

Isotretinoin, depression and suicide: a review of the evidence

Parker Magin, Dimity Pond and Wayne Smith

ABSTRACT

There is currently considerable controversy regarding a proposed causal relationship between the use of isotretinoin and depression and suicide. A search was made of the MEDLINE, EMBASE and PsychINFO databases using the search terms 'isotretinoin', 'depression' and 'suicide'. Despite numerous case reports linking isotretinoin to depression, suicidal ideation and suicide, there is, as yet, no clear proof of an association. While isotretinoin, used to treat acne vulgaris, has not been demonstrated to be associated with depression or suicide, the possibility of a relatively rare idiosyncratic adverse effect remains. GPs have a role in the clinical application of these findings.

Keywords

acne vulgaris; depression; isotretinoin; suicide.

INTRODUCTION

Isotretinoin is an efficacious and widely-used therapy for severe acne.^{1,2} Its introduction has been hailed as 'an incredible triumph ... in the treatment of acne vulgaris'.³ But it is recognised as having a wide range of adverse effects. The most notable of these is teratogenicity,³ but mucocutaneous, ophthalmic, and musculoskeletal effects and effects on plasma lipids and liver function tests are also acknowledged side effects.^{1,2,4} The relationship of isotretinoin to depression and suicide is more controversial and will be discussed in this article.

METHOD

Searches were made of the MEDLINE, EMBASE and PsychINFO databases. Search terms used were isotretinoin, depression and suicide. The search was confined to English language articles. Reference lists

of identified articles were examined for further relevant studies. There were no pre-specified quality criteria for study inclusion. Given the relative paucity of methodologically rigorous studies in this area, and the considerable influence on current practice of case reports, no evidence was excluded on methodological grounds.

RESULTS

Warnings regarding isotretinoin, depression and suicide

In 1998 the US Food and Drug Administration (FDA) issued a warning to physicians regarding a possible association with depression, psychosis, suicidal ideation and suicide.^{5,6} The FDA recommends the use of signed informed consent forms and a printed patient medication guide for patients prescribed isotretinoin.^{7,8} The FDA's 1998 warning was noted in the *Lancet* as being in response to a 'possible connection ... although there is no evidence'.⁹

What is the evidence for an association?

Case reports. A number of case reports and case series linking isotretinoin to depression or suicide have appeared in the medical and psychological literature since 1982.¹⁰⁻¹⁹ Between 1982 and 2000 the FDA has received reports of 394 cases of depression, and 37 suicides occurring in patients exposed to isotretinoin.^{7,20} It is the fifth most common drug reported to the US Adverse Event Reporting System (AERS) in association with depression, and the tenth most common (and the only non-psychotropic drug) in suicide reports.⁷ In Canada, psychiatric adverse effects in patients taking isotretinoin have been reported to Health Canada²¹ — 56 events between 1983 and 2003.²² Forty-two psychiatric reactions were reported to the British Medicines Control Agency between 1982 and 1998,²³ including a small number of suicides.²⁴ In Australia from 1995 to 1998 the Adverse Drug Reactions Advisory Committee received 12 reports of depression in patients taking isotretinoin.²⁵ Two cases were described as severe, in four there were psychotic features, in three there was suicidal ideation and there were three suicide attempts (with one completed suicide).

In a number of these case reports, including 25 documented by the FDA,^{7,20} cessation of the drug has been associated with resolution of the mood

P Magin, FRACGP, senior lecturer; **D Pond**, PhD, FRACGP, professor, discipline of general practice, University of Newcastle, New South Wales, Australia. **W Smith**, PhD, professor, Centre for Clinical Epidemiology and Biostatistics, University of Newcastle, New South Wales, Australia.

Address for correspondence

Dr Parker Magin; Discipline of General Practice, Newbolds Building, University of Newcastle, University Drive, Callaghan 2308 New South Wales, Australia.
E-mail: Parker.Magin@newcastle.edu.au

Submitted: 18 March 2004; **Editor's response:** 28 May 2004; **final acceptance:** 1 July 2004.

©British Journal of General Practice 2005; 55: 134-138.

disturbance and reinstatement of treatment has been followed by recurrence of depression.

