A prospective controlled trial of the effects of isotretinoin on quality of life and depressive symptoms

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Introduction

Acne is the most prevalent skin disease treated by dermatologists, affecting up to 85% of people during their lives[1,2,3]. The detrimental effects on quality of life (QoL) in those with acne are now well recognised, and are comparable with other chronic diseases such as diabetes, asthma and arthritis[4],[3,5,6]. Depressive symptoms are also common during chronic illness and well recognised in individuals affected with acne[7].

The most effective treatment for acne yet discovered is isotretinoin (13-*cis*-retinoic acid); a retinoic acid derivative released in 1982. Since then there have been over 2 million users in the USA alone[8] and the associated side effects have been well documented: these include drying effects on skin and mucous membranes, and teratogenicity[9].[10]. There have been several reports in the media and medical literature of depression among individuals on the drug, and in some cases this has been shown to improve on drug withdrawal and recur on re-challenge[11,12]. Some well-publicised cases of suicide have also been attributed to isotretinoin.[13] Studies have failed to demonstrate a convincing causal link between isotretinoin treatment and depression or suicide, however, and are complicated by the high background prevalence of depression among adolescents[14]. Conversely, it has been demonstrated that isotretinoin therapy for acne frequently improves anxiety, depression, and QoL, due to its efficacy[15]. The possibility of an idiosyncratic side-effect has not been excluded by studies to date, however, and thus prescribing guidelines recommend warning patients about the risk of depression. Studies examining characteristics of patients who have developed depression whilst on isotretinoin have also failed to demonstrate predictive factors that might aid physicians in identifying high-risk patients before commencing the drug. Few large controlled studies have prospectively measured changes in both QoL and depression in patients taking isotretinoin; an Australian study[16] found no significant difference in either measure between patients taking isotretinoin compared with those receiving antibiotic and topical treatment.

Many tools for the measurement of QoL have been devised for use with patients with skin disease. These include the Dermatology Life Quality Index (DLQI) [17] and the acne specific

Cardiff Acne Disability Index (CADL)[18,19]. The World Health Organisation has developed a generic health-related QoL questionnaire – the WHOQOL. This is a valid and reliable tool, covering 25 international facets of QoL. Generic measures have the advantage of allowing comparisons of health-related QoL across differing diseases and conditions for audit purposes, can accommodate the effects of comorbid conditions, and are designed for use with healthy populations. The WHOQOL measures can be used in multinational clinical trials and cross-cultural research[20,21]. The present study is the first to administer this measure to adolescents under 18 years of age and so provides additional originality to this study. However, although the WHOQOL-100 was successfully validated in our department with patients undergoing psoriasis treatment[22] and has been used to assess QoL during antidepressant treatment in primary care[23], the WHOQOL instruments have rarely been tested in patients with skin disease.

The aim of the research was to investigate the quality of life and depression scores of two groups of acne patients receiving isotretinoin or antibiotic/topical treatment and to compare them with healthy controls.

Design

The current study is a prospective trial comparing QoL and depression in patients taking isotretinoin with patients on antibiotics/ topical treatment for acne over a 6-month period, and comparing them to reported levels of QoL and depression in a matched healthy control group. Secondary outcome measures include self-reported and physician-graded acne severities, in order to assess their association with QoL and depression.

Methods

Local NHS ethics committee approval was granted for the study in June 2006. Written consent was obtained from all adult participants, or their parents in the case of minors.

Procedure

Sampling and recruitment

Acne Treatment Groups

Between September 2006 and September 2007 consecutive patients commencing acne treatment in a designated outpatient clinic at the Royal United Hospital, Bath were invited to take part in the study. All patients had been referred by their general practitioners for further management of acne, and prior to attending the clinic were posted an information leaflet explaining the nature of the study. Patients were informed that their treatment would not be

affected in any way if they chose not to take part. Patients under 12 or over 50 years were excluded from the study, also pregnant or lactating females, because of the teratogenic effect of isotretinoin.

