Acta Psychiatr Scand 2008: 118: 116–122
All rights reserved
DOI: 10.1111/j.1600-0447.2008.01179.x

ACTA PSYCHIATRICA SCANDINAVICA

Antidepressant treatment is associated with a reduction in suicidal ideation and suicide attempts

Mulder RT, Joyce PR, Frampton CMA, Luty SE. Antidepressant treatment is associated with a reduction in suicidal ideation and suicide attempts.

Objective: To measure changes in suicidal behaviours during 6 months of treatment with antidepressants.
Method: A group of depressed patients (n = 195) were assessed for suicidal behaviours in the 6 months prior to treatment. They were prospectively assessed for suicidal behaviours during 6 months of treatment with antidepressants.
Results: Patients who made suicide attempts fell from 39 in the 6 months prior to treatment to 20 during treatment. Significant suicidal ideation reduced from 47% at baseline to 14% at 3 weeks remaining below this during the rest of the treatment. Twenty patients had emergent suicidal ideation; five of them had not experienced some level of suicidal behaviour in the 6 months prior to treatment.
Conclusion: Suicide behaviours are common in depressed out-patients. Antidepressant treatment is associated with a rapid and significant reduction in suicidal behaviours. The rate of emergent suicidal behaviour was low and the risk benefit ratio for antidepressants appears to favour their use.

R. T. Mulder, P. R. Joyce, C. M. A. Frampton, S. E. Luty

Department of Psychological Medicine, University of Otago, Christchurch, New Zealand

Key words: antidepressants; suicide behaviours; depression

Professor Roger Mulder, Department of Psychological Medicine, University of Otago, Christchurch, PO Box 4345, Christchurch Mail Centre, Christchurch, New Zealand.
E-mail: roger.mulder@otago.ac.nz

Accepted for publication February 27, 2008

Significant outcomes

- Unselected depressed out-patients have high levels of suicidal behaviours with 79% having at least occasional suicidal ideation and 23% attempting suicide in the prior 6 months.
- Treatment of depression with antidepressants is associated with a rapid and sustained reduction in suicidal ideation and a halving in the rate of suicide attempts.
- Emergent suicidality is uncommon and is usually in patients with prior episodes of suicidal ideation and/or attempts.

Limitations

- Suicidal behaviours prior to baseline assessment were collected retrospectively and are therefore subject to recall bias.
- The sample size precludes any evidence of the effect of treatment on completed suicides.
- There is no placebo arm; so, the reduction in suicidal behaviour may be due to non-specific treatment factors.

Introduction

Antidepressant drugs have not been demonstrated to reduce short-term suicide risk (1). There has been concern that some antidepressants might be associated with an increased risk of suicidal ideation and behaviour in some patients (2). Evidence for this association has been convincing enough for health authorities, such as the UK Medicine and Healthcare Products Regulatory Agency and the Food and Drug Administration (FDA) to issue warnings about selective serotonin reuptake

inhibitors (SSRIs) increasing the likelihood of suicidal behaviour in children and adolescents.

Clinicians are left in a difficult position. The utility of trial results and regulatory pronouncements as a basis for clinical practice is limited by methodological problems. The evidence used to assess risk of suicidal behaviour generally originates from industry-sponsored antidepressant studies (2–5). Such trials, especially if they involve the use of a placebo arm, exclude high-risk subjects known to be suicidal and/or have alcohol and drug problems and/or have borderline personality disorder. Estimates of the effect of antidepressants on suicidality are therefore biased towards detecting emergent suicidal ideation or behaviour. The impact of beginning antidepressants in patients with a moderate risk of suicidal behaviours cannot be measured as these patients are excluded. Investigators might also underestimate suicidality at entry to the trial to enhance recruitment resulting in the apparent emergence of suicidality soon after beginning medication.

The data from these industry studies may not be consistent with other forms of evidence. The recent American College of Neuropsychopharmacology Task Force Report on SSRIs and suicidal behaviour in youths pointed out that while meta-analyses of FDA clinical trials showed a small increase in suicidal behaviours, data from toxicology and epidemiology studies suggest that SSRIs may actually lower the suicide risk (3).