But pitfalls inherent in making inferences of causality from case reports or case series are illustrated by the case reported by Kovacs and Mallory.²⁶ They describe a 17-year-old Korean boy who developed mood and behaviour changes while taking isotretinoin. Symptoms resolved with isotretinoin withdrawal, but re-emerged with rechallenge, and the boy's psychological morbidity was attributed to isotretinoin. It later emerged that the boy's symptoms also coincided with periods of recreational LSD and cannabis use.

Secondary analyses of large data sets. Jick *et al*²⁷ analysed data from the Canadian Health Database and the UK General Practice Research Database and found no increase in relative risk of incident depression, psychosis, suicide or attempted suicide in users of isotretinoin over users of antibiotics for acne. Similarly, there was no increase in relative risk of these outcomes for prior treatment with isotretinoin versus post-treatment. This was an industry-sponsored study and its methodology has been criticised.²⁸ Specifically, possible underascertainment of psychiatric disorder and suicide, the lack of a non-acne control group, a lack of power for detecting differences in suicide rates, and lack of consideration of acne severity or of isotretinoin dose and duration were claimed to be methodological shortcomings.²⁸

Hersom *et al*²⁹ performed a retrospective prescription sequence symmetry analysis of isotretinoin and antidepressant pharmacotherapy using a large US database (examining which drug was prescribed first in patients prescribed both isotretinoin and an antidepressant) and demonstrated no support for an association between the use of isotretinoin and the onset of depression.

Wyskowski *et al* observed that a statistical data mining analysis of all adverse events and drug combinations in the AERS database had calculated that six reports of suicide were expected for isotretinoin compared with the 36 suicides actually reported⁷ (Table 1).

Assessments of depression as an adverse event in clinical trials and follow-up of treatment with isotretinoin. Prospective Canadian³⁰ and US³¹ studies found an incidence of depression in patients during a course of isotretinoin therapy of 4% and 11%, respectively. However, these trials were uncontrolled and depression was self-reported in response to a questionnaire item. There was no objective measure of depression. The study of Scheinman *et al*¹² has been quoted as finding an 1% incidence of depression in isotretinoin therapy,²⁶ but did not specifically examine for depression or other psychiatric morbidity. It

describes seven patients who spontaneously reported depressive symptoms during clinical trials of isotretinoin, and is best considered a case series (and is cited as such above). A British study³² elicited no long-term side effects of isotretinoin in 88 patients up to 10 years post-therapy, but the authors do not seem to have specifically enquired about depression or other psychiatric effects. Similarly, Goulden *et al*³³ reported on 720 patients who had received one or more courses of isotretinoin and were followed up every 4–6 months for 2–12 years. They found only three cases of depression occurring in this population (all occurring in patients with dysmorphophobia and mild acne). But this was an uncontrolled study and, while adverse effects of the medication were enquired about generally, depression and suicidal ideation were not among the side effects specifically asked about. A further study of adverse effects in 466 isotretinoin recipients in the US³⁴ recorded no instances of depression or other psychiatric effects, but this was a study of data abstracted from clinical notes for self-reported side effects rather than an examination of psychiatric morbidity.

McLane³⁵ reports incidence of 'psychiatric disorders' as adverse events of isotretinoin therapy as being 0% and 0.3% in industry-sponsored trials with 69 and 300 subjects, respectively. But these trials were uncontrolled, and the means of ascertainment of psychiatric disorder is not specified (Table 1).

Improvement in depression in clinical trials with isotretinoin. A number of studies have demonstrated an improvement in depression scores in patients with acne during and/or after treatment with isotretinoin.^{36–38} Interpretation of these treatment studies with regard to the direction of causality in the association between acne and depression is limited by them being uncontrolled and/or not correlating changes in depression with changes in acne severity.

DISCUSSION

Further considerations

A plausible biological mechanism underlying the proposed causative relationship — the effect of retinoids on brain dopamine systems^{39,40} — has been suggested, although this remains speculative. Etretinate, another retinoid used as therapy in cutaneous disease, has been linked in case reports

How this fits in

There is currently a controversy regarding the risk of depression and suicide in treatment with isotretinoin. The controversy, thus far, has largely by-passed the general practice audience, but has significant implications for general practice approaches to the management of acne vulgaris.

