (n= 9 (15%)) compared to placebo patients (n= 35 (57.4%), p<0.001)

Limitations: Very stringent definition of recurrence.

2. Franchini et al; 1998:

Study design:

- 6 week open acute treatment phase (n=90) paroxetine 20-40mg.
- 4 months open continuation phase (n=72)
- 28 month double-blind, maintenance phase (paroxetine 20mg or 40mg) (n=68)

Reponders:

- HAMD ≤8 for 3 consecutive weeks (acute phase)
- HAMD score <8 (continuation phase)

Recurrence:

- HAMD score >15

17/33 (51.5%) paroxetine 20mg and 8/34 (23.5%) paroxetine 40mg experienced a single recurrence of depression.

Limitations: Small numbers of patients and not placebo controlled.

Fluoxetine (Montgomery et al; 1988)

Study design:

- 6 weeks open label acute treatment (n=456)
- 18 weeks open label continuation phase
- 1 year double-blind, placebo controlled, maintenance phase (n=220)

Patients with at least one previous major depressive episode during the past 5 years, with an interval of at least 6 months between the end of the previous episode and the beginning of the present one. Treated with fluoxetine 40-80mg.

Responders:

- HAMD (21) $\leq$12 at week 6
- Maintained over 18 weeks (HAMD $\leq$8)

Recurrence:

- HAMD >18

182 patients completed the 12 month prophylactic phase. 26% (n=23/88) of fluoxetine-treated patients had a recurrence, compared with 57% (n= 54/94) in the placebo-treated group ($p<0.001$).

Limitations: high doses of fluoxetine (mean dose 40mg)

Fluvoxamine (Terra and Montgomery, 1998)

Patients 18-70 years suffering from moderate-severe depression (DSM IIIR), minimum severity score >25 MADRS and a history of at least 2 episodes of major depression within past 5 years, separated by a symptom-free interval of at least 6 months, were included in this study.

Study design:

- 6 weeks acute (open label) phase (300mg fluvoxamine) (n=436).
- Responders entered an 18 weeks (open label) continuation phase (all patients received 100mg/day fluvoxamine during the final 4 weeks of this phase) (n=283)

- Double-blind maintenance phase (n=204). Randomisation to fluvoxamine (100mg/day) or placebo for a further 12 months.

Responders

- Acute phase: MADRS score <10 and CGI score of 1 or 2 (severity of illness) at week 6
- Continuation phase: Maintained MADRS score <12 and score no higher than 1 or 2 on CGI.

Recurrence:

- Reappearance of at least 5 symptoms outlined in DSM IIIR diagnosis of major depression (2 assessments –8 days apart)
- Attempted suicide.

The incidence of recurrence was significantly lower in the fluvoxamine group when compared with placebo (13% vs 35%, p<0.001) and the mean time to recurrence was significantly longer for fluvoxamine compared with placebo (181 vs 96 days, p<0.005). Fluvoxamine was well tolerated and the incidence of side-effects was similar to that in the placebo group.

Limitations: Patients initially treated with 300mg/day fluvoxamine (first 20 weeks). Recurrence not clearly defined.

Citalopram

Data from three studies are available:

1. Wade et al 1999 (poster presentation)

Study design:

- Acute phase: 6-9 weeks open acute treatment with citalopram 20-60mg (n=427 enrolled)
- Continuation phase: Responders continued on citalopram (at the established effective dose) for another 16 weeks (n=327)
- Double-blind maintenance phase: Patients with sustained therapeutic response were randomised to double-blind treatment with citalopram or placebo for 48 weeks (n=269).

Patients with a history of at least 2 prior episodes of major depression (according to DSM IV criteria) were included in the study.

Responders:

- MADRS <12

Recurrence:

- MADRS >22

The time to recurrence of depression in patients treated with citalopram was statistically longer compared to placebo at all three dose levels (p=0.04, p=0.08 & p=0.016 for 20mg, 40mg and 60mg respectively).

Limitations:

The poster does not provide any data on recurrence rates with citalopram in comparison to placebo.

Notes:

Although the poster does not provide information on recurrence rates with citalopram, a recent review (Keller 2000) indicates that 80% of citalopram treated patients remained free of recurrence throughout the maintenance phase of the study, compared with 50% of patients assigned to placebo (p<0.0001). It is unclear, however, how these figures have been calculated and so caution must be exercised when referring to these data.

2. Klysner et al 2000 (poster presentation):

Study design: (This is similar to study 1 with the exception that it was performed in the elderly population).

- Acute phase: 8-12 weeks open acute treatment with citalopram 20-40mg (n=230 enrolled)
- Continuation phase: Responders continued on citalopram (at the established effective dose) for another 12-16 weeks (n=172)
- Double-blind maintenance phase: Patients with sustained therapeutic response were randomised to double-blind treatment with citalopram (at the established effective dose) or placebo for 48-120 weeks (n=121).