Aims of the study

The aim of this study was to report on the prevalence of suicidal ideation and suicide attempts and changes in these behaviours during drug treatment for depression in a group of *unselected* out-patients over a period of 6 months. Suicidal patients, patients with borderline personality disorder, and those suffering from moderate alcohol or drug dependence were included in the study. This allows us to assess the effect of antidepressant treatment on existing suicidal behaviours as well as their association with emergent suicidality. It enables a more balanced assessment of the risks and benefits of using antidepressants in patients with major depression.

Material and methods

Subjects

Depressed patients were referred from a variety of sources including a psychiatric emergency service, community mental health centres and general practitioners. No patients were recruited by advertising. Subjects were screened over the telephone by a research nurse and then seen for initial assessment by a psychiatrist or senior psychiatric registrar. Following this initial assessment, eligible patients were invited to participate in the study after giving written informed consent. The study was approved by the Canterbury (New Zealand) Ethics Committee and took place from 1993 to 2001.

The inclusion criteria were age 18 years or over and able and willing to give informed consent. DSM-III-R major depression was the principle current diagnosis and treatment with an antidepressant was appropriate management.

The exclusion criteria were current breastfeeding or pregnancy or the likelihood of pregnancy, a major medical disorder that could interfere with assessment and treatment, current severe alcohol or drug dependence (mild to moderate alcohol or drug dependence was acceptable) and a history of schizophrenia, schizoaffective disorder or mania (a history of hypomania was permitted).

Baseline assessment

All patients were assessed using the Structured Clinical Interview for DSM-III-R – Patient Version (SCID-P) (6). Patients were rated on the Montgomery Asberg Depression Rating Scale (MADRS) (7), the 17-item Hamilton Depression Rating Scale (HDRS) (8), and the Clinical Global Impression (CGI) (9). A structured interview covered lifetime suicide attempts, and suicide attempts and suicidal ideation over the past 6 months. Suicidal ideation was categorized as none (no suicidal ideation), occasional (some suicidal ideation but for less than 14 days), moderate (suicidal ideation at least once a day for more than 14 days), regular (persistent suicidal ideation for more than 14 days).

Assessment of suicide attempts and suicidal ideation during treatment

At 3, 6, 9, 13, 20 and 26 weeks, patients were asked about suicide attempts since the last visit. All patients were assessed using the MADRS at these visits. The prespecified measure of significant suicidal ideation was a score of three or more on the MADRS suicidal thoughts item rated over the previous week (see Appendix).

Treatment

Patients were randomly allocated to receive fluoxetine or nortriptyline for an initial period of

6 weeks. At 6 weeks, the mean fluoxetine dose was 28.1 mg/day (range 10–80), and the mean nortriptyline dose was 93.5 mg/day (range 50–175) (10). At 6 weeks, patients continued taking their medication if they had responded. Unless clinically contraindicated patients who did not respond were switched to the alternative medication. If the patient was unresponsive to the second drug, clinicians generally combined the two medications. If this failed, the clinician was free to use whatever medication was clinically indicated, usually switching to an alternative antidepressant or augmenting the current treatment with lithium. All patients who responded were strongly encouraged to continue taking their medications for 6 months. Formal assessments were performed at 3, 6, 9, 13, 20, and 26 weeks with the MADRS, HDRS and CGI.

Treatment outcome

The sample was divided into three groups based on treatment outcome. These were: i) patients who recovered (i.e. a CGI score of much improved or very much improved for more than 8 weeks) and remained well until the 6-month assessment; ii) patients who achieved remission (i.e. a CGI score of much improved for very much improved for 2–8 weeks) or recovery but also relapsed; and iii) patients with persistent depression (i.e. no CGI score of much improved or very much improved) for 6 months (11).

Statistics

Baseline characteristics for treatment outcome profiles were analysed with pattern of suicide ideation over time using chi-squared tests.

Results

Patient characteristics at baseline

One hundred and ninety-five patients were randomly assigned to treatment. Of these 101 (57.4%) were female with a mean age of 32.2 years (SD 11.4). According to DSM-III-R criteria 18 (9%) had bipolar II disorder, 86 (44%) had melancholia, 16 (8%) had atypical depression, 121 (52%) had recurrent depression and 125 (64%) had chronic depression (defined as being depressed for more than two of the past 5 years). The mean MADRS baseline score was 31.0 (SD 6.8) and the mean HAM-D score was 19.9 (SD 4.4). For a more detailed description of the original patient group see our earlier papers (10, 11).