with depression.⁴¹ Additionally, it has been suggested that hypervitaminosis A is associated with psychiatric symptoms including depression, and hypervitaminosis A syndrome has been proposed as a paradigm of retinoid side effects.^{17,42} Other 'neuropsychological' adverse effects — irritability, emotional lability, amnesia, abnormal thinking, headache, fatigue, lethargy, pseudotumour cerebri, incoordination and sustained dreaming — have been reported with use of isotretinoin.^{1,2,21,30,31,34,35,43}

It is likely that the surveillance systems cited above underestimate the true incidence of adverse effects. However, the background incidence of depression, suicide attempts and completed suicide in adolescents, and the number of patients who have used the drug must also be considered when interpreting the significance of case reports and adverse event monitoring in isotretinoin therapy. Over 8 million patients had used isotretinoin worldwide by 1998.⁵ The 12-month prevalence of major depression in the US has been found to be 10.3% and of dysthymia to be 2.5% in a major study,⁴⁴ although

prevalence has been somewhat lower in some studies.⁴⁵ Thirty-day prevalence among adolescents and young adults of major depression was 5.8% and minor depression was 2.1%.⁴⁶ Depression is more common in the age group affected by acne than in the general population.^{44,45,47} In 1994, the US suicide rate was 12 per 100 000 population.⁴⁸ Reported lifetime suicidal ideation in the US is 13.5% and lifetime prevalence of suicide attempt is 4.6%.⁴⁹ In prospective studies of US⁵⁰ and Norwegian⁵¹ high school students, the 12-month incidence of suicide attempt was 1.7% and 1.3 %, respectively.

It has also been suggested that many of the reported depressive adverse effects in isotretinoin therapy represent depressive or mood symptoms rather than major depression or other clinical depression syndromes.⁵² In this context it should be noted that an Australian population-based study of high school students has shown 19% of students without clinical depression to have depressed mood.⁵³ Significantly, while in some of the case reports and study findings of depression cited in this review the diagnosis was

Table 1. Studies examining isotretinoin, depression and suicide.

Reference	Study type	Subject numbers	Results/comments
27	Retrospective cohort studies using Canadian and UK health databases	7195 users of isotretinoin 13 700 users of antibiotics (Canada) 340 users of isotretinoin 676 users of antibiotics (UK)	Prevalence rates of neurotic and psychotic disorders, suicide and attempted suicide were compared between isotretinoin and antibiotic users and within isotretinoin users (pre- and post-treatment). No increased risk of depression, suicide or suicidal ideation
29	Retrospective prescription sequence symmetry analysis	2821 users of isotretinoin in a US pharmacy database	Patients treated with both isotretinoin and antidepressant. Adjusted ratios (of numbers of patients filling isotretinoin prescriptions first versus numbers filling antidepressant prescriptions first) was not significantly greater than 1.0
20	Statistical data mining analysis	Of all adverse effects and drug combinations in FDA's AERS database	Six suicides could be expected in patients taking isotretinoin compared to the 36 suicides observed
30	Prospective, uncontrolled study	189 patients commenced on isotretinoin and treated for 4 months	4% reported depression — by self-report in response to questionnaire item at clinical reviews. No objective ascertainment of depression
31	Prospective, uncontrolled study	92 patients commenced on isotretinoin and treated for 16 weeks	11% reported depression — by self-report at clinical review. No objective ascertainment of depression
32	Prospective, uncontrolled study	88 patients treated with isotretinoin, followed annually for 10 years	'No long-term clinical side effects were identified in any of the patients.' It is not reported whether evidence of depression or other psychiatric symptoms were specifically sought
33	Prospective, uncontrolled study	720 patients treated with one or more courses of tretinoin	Patients followed up for 2–10 years. Asked at each follow-up visit (4–6 months) re symptoms — not specifically asked about psychiatric symptoms. Three subjects reported persistent depression
34	Prospective, uncontrolled study	466 patients treated with isotretinoin, observed through a 4–5 month course	No depression or other psychiatric effects recorded — but depression and psychiatric morbidity seemingly not specifically sought
35 (Study 1)	Prospective, uncontrolled study	67 patients receiving isotretinoin for 16–20 weeks	No psychiatric side effects in any subjects. Study incompletely reported
35 (Study 2)	Prospective, uncontrolled study	300 patients receiving isotretinoin for 20 weeks	0.3% of subjects reported psychiatric adverse events (nature not specified). Study incompletely reported

An extended version of this table can be found at <http://www.rcgp.org.uk/journal/index.asp>.