At the first visit, following the collection of written consent, socio-demographic details were obtained with family, medical, psychiatric, family and drug histories. Patients were commenced on antibiotics plus topical treatment, or isotretinoin, according to clinical indications as stated in the British Association of Dermatologists national guidelines[24]. Randomization was not possible for ethical reasons, since isotretinoin is known to be more efficacious. Fasting lipids and liver function tests were measured at baseline and after 4-6 weeks of treatment in all patients taking isotretinoin, to screen for drug-induced hyperlipidaemia or liver dysfunction.

The treatment regimen for oral isotretinoin consisted of isotretinoin at 0.5mg/kg/day for the first two weeks, followed by 1mg/kg/day until a cumulative dose of 120mg/kg was obtained. Patients who were unable to tolerate the 1mg/kg dose were given the next highest dose possible according to side effects. All patients were given written and verbal information regarding side effects of treatment. The regimen for the antibiotic/ topical treatment group was lymecycline 408mg daily (or minocycline 100mg daily if lymecycline was previously ineffective or unacceptable), plus adapalene cream.

Control Group

A community sample was recruited, using convenience sampling for reasons of availability and cost efficiency, from three sources: (i) two coeducational schools in South West England (aged 14-18), (ii) adults aged 18-30 recruited from a University campus, (iii) opportunist sampling at venues in a city centre. Participants were excluded from the community sample if they were under 14 or over 30 years old, and if they were currently receiving hospital treatment for acne.

Information leaflets were given to all participants, and in addition to parents and head teachers for school children. For children, written consent was obtained from the headteacher of both schools allowing students to take part, in addition to passive parental consent (i.e., a letter sent home to parents and returned if parents wished their child not to take part). Students were informed that participation in the study was optional, and that their schooling would not be affected in any way if they would prefer not to take part. They were reminded of their right to opt out of the study at any time.

Adults were provided with a verbal description of the project and invited to participate in a short 10-minute on-line research study. Those who expressed an interest read an information sheet, and could ask the researcher questions. Written consent was then obtained. Participants were logged into the study website on a computer, and invited to work through the study questions at their own pace.

Outcome measures

The outcome measures were obtained at the first clinical consultation (baseline), then subsequently at 3 and 6 months, for all patients in the two treatment groups. Participants in the community sample completed the WHOQOL-BREF, CES-D, and visual analogue score on one occasion only.

The WHOQOL-BREF (UK) is a health-related QoL measure which is a 26-item, short-form version of the longer WHOQOL-100 questionnaire scored in four QoL domains: physical, psychological, social relationships and environment[25], on a range from 0-100. We used CD-ROM software to obtain UK WHOQOL-BREF assessments on a desktop computer. This measure is reliable, valid, and sensitive to changes in clinical condition during treatment[26].

The Leeds Acne severity scale. Acne was formally graded by a dermatologist using the revised acne grading scale[27] which assesses disease severity on the face (from 1-12), back (1-8) and chest (1-8). This provides an objective assessment of acne severity.

A five-point Likert rating scale for self perceived acne severity was also completed by each participant. This provides a subjective assessment of acne.

Centre for Epidemiological Studies Depression Scale (CES-D)[28]. Depressive symptoms were assessed using this well-established and sensitive tool for the detection of depression in adolescent groups. It consists of 20 items, addressing depressive symptoms across the four dimensions of depressed affect, positive affect, somatic symptoms and interpersonal affect. It is a self-reported scale, and participants indicate how often they experienced each symptom in the preceding week. Scores range from 0-60, where higher scores indicate more depressive symptoms.

Internal reliability (Cronbach's alpha = .86) has been shown to be very good[29]. Content, construct and criterion validity of the CES-D has also been established (ref). Scores above the cut-off point of 15 are indicative of depression[30]. Participants under age 18 completed the companion questionnaire for children (CES-DC). The same 20 items are included but reworded for greater clarity and relevance to a younger age group.