Treatment

Figure 1 shows how the subjects moved through the trial; 195 were randomly assigned to fluoxetine or nortriptyline and at 6 months 176 remained in the study, 10 dropped out (i.e. did not keep follow-up appointments), nine left the area, one withdrew without being treated and later committed suicide. By 6 months, the majority of subjects (66%) were taking fluoxetine or nortriptyline. Twenty-four patients had elected to stop taking medication or found it intolerable but remained in the study. The remaining 36 (21%) were either taking a combination of fluoxetine and nortriptyline or were taking other medications (see Fig. 1). The results pre-

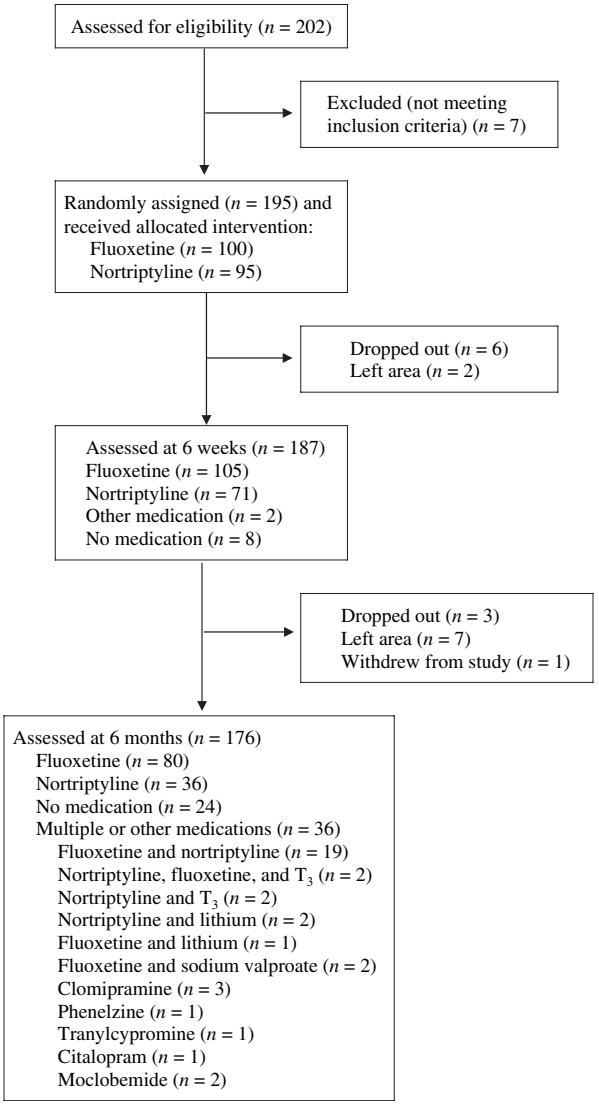

Fig. 1. Disposition of subjects recruited for 6-month study on outcome of major depression treated with fluoxetine or nortriptyline.

sented are those of the 176 patients who completed follow-up at 6 months.

Suicide ideation and behaviour in the 6 months prior to treatment

Table 1 shows the estimated prevalence of suicidal ideations and suicide attempts during the 6 months prior to beginning treatment. It can be seen that, while the majority of patients had occasional or no suicidal ideation, 34.6% had at least moderate suicidal ideation. Thirty-nine patients (23.3%) reported attempting suicide in the 6 months prior to treatment. Twelve of these made more than one attempt (five made two attempts, six made three and one made eight suicide attempts).