confirmed by psychiatric opinion,^{13,14,17,18} others seemed not to be,^{10,11,19,30,31} while in one case series some diagnoses were psychiatrist-confirmed and some were not.¹²

Prospective, controlled trials to examine the relationship might seem to be apposite. But recruitment of adequate numbers of subjects into studies powered to detect an increase in suicide would be a daunting prospect. Controlled trials of depression and suicidal ideation may also be problematic — it has been suggested that, given the superior efficacy of isotretinoin and the propensity for severe acne to cause permanent scarring, a randomised trial of isotretinoin compared with a less efficacious control in severe acne would be unethical.³² In this situation, large case-control studies would be welcome.

The context of the debate

While acne may have been, in some quarters, considered a trivial complaint, there is convincing evidence that this is not so. Case reports have suggested depression as a sequela of acne.⁵⁴ Studies have suggested acne is associated with greater mental health impairment than asthma, epilepsy, diabetes, back pain or arthritis.⁵⁵ Acne has been associated with depression,⁵⁶⁻⁵⁹ suicidal ideation⁵⁶ and (in a case series) with suicide,⁶⁰ along with a number of other psychological problems — anxiety, self-consciousness, emotional difficulties and embarrassment.^{38,61-66} Studies of treatment with isotretinoin show improvements in depression scores following treatment (as above). The balance of evidence suggests that acne is associated with considerable psychological morbidity, possibly including depression, and that acne is more likely to cause psychological morbidity than to be caused by it.

In fact, the presence of psychological distress in a patient with acne has been proposed as an indication for a more aggressive approach to acne treatment, including the use of isotretinoin.⁶⁷

Interpretation of the available evidence and the clinical context

The evidence in this area is incomplete. The incidence of depression and suicide during isotretinoin therapy may be no greater than the background incidence. A causal relationship between isotretinoin and psychiatric morbidity, including depression and suicide, has not been demonstrated. In fact, there is evidence that acne itself is associated with psychiatric morbidity and that isotretinoin may attenuate the effect of acne on this psychiatric morbidity. Nevertheless, major depression and suicidal ideation occurring as an idiosyncratic reaction to isotretinoin, as suggested by case reports, remains a possibility — although, if so, this would seem to be a relatively rare occurrence.

Relevance to general practice

In Australia and the UK isotretinoin is not prescribed by GPs.^{32,68} In the US, many family physicians choose not to prescribe it.⁶⁹ Referral of patients with acne who would benefit from isotretinoin is the responsibility of the GP, and, therefore, the debate about isotretinoin and depression and suicide in the media,^{70,71} is of vital interest. GPs are in a position not only to make suggestions or recommendations to patients regarding referral for consideration of isotretinoin treatment, but also to ensure patient decisions are based on a realistic understanding of the benefits and risks of therapy.

It would seem prudent to carefully monitor patients undergoing treatment with isotretinoin for evidence of depression or suicidal ideation. GPs are likely to be better equipped than dermatologists to do so,⁷²⁻⁷⁴ and to further manage, or refer for specialist psychiatric care, any emergent psychiatric symptoms or psychological morbidity. A close partnership between dermatologist and GP on a 'shared-care' basis is likely to be optimal in this situation.

Conclusions

Consideration of the limited data available would suggest that the incidence of depression and suicide during isotretinoin therapy may be no greater than the background incidence. A causal relationship has not been demonstrated. The occurrence of an idiosyncratic reaction to isotretinoin producing major depression and suicidal ideation, as suggested by case studies, remains a possibility — although, if so, this would seem to be a relatively rare occurrence. Given the evidence suggesting that isotretinoin treatment may attenuate psychiatric associations of acne, and given the evidence that acne is often not a trivial complaint, withholding therapy because of concerns regarding depression or potential for suicide is not justified. Nevertheless, there are grounds for carefully monitoring patients undergoing treatment with isotretinoin for the emergence of depressive and suicidal ideation. Ideally, the patient's GP, as well as their dermatologist, should be involved in this surveillance.