Statistical analysis

Differences in QoL between the three groups at baseline were assessed using one-way analysis of variance (ANOVA). The main effect of change in QoL over time for the clinical

group was assessed using ANCOVA with repeated-measures, controlling for the covariate of depression level. This investigates the main effect of change over time of individuals within each treatment group and adjusts the results for the level of depression that each individual reports at baseline. The within-group effect of time is then statistically compared between groups.

Results

Isotretinoin group: Sixty-five patients were recruited to the isotretinoin group, of which 45 (65%) were male. Ages ranged from 14.4 to 32 years (mean 19.8 years, SD 3.8).
Antibiotic group: Thirty-one patients were recruited to the group receiving standard antibiotics and a topical retinoid. This group was proportionately smaller, as the study selected consecutive patients attending a dedicated acne clinic, of which the majority were deemed to be clinically suitable for isotretinoin. 16 (51%) were male, and ages ranged from 13.4 to 27.2 years (mean 19.3 years, SD 3.9).
Control Group: Community participants were over sampled to provide a pool of cases (N= 348) from which equivalent participants could be drawn to match against patients in the clinical treatment groups[1]. Cases matched with a participant from the control group were paired with reference to gender, age band and depression level. The final control comparison group comprised 94 participants (50 [53%] male, age range 13.21 to 31.97).

Baseline results (Time 1)
Descriptive statistics comparing the community sample and acne treatment groups are shown in Table 1.

The matching process was successful in that there were no significant differences between groups between community and either treatment group on any of the matching variables (age, gender, and depression scores).

Insert Table 1 here

Patients in the two treatment groups had higher perceived acne severity scores ($p<0.001$) than control group participants, as expected.
Treatment groups also reported higher environmental QoL on the WHOQOL-BREF than the community group. Following the analysis of each item in the environmental domain, this was found to be due to the effect of two particular questions; one on the quality of access to health and social care “How satisfied are you with your access to health care”, and a second

[1] This resulted in a larger community sample group than treatment groups, as it contained matched pairs for both isotretinoin and antibiotic patients.

on physical safety and security “How safe do you feel in your daily life?” On both these aspects, QoL was significantly better for the two treatment groups (both p<0.05). Two other questions (items) from the psychological domain of the WHOQOL-BREF showed significant differences between groups at baseline, although this domain as a whole did not show a significant difference in scores between the groups. These items related to body image and appearance, where the two treatment groups reported significantly poorer QoL than controls (p<0.001); e.g. ‘Are you able to accept your bodily appearance?’.. Furthermore, both treatment groups reported significantly poorer self-esteem than controls (p=0.004); ‘How satisfied are you with yourself?’, as expected from previous literature.

Relationships between scores at baseline

Correlational analyses were conducted to test whether level of depression, perceived acne severity, and gender were significantly associated with QoL rating. As predicted from previous research (Skevington & Wright, 2000) depression was significantly and negatively correlated with all four domains: physical (r = -.60, p<. 001), psychological (r = -.66, p<.001), social (r = -.30, p<.001), environmental (r = -.40, p<.001), and with overall QoL (r = -.33, p<.001). Depression was therefore included as a covariate in the repeated-measures analyses for the QoL outcomes. The perceived acne severity rating was significantly negatively associated with psychological QoL (r = -.19, p<.05) but with no other outcome variable. There was no significant correlation between the self-assessed acne rating and physician-rated acne (Leeds score) in either treatment group. Depression scores were higher in women than men (M= 13.31 (SD=9.91) and M = 9.44 (SD=7.62) respectively). Therefore gender was included as a covariate in the repeated-measures analysis of depression.

Changes in scores over time

A series of repeated measures ANOVAs were conducted to explore whether there was a change in QoL or depression over time and also whether this differed between patients treated with isotretinoin versus those treated with antibiotics. The number of participants providing useable data on all three occasions was too small for meaningful statistical analysis due to high non-attendance rates in both treatment groups (N=42). Data analysis was therefore carried out on the first two time points only. Statistics for both groups are shown in Table 2.