Suicidal behaviours during 6 months of treatment

i) *Suicidal ideation:* Figure 2 shows the percentage of patients with a MADRS greater than or equal to three during the 6 months of treatment. There is an obvious and sustained reduction in suicidal ideation over the 6 months. No patients recorded a score of three or more over all six measurement points. Two patients had a MADRS suicide item score of three or more on five occasions, three patients on four occasions, four patients on three occasions, 10 patients on two occasions and 30 on one occasion. When we confined our analysis to only those patients (n = 109) who had a MADRS score recorded at all six postbaseline assessments, the results were not significantly different.

ii) *Suicide attempts*. Twenty patients attempted suicide over the 6 months of treatment. There was one completed suicide by hanging in a patient who had dropped out of the study. Of the patients who attempted suicide, one patient made five attempts, one three attempts, one two attempts and the rest made one suicide attempt each. The majority (n = 16) were by overdose with one having medically serious complications. Two patients attempted suicide using carbon monoxide and one used a knife.

iii) *Emergent suicidality*. Twenty (22%) of 91 patients with a score of less than three on the MADRS suicidal item at baseline recorded a score of three or more at least once during treatment.

iv) *Reducing suicidality*. Fifty-six (66%) of 85 patients who had a suicide item score of three or more at baseline did not have a score of three or more at any stage during the 6 months.

Table 1. Frequency of suicidal ideation and number of attempts in the 6 months prior to treatment (n = 176)

	Numbers	%
Suicidal ideation – none	37	21.0
Occasional	76	43.2
Moderate	53	30.1
Regular	8	4.5
Suicide attempts	39	23.3

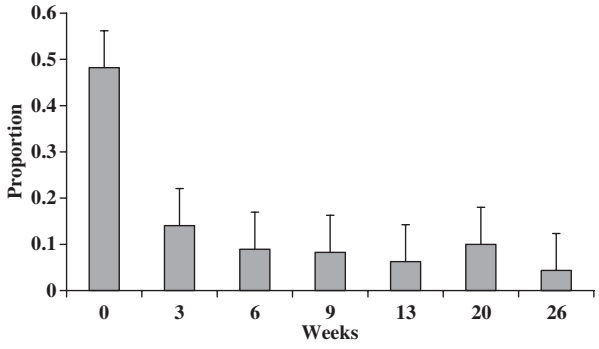

Fig. 2. Proportion with MADRS suicide item ≥3 over the course of treatment.

Changes in suicidal ideation during 6 months of treatment

The sample was divided into four groups based on changes in MADRS suicide item during treatment.

i) *Never* – those with MADRS suicide item scores of <3 at baseline and at any point during treatment (n = 71, 40.3%).

ii) *Lost* – those with a score of ≥3 at baseline who had no further scores ≥3 at any point during treatment (n = 56, 31.8%).

iii) *Gained* – those with a score of <3 at baseline who received a score of ≥3 at least one time during treatment (n = 20, 11.4%).

iv) *Kept* – those with a score of ≥3 at baseline who scored ≥3 at least one further time point during treatment (n = 29, 16.5%).

If the division into these four groups is restricted to those having all six postbaseline assessments (n = 109) the percentages are very similar. The percentages for the four groups being: Never 40% (n = 44), Lost 29% (n = 32), Gained 11% (n = 12), Kept 19% (n = 21).

Table 2 shows that these changes in MADRS suicide item score were not related to gender, age (divided into youth 18–24 years and adult 25–64 years) or the initial drug prescribed. They were related to the course of illness over the 6 months of treatment. Those with persistent depression were more likely to gain or keep suicidal

Table 2. Effect of age, gender, drug type and response on changes in suicidal ideation during treatment (n = 195)

Variable	Never (%)	Lost (%)	Gained (%)	Kept (%)	ψ^2	df	P
Gender							
Male (n = 84)	36.0	30.7	12.0	21.3	2.6	3	0.461
Female (n = 111)	43.6	32.7	10.9	12.9			
Age							
18–24 years (n = 72)	40.4	31.6	10.5	17.5	0.43	3	0.934
24–65 years (n = 123)	40.3	32.3	12.9	14.5			
Drug							
Fluoxetine (n = 82)	39.3	29.2	11.2	20.2	2.0	3	0.579
Nortriptyline (n = 87)	41.4	34.5	11.5	12.6			
Persistent depression vs. remission or recovery							
Remission or recovery (n = 155)	43.2	34.8	9.0	12.9	22.69	3	<0.001
Persistent depression (n = 21)	19.0	9.5	28.6	42.9			
Persistent recovery vs. non-persistent recovery							
Non-persistent recovery or non-recovery (n = 75)	30.7	25.3	18.7	25.3	17.11	3	<0.001
Persistent recovery (n = 101)	47.5	36.6	5.9	9.9			

ideation, while those who recover and remain well were least likely to do so.