Funding body and reference number

This article was written with support from a NHMRC post-graduate medical scholarship and a NSW Primary Health Care Research Bursary

Competing interests

None

REFERENCES

1. Brecher AR, Orlow SJ. Oral retinoid therapy for dermatological conditions in children and adolescents. *J Am Acad Dermatol* 2003; **49**: 171–182.
2. Ellis CN, Krach KJ. Uses and complications of isotretinoin therapy. *J Am Acad Dermatol* 2001; **45**(5): S150–S157.
3. Lowenstein EJ. Isotretinoin made S.M.A.R.T. and simple. *Cutis* 2002; **70**(2): 115–120.
4. Hanson N, Leachman S. Safety issues in isotretinoin therapy. *Semin Cutan Med Surg* 2001; **20**(3): 166–183.
5. Josefson D. Acne drug is linked to severe depression. *BMJ* 1998; **316**(7133): 723.

6. Lamberg L. Acne drug depression warnings highlight need for expert care. *JAMA* 1998; **279**(14): 1057.
7. Wysowski D, Pitts M, Beitz J. An analysis of reports of depression and suicide in patients treated with isotretinoin. *J Am Acad Dermatol* 2001; **45**: 515–519.
8. Schwetz BA. New measures to manage risks associated with accutane. *JAMA* 2001; **285**(5): 1146.
9. Ault A. Isotretinoin use may be linked with depression. *Lancet* 1998; **351**(9104): 730.
10. Hazen PG, Carney JF, Walker AE, Stewart JJ. Depression — a side effect of 13-*cis*-retinoic acid therapy. *J Am Acad Dermatol* 1983; **9**(2): 278–279.
11. Meyskens FL. Short clinical reports. *J Am Acad Dermatol* 1982; **6**(4(2)): 732.
12. Scheinman PL, Peck GL, Rubinow DR, et al. Acute depression from isotretinoin [comment]. *J Am Acad Dermatol* 1990; **22**(6 Pt 1): 1112–1114.
13. Gatti S, Serri F. Acute depression from isotretinoin [comment]. *J Am Acad Dermatol* 1991; **25**(1 Pt 1): 132.
14. Byrne A, Hnatko G. Depression associated with isotretinoin therapy. *Can J Psychiatry* 1995; **40**(9): 567.
15. Lindemayr H. Isotretinoin intoxication in attempted suicide. *Acta Derm Venereol* 1986; **66**(5): 452–453.
16. James M. Isotretinoin for severe acne [comment]. *Lancet* 1996; **347**(9017): 1749–1750.
17. Ng CH, Tam MM, Hook SJ. Acne, isotretinoin treatment and acute depression. *World J Biol Psychiatry* 2001; **2**(3): 159–161.
18. Byrne A, Costello M, Greene E, Zibin T. Isotretinoin therapy and depression — Evidence for an association. *Ir J Psychol Med* 1998; **15**(2): 58–60.
19. Duke EE, Guenther L. Psychiatric reactions to te retinoids. *Canadian Journal of Dermatology* 1993; **5**(4): 467.
20. Wysowski D, Pitts M, Beitz J. Depression and suicide in patients treated with isotretinoin. *New Engl J Med* 2001; **344**(6): 460–461.
21. Wray CM. Isotretinoin: depression. *Canadian Adverse Drug Reaction Newsletter* 1999; **9**(1): 1.
22. Wooltorton E. Accutane (isotretinoin) and psychiatric adverse effects. *CMAJ* 2003; **168**(1): 66.
23. Medicines Control Agency. In focus: isotretinoin. *Current Problems in Pharmacovigilance* 1998; **24**: 2.
24. Chu A, Cunliffe WJ. The inter-relationship between isotretinoin/acne and depression. *J Eur Acad Dermatol Venereol* 1999; **12**(3): 263.
25. Adverse Drug Reactions Advisory Committee. Depression and isotretinoin. *Australian Adverse Drug Reaction Bulletin* 1998; **17**(3): 11.
26. Kovacs SO, Mallory SB. Mood changes associated with isotretinoin and substance abuse. *Pediatr Dermatol* 1996; **13**(4): 350.
27. Jick S, Kremers H, Vasilakis-Scaramozza C. Isotretinoin use and risk of depression, psychotic symptoms, suicide and attempted suicide. *Arch Dermatol* 2000; **136**(10): 1231.
28. Wysowski D, Beitz J. Methodological limitations of the study 'isotretinoin use and risk of depression psychotic symptoms, suicide and attempted suicide'. *Arch Dermatol* 2001; **137**(8): 1102.