Responders

- MADRS total score <12

Recurrence

- MADRS total score >22

The time to recurrence of depression in elderly patients treated with citalopram (at all doses) was statistically longer compared to placebo (p<0.0001).

Limitations:

The poster does not provide any data on recurrence rates with citalopram in comparison to placebo.

3. Franchini et al 1999

Study design:

- 4 months open label treatment phase with citalopram 40mg/day (n=50)
- 20 months maintenance phase with citalopram 20mg/day (n=32)

Responders

- 21 item HAM-D score <8

Recurrence

- 21 item HAM-D score >15

50% (16/32) of patients who entered the 24 month maintenance phase experienced a recurrence of their depression.

Limitations

Lack of placebo in the study. Dose reduction to 20mg citalopram during the maintenance phase from citalopram 40mg during the acute phase of the study.

Venlafaxine (Aguiar; 1998)

Study design:

- 6 months open label treatment phase (n=483)
- 12 months double-blind maintenance phase (n=237)

Recurrence:

- CGI $\geq$4

Limitations: limited details available (no definition of response), abstract form only. Definition of recurrence not as well defined as an increase in HAMD score.

Milnacipran (presented at the Pierre Fabre symposium, ECNP, Paris, 1998)-not published

Pierre fabre have conducted a large prophylactic prevention/maintenance study in recurrent depression.

Study design:

- A 6 week acute (open label) treatment phase
- Continuation phase: Responders continued treatment for a further 18 weeks
- Patients then re-randomised to milnacipran or placebo for a further 12 months treatment (maintenance phase)

Response was defined as;

- a HAMD total score $\leq$12 (acute phase)
- a HAMD total score $\leq$8 (continuation phase)
- improvement or disappearance of symptoms (continuation phase)
- CGI score of 1 or 2 (continuation phase)

Enrolled 500 patients with recurrent depression- at least 2 episodes of depression in the previous 3 years (63.4% achieved a HAMD score $\leq$12). 323 patients entered the 18 week continuation phase (70.3% achieved a HAMD score $\leq$8). 104 patients were maintained on milnacipran and 110 re-randomised to placebo in the double-blind maintenance phase 16.3% of milnacipran patients had a recurrence (n=17) vs 23.6% (n=26) of placebo patients ($p<0.05$).

Limitations: details of definition of recurrence not available.

Table 2: Prophylactic Study designs

Treatment	Acute phase (6 weeks) Response	Continuation phase (18 weeks) Response	Maintenance phase (12 months) Recurrence
Paroxetine@ (20-50mg/day)	$HAMD_{17}$ ≤7 (3 consecutive visits)	HAMD ≤10	HAMD ≥15 (2 consecutive visits)
Fluoxetine (40-80mg/day)	$HAMD_{21}$ ≤12 (week 6)	HAMD ≤8	HAMD >18
Fluvoxamine (100-300mg/day first 20 weeks; tapered to 100mg/day)	MADRS <10 and CGI (SOI) of 1 or 2	MADRS <12 and CGI (SOI) of 1 or 2	Return of 5 or more symptoms outlined in DSM IIIR for major depression and/or Attempted suicide
Citalopram* (20-60mg/day flexible dose)	MADRS <12	MADRS <12	MADRS ≥22
Venlafaxine (100-200mg/day)	?	?	CGI ≥4
Milnacipran (doses not known)	HAMD ≤12 (week 6)	HAMD ≤8 CGI (SOI) of 1 or 2 Improvement or disappearance of symptoms	?

@ NB for paroxetine, acute phase = 12 weeks, continuation phase = 20 weeks (5 months), maintenance phase = 18 months

* For citalopram, acute phase = 6-9 weeks, continuation phase = 16 weeks, maintenance phase = 48-120 weeks

Table 3: Recurrence rates for long-term prophylactic studies

	% (n) DRUG	% (n) Placebo	% - Treatment difference
Paroxetine (18 months)	8.3 (5/60)	19.7 (12/61)	11.4
Fluoxetine (12 months)	26 (23/88)**	57 (54/94)	31.0
Fluvoxamine (12 months)	13 (14/109)***	35 (33/94)	22.0
Citalopram* (12 months)	20***	50	30.0
Venlafaxine (12 months)	20 (21/106)****	51 (52/104)	31.0
Milnacipran (12 months)	16.3 (17/104)*	23.6 (26/110)	7.3

* Note that for citalopram, these figures are quoted from the review (Keller 2000) and not the clinical study.

NB Studies can not be directly compared. No direct comparator studies have been conducted.

* $p<0.05$, ** $p<0.01$,, *** $p<0.001$, **** $p<0.0001$

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