Characteristics of the suicidal ideation groups

Table 3 shows the suicidal ideation and behaviours of the four groups during the 6 months prior to treatment. It suggests that suicidal ideation and behaviour fluctuates quite markedly. Of the 78 patients with no MADRS suicidal ideation score ≥3 at baseline or during treatment, 12 (14%) had suffered regular or frequent suicidal thoughts prior to treatment and nine (12%) had attempted suicide in the 6 months prior to treatment. Those who had a MADRS suicide item score of three or more at baseline but at no subsequent assessments had the highest rate of suicide attempts prior to treatment; both in the 6 months prior to treatment and during their lifetime. This was higher than those who continued to have at least one MADRS suicidal item score of three or more during treatment.

Possibly the most interesting group are the 20 patients who had a MADRS score of less than three at baseline but then received a score of three or more during treatment (gained). These patients also demonstrate marked fluctuations in suicidal ideation and behaviour. Only five (20%) had reported no suicidal ideation and/or attempts prior to treatment. None of these five patients attempted suicide during treatment. Of the other 15, four had made a suicide attempt in the 6 months prior to treatment and six during their lifetime.

Table 3. Relationship of suicidal ideation and behaviour in the 6 months prior to treatment to suicidal ideation and behaviour during the 6 months of treatment (n = 174) and number of patients in each group

	Never (n = 69)	Lost (n = 56)	Gained (n = 20)	Kept (n = 29)
Suicidal ideation in the 6 months prior to treatment				
1. None (n = 37)	24 (65.9)	5 (13.5)	5 (13.5)	3 (8.1)
2. Little (n = 76)	34 (44.7)	25 (32.9)	10 (13.2)	7 (9.2)
3. Regular (n = 53)	9 (17.0)	23 (43.4)	5 (9.4)	16 (30.2)
4. Frequent (n = 8)	2 (25.0)	3 (37.5)	0 (0)	32 (37.5)
Suicide attempts in the 6 months prior to treatment (n = 39)	8 (20.5)	20 (51.3)	4 (10.3)	7 (17.9)
Lifetime suicide attempts (n = 58)	15 (25.8)	26 (48.8)	6 (10.4)	11 (19.0)

Values in parentheses are percentage.

Discussion

Suicidal ideation and behaviour is common in non-selected, moderately depressed out-patients. In this sample, three-quarters of patients reported at least some suicidal ideation and over 20% had attempted suicide in the 6 months prior to their treatment. One-third of patients reported making at least one suicide attempt in the past.

Antidepressant treatment is associated with a significant reduction in suicidal ideation and attempts. The proportion of patients with significant suicidal ideation (i.e. a MADRS suicide item score of 3 or more) falls from 47% to 14% over the first 3 weeks of treatment and averages around 9% throughout the 6-month period. The number of suicide attempts during the 6 months of treatment drops by half when compared with the 6-month period prior to treatment.

Around 10% of patients have emergent suicidality. Three-quarters of these had reported some level of suicidality during the 6 months prior to treatment, although not at baseline. Nineteen per cent of this group had attempted suicide during the 6 months prior to treatment. Only five patients in this group had no suicidal ideation and/or suicide attempts in the 6 months prior to starting treatment. Therefore, in the total sample, 3% of patients had emergent suicidality when starting antidepressants who did not have a prior history of suicidal ideation or attempts. None of these five patients attempted suicide.

Changes in suicidal ideation were not related to whether nortriptyline or fluoxetine was first prescribed. Changes were also not related to gender or age but were related to treatment outcome. Not surprisingly those with persistent depression were more likely to have persistent or emergent suicidal ideation compared with those who recovered and remained well.

Comparable studies are rare and virtually all information about suicidality and its association with antidepressants come from industry-sponsored studies. In these studies, rates of suicidality during treatment appear much lower than the rates we report. In an attempt to compare our results with these studies, we have calculated standardized suicidal behaviour rates as attempts per 1000 patient years. Prior to treatment in our study, the suicide attempt rate is 390 per 1000 patient years. During treatment, it declines to 200 per 1000 patient years. We could not find any studies which systematically reported suicidal ideation or attempts prior to initiating treatment. The largest and most up-to-date meta-analysis of suicide attempts during drug treatment (4) reported a suicide attempt rate of 18.2 per 1000 patient years during antidepressant treatment. Therefore, our suicide attempt rate during treatment is over 10 times the mean rate of the antidepressant studies included in this meta-analysis.