29. Hersom K, Neary MP, Levaux HP, Klaskala W, Strauss JS. Isotretinoin and antidepressant pharmacotherapy: a prescription sequence symmetry analysis. *J Am Acad Dermatol* 2003; **49**(3): 424–32.
30. Hull PR, Demkiw-Bartel C. Isotretinoin use in acne: prospective evaluation of adverse events. *J Cutan Med Surg* 2000; **4**(2): 66–70.
31. Bruno NP, Beacham BE, Burnett JW. Adverse effects of isotretinoin therapy. *Cutis* 1984; **33**(5): 484–486, 489.
32. Layton A, Knaggs H, Taylor J, Cunliffe WJ. Isotretinoin for acne vulgaris — ten years later: a safe and successful treatment. *Br J Dermatol* 1993; **129**: 292–296.
33. Goulden V, Layton AM, Cunliffe WJ. Long-term safety of isotretinoin as a treatment for acne vulgaris. *Br J Dermatol* 1994; **131**(3): 360–363.
34. McElwee NE, Schumacher MC, Johnson SC, et al. An observational study of isotretinoin recipients treated for acne in a health maintenance organization. *Arch Dermatol* 1991; **127**(3): 341–346.
35. McLane J. Analysis of common side effects of isotretinoin. *J Am Acad Dermatol* 2001; **45**(5): S188–S194.
36. Strauss JS, Leyden JJ, Lucky AW, et al. Safety of a new micronized formulation of isotretinoin in patients with severe recalcitrant nodular acne: A randomized trial comparing micronized isotretinoin with standard isotretinoin [comment]. *J Am Acad Dermatol* 2001; **45**(2): 196–207.
37. Rubinow DR, Peck GL, Squillace KM, Gantt GG. Reduced anxiety and depression in cystic acne patients after successful treatment with oral isotretinoin. *J Am Acad Dermatol* 1987; **17**(1): 25–32.
38. Schulpis K, Georgala S, Papakonstantinou ED, Michas T. Psychological and sympatho-adrenal status in patients with cystic acne. *J Eur Acad Dermatol Venereol* 1999; **13**(1): 24–27.
39. McCaffery P, Drager UC. High levels of a retinoic acid-generating dehydrogenase in the meso-telencephalic dopamine system. *Proc Natl Acad Sci U S A* 1994; **91**(16): 7772–7776.
40. Samad TA, Krezel W, Chambon P, Borrelli E. Regulation of dopaminergic pathways by retinoids: activation of the D₂ receptor promoter by members of the retinoic acid receptor-retinoid X receptor family. *Proc Natl Acad Sci U S A* 1997; **94**(26): 14349–14354.
41. Henderson CA, Highet AS. Depression induced by etretinate. *BMJ* 1989; **298**(6678): 964.
42. Silverman AK, Ellis CN, Voorhees JJ. Hypervitaminosis A syndrome: a paradigm of retinoid side effects. *J Am Acad Dermatol* 1987; **16**(5 Pt 1): 1027–1039.
43. Gupta MA, Gupta AK. Isotretinoin use and reports of sustained dreaming. *Br J Dermatol* 2001; **144**(4): 919–920.
44. Kessler RC, McGonagle KA, Zhao S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. *Arch Gen Psychiatry* 1994; **51**(1): 8–19.
45. Kessler RC, Berglund P, Demler O, et al. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R) [comment]. *JAMA* 2003; **289**(23): 3095–3105.
46. Kessler RC, Walters EE. Epidemiology of DSM-III-R major depression and minor depression among adolescents and young adults in the National Comorbidity Survey. *Depress Anxiety* 1998; **7**(1): 3–14.
47. Henderson S, Andrews G, Hall W. Australia's mental health: an overview of the general population survey. *Aust N Z J Psychiatry* 2000; **34**(2): 197–205.
48. Anonymous. From the Centers for Disease Control and Prevention. Regional variations in suicide rates — United States, 1990–1994. *JAMA* 1997; **278**(12): 974–975.
49. Kessler RC, Borges G, Walters EE. Prevalence of and risk factors for lifetime suicide attempts in the National Comorbidity Survey. *Arch Gen Psychiatry* 1999; **56**(7): 617–626.
50. Lewinsohn PM, Rohde P, Seeley JR. Psychosocial risk factors for future adolescent suicide attempts. *J Consult Clin Psychol* 1994; **62**(2): 297–305.
51. Wichstrom L. Predictors of adolescent suicide attempts: a nationally representative longitudinal study of Norwegian adolescents. *J Am Acad Child Adolesc Psychiatry* 2000; **39**(5): 603–610.
52. Jacobs D, Deutsch N, Brewer M. Suicide, depression, and isotretinoin: is there a link? *J Am Acad Dermatol* 2001; **45**: S168–S175.
53. Patton GC, Coffey C, Posterino M, et al. Adolescent depressive disorder: a population-based study of ICD-10 symptoms. *Aust N Z J Psychiatry* 2000; **34**(5): 741–747.
54. Finlay SE. Physical diseases in university students. *BMJ* 1976; **2**(6047): 1312–1314.
55. Mallon E, Newton JN, Klassen A, et al. The quality of life in acne: a comparison with general medical conditions using generic questionnaires. *Br J Dermatol* 1999; **140**(4): 672–676.
56. Gupta MA, Gupta AK. Depression and suicidal ideation in dermatology patients with acne, alopecia areata, atopic dermatitis and psoriasis. *Br J Dermatol* 1998; **139**(5): 846–850.
57. Polenghi MM, Zizak S, Molinari E. Emotions and acne. *Dermatology and Psychosomatics* 2002; **3**: 20–25.
58. Koo J. The psychosocial impact of acne: patients' perceptions. *J Am Acad Dermatol* 1995; **32**(5 Pt 3): S26–S30.
59. Kellett SC, Gawkrödger DJ. The psychological and emotional impact of acne and the effect of treatment with isotretinoin. *Br J Dermatol* 1999; **140**(2): 273–282.
60. Cotterill JA, Cunliffe WJ. Suicide in dermatological patients. *Br J Dermatol* 1997; **137**(2): 246–250.
61. Wu SF, Kinder BN, Trunnell TN, Fulton JE. Role of anxiety and anger in acne patients: a relationship with the severity of the disorder. *J Am Acad Dermatol* 1988; **18**(2 Pt 1): 325–333.
62. Grahame V, Dick DC, Morton CM, et al. The psychological correlates of treatment efficacy in acne. *Dermatology and Psychosomatics* 2002; **3**: 119–125.
63. Aktan S, Ozmen E, Sanli B. Anxiety, depression, and nature of acne vulgaris in adolescents. *Int J Dermatol* 2000; **39**(5): 354–357.
64. Smithard A, Glazebrook C, Williams HC. Acne prevalence, knowledge about acne and psychological morbidity in mid-adolescence: a community-based study. *Br J Dermatol* 2001; **145**(2): 274–279.
65. Pearl A, Arroll B, Lello J, Birchall NM. The impact of acne: a study of adolescents' attitudes, perception and knowledge. *N Z Med J* 1998; **111**(1070): 269–71.
66. Krowchuk DP, Stancin T, Keskinen R, et al. The psychosocial effects of acne on adolescents. *Pediatr Dermatol* 1991; **8**(4): 332–338.
67. Cooper AJ, Australian Roaccutane Advisory B. Treatment of acne with isotretinoin: recommendations based on Australian experience. *Australas J Dermatol* 2003; **44**(2): 97–105.
68. Writing Group for Therapeutics Guidelines. *Dermatology Therapeutics Guidelines: Dermatology*. Melbourne: Therapeutics Guidelines Limited, 1999.
69. Van Durme DJ. Family physicians and accutane [comment]. *Am Fam Physician* 2000; **62**(8): 1772, 1774, 1777.
70. Weinberg JM. Scars: the battle over isotretinoin. *Cutis* 2001; **68**(1): 18.
71. Duenwald M. Debate on acne drug's safety persists over two decades. *The New York Times* 2002; **Jan 22**: Sect. 7.
72. Millard L. Suicide and the skin. *Clin Exp Dermatol* 2001; **26**(2): 211.
73. Bower P, Rowland N, Mellor C, Heywood P, Godfrey C, Hardy R. Effectiveness and cost effectiveness of counselling in primary care. *Cochrane Collaboration. The Cochrane Library*, Issue 4. Chichester: John Wiley & Sons, 2004.
74. Hickie IB. An approach to managing depression in general practice. *Med J Aust* 2000; **173**(2): 106–110.