This is a major discrepancy which would distort any assessment of the relationship between antidepressants and suicidality. There are three possible reasons for this difference. First, the assessment of suicidality and rates of suicide attempts in drug studies are biased and grossly underestimate rates. This is unlikely as regulatory and ethical authorities are assiduous about collecting and examining this data during treatment. Second, the assessment of suicidality and suicidal behaviour in our study grossly overestimates the rate. This also seems unlikely. Suicidal ideation was based on clinician rating, suicide attempts were enquired in a systematic way and all patients were followed prospectively. Third, depressed individuals in drug studies are different from those seen at psychiatric out-patient clinics.

The third explanation is most likely. Industry-sponsored studies appear to treat different patients from those that are seen in psychiatric out-patient clinics particularly with regard to suicidality. As noted in the introduction much of this is deliberate. It is difficult to justify placebo arms in trials which contain subjects with significant suicidal ideation and recent histories of suicide attempts. It may also reflect recruitment methods: using advertising as well as referral to enlist patients, and the type of patient wishing to enrol in an industry-sponsored drug trial. Whatever the reason, the result is an atypical sample: depressed patients without suicidal ideation or recent suicide attempts. This finding is consistent with a number of studies questioning whether the results of antidepressant efficacy trials can be applied to clinical populations (12, 13).

It seems that patients in industry-sponsored trials are an inappropriate group to use to calculate the relationship of risks and benefits of antidepressants to suicidality. Even in general population samples of depressed individuals, the rates of suicide attempt appear to be higher. The recent New Zealand epidemiological study, for example, reported a suicide attempt rate of 40 per 1000 patient years in randomly selected individuals in the community who had a diagnosis of major depression over the past 12 months (14). This is more than twice the rate of patients undergoing treatment included in meta-analyses of suicidal behaviour.

Further evidence comes from researchers who have studied the association between antidepressants and suicidal behaviour using clinical epidemiological methods. While the assessment of suicidal behaviours may be less robust the patients are largely unselected. Simon et al. (15) using computerized health records reported that the prescription of antidepressants was associated with a progressive decline in suicide attempts over 10 months. Henriksson and Isacsson (16) reported a trend towards greater prescription of antidepressants and fewer suicides after an educational programme for GPs in Jamtland country, Sweden. Sondergard et al. (17) concluded that a more pronounced decrease in suicide rates was found among persons treated with antidepressants than among persons not treated with antidepressants.

Limitations of the study

Suicidal behaviour prior to baseline assessment was collected retrospectively and is subject to recall bias. If anything, this would reduce rates of suicidal ideation and suicide attempts prior to treatment. It might be argued that the low rates of patients receiving high scores on the MADRS suicidal ideation item was due to missing data. We had complete data at all six assessments for over 60% of patients. When we analysed this separately, the results were no different to those in the total sample. It might also be argued that some of the 19 patients who dropped out may have made a suicide attempt. To our knowledge, none of these patients presented to a hospital with a suicide attempt but one committed suicide.

The number of patients in this study precludes any comment on the efficacy of antidepressants on completed suicide. The results apply to depressed adult out-patients and may not be generalizable to all depressed patients including adolescents. As there is no placebo (which would be difficult to

justify in patients with this level of suicidal behaviour), the reduction in suicidal behaviour may be entirely due to non-specific treatment factors.

In summary, suicidal ideation and behaviour are common in depressed out-patients and reduce significantly when antidepressant treatment is initiated. The risk of emergent suicidality appears low, occurring in 11% of patients three-quarters of whom had experienced suicidal ideation or behaviour in the 6 months prior to treatment. The risk benefit ratio for suicidal behaviours for using antidepressants in depressed out-patients appears to strongly favour their use. The study suggests that if the prescription of antidepressants is associated with suicidal behaviours, then it is being prescribed for the right indication. Antidepressant treatment is associated with a rapid and sustained reduction in suicidal ideation and suicide attempts.

Acknowledgements

This study was sponsored by the Health Research Council of New Zealand, Lottery Health, the Canterbury District Health Board and an unrestricted grant from Eli Lilly (NZ). The sponsors had no role in study design, collection, analysis or interpretation of data, writing the report or the decision to submit paper for publication.

Declaration of interests

Roger Mulder has during the past 3 years received honoraria for speaking and travel assistance from Douglas Pharmaceuticals, Janssen-Cilag and AstraZenica.
Peter Joyce and Christopher Frampton have no conflicts of interest.
Suzanne Luty has during the past 2 years received travel assistance and conference support from Eli Lilly.

References

1. Baldessarini RJ, Pompili M, Tondo L. Suicidal risk in antidepressant drug trials. Arch Gen Psychiatry 2006;**63**: 246–248.
2. Hammad TA, Laughren T, Racoosin J. Suicidality in pediatric patients treated with antidepressant drugs. Arch Gen Psychiatry 2006;**63**:332–339.
3. Mann JJ, Emslie GJ, Baldessarini RJ et al. ACNP Task Force report on SSRIs and suicidal behaviour in youth. Neuropsychopharmacology 2006;**31**:473–492.
4. Fergusson D, Doucette S, Cranley Glass K et al. Association between suicide attempts and selective serotonin reuptake inhibitors: systematic review of randomised controlled trials. Br Med J 2005;**330**:396.
5. Khan A, Khan S, Kolts R, Brown WA. Suicide rates in clinical trials of SSRIs, other antidepressants, and placebo: analysis of FDA reports. Am J Psychiatry 2003;**160**:790–792.
6. Spitzer RL, Williams J, Gibbon M, First M. Structured clinical interview for DSM-III-R: patient version (SCID-P). New York: Biometrics Research Department, New York State Psychiatric Institute, 1988.
7. Montgomery SA, Asberg MA. A new depression scale designed to be sensitive to change. Br J Psychiatry 1979; **134**:382–389.
8. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;**23**:56–62.
9. Guy W. ECDEU assessment manual for psychopharmacology – revised. Rockville, MD: National Institute of Mental Health, 1976.
10. Joyce PR, Mulder RT, Luty SE et al. Patterns and predictors of response, remission and recovery in major depression treated with fluoxetine or nortriptyline. Aust NZ J Psychiatry 2002;**36**:384–391.
11. Mulder RT, Joyce PR, Frampton CMA, Luty SE, Sullivan PF. Six months of treatment for depression: outcome and predictors of the course of illness. Am J Psychiatry 2006;**163**:95–100.
12. Zimmerman M, Chelminski I, Posternak MA. Generalizability of antidepressant efficacy trials: differences between depressed psychiatric outpatients who would or would not qualify for an efficacy trial. Am J Psychiatry 2005; **162**:1370–1372.
13. Posternak MA, Zimmerman M, Keitner GI, Miller IW. A reevaluation of the exclusion criteria used in antidepressant efficacy trials. Am J Psychiatry 2002;**159**:191–200.
14. Beautrais AL, Wells JE, McGee MA, Oakley Browne MA. Suicidal behaviour in Te Rau Hinengaro: the New Zealand Mental Health Survey. Aust N Z J Psychiatry 2006;**40**: 896–904.
15. Simon GE, Savarino J, Operskalski B, Wang PS. Suicide risk during antidepressant treatment. Am J Psychiatry 2006; **163**:41–47.
16. Henriksson S, Isacsson G. Increased antidepressant use and fewer suicides in Jamtland county, Sweden, after a primary care educational programme on the treatment of depression. Acta Psychiatr Scand 2006;**114**:159–167.
17. Sondergard L, Kvist K, Lopez AG, Andersen PK, Kessing LV. Temporal changes in suicide rates for persons treated and not treated with antidepressants in Denmark during 1995–1999. Acta Psychiatr Scand 2006;**114**:168–176.

Appendix: The MADRS suicidal thoughts item (rated for the past week)

0. Enjoys life or takes it as it comes.
1.
2. Weary of life. Only fleeting suicidal thoughts.
3.
4. Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention.
5.
6. Explicit plans for suicide when there is an opportunity. Active preparation for suicide.