Insert Table 2 here

Acne severity: There was a significant decrease in patient perceived acne severity over time (F (1, 63) = 82.53, p<.001) but this was not statistically different across treatment groups (F (1,63) = 1.39 NS). There was also a significant decrease in physician-rated objective acne severity over time (F (1,29) = 48.21, p< .001), which was similar in both treatment groups (difference between groups; F(1,29) = 4.12, NS).

Depression: There was no significant change in depression scores over time (F (1, 64) = 1.06, NS), and no difference in changes in depression relating to gender. As depression correlated significantly with QoL at baseline, it was added as a covariate to the repeated measures ANCOVA assessing changes in QoL over time.

Changes in Quality of Life during treatment, controlling for depression

It was important to know whether QoL changed significantly during the course of acne treatment once the influence of depression was statistically removed. The results of the repeated-measures ANCOVA for changes in QoL over time in each treatment group are summarised in Table 3 and outlined below.

Insert Table 3

Overall QoL: There was no significant change in overall QoL scores over time controlling for level of depression (F (1,70) = 0.06, NS), and no difference between treatment groups.

Physical QoL: There was a significant improvement in physical QoL over time in both treatment groups (F (1, 70) = 11.34, p<.01). There was also an interaction between time and depression, such that patients with higher levels of depression at the outset (Time 1) reported a greater improvement in QoL following treatment (F (1, 70) = 20.63, p< .001).

Psychological QoL: There was no significant change in psychological QoL over time in the treatment groups (F (1, 70) = 1.11, NS). However, there was an interaction effect between QoL and depression, showing that patients with higher levels of depression at baseline (T1) reported a greater improvement in QoL following treatment than those with lower initial levels of depression (F (1, 70) = 22.01 p<.001).

Social QoL: Social QoL improved significantly over time (F (1, 69) = 4.27, p<.05). This effect was significantly greater in the Isotretinoin group than the antibiotic group (F(1, 70) = 4.36, p<.05) as the interaction shows. There was also a significant interaction between time and depression, such that patients with higher depression at the outset, reported a greater

improvement in QoL following treatment than those with lower depression levels initially ($F(1, 70) = 13.43$, $p < .001$).

Environmental QoL: There was no significant change in environmental QoL over time ($F(1, 69) = 0.14$ NS), or when controlling for the effect of depression.

Discussion

Acne improved following treatment and this was detected both by the patients, through the perceived severity rating, and by physician ratings of acne using the Leeds score, indicating that the measures are similarly sensitive to change. Concurrent with this physical change, the results showed that there was a significant improvement in physical QoL for the treatment groups and also in social QOL, especially for the groups receiving isotretinoin. Improvements to these two important domains provide insights into why isotretinoin is so popular among those with acne despite the inconveniences of monitoring, especially for women, and the risks of side-effects. Changes in physical QoL reflect the improvements relating to pain, fatigue etc relating to the condition per se, and to the impact on social, personal and sexual relationships reported by those with acne. However, depression did not change over the same time period even though the acne had improved. This finding could mean that these drugs do not significantly affect depression associated with acne. Alternatively, it could mean that the depression is linked to important issues in the life of young adults other than acne. The latter explanation may also account for the very low incidence of suicide in patients taking isotretinoin for acne, namely that it is an event that is largely disconnected from this illness and its treatment. However, it seems important that clinicians should continue to monitor patients closely for depressive symptoms and where detected, treat them as they are negatively correlated with a good QoL.

In this study we showed that treatment had a greater beneficial effect on the QoL of those patients reporting more depressive symptoms at baseline than those with few depressive symptoms. This was reported in three out of four quality of life domains: physical, psychological and social relations. The implication here is that considering and treating depressive symptoms as an integral part of acne, may be important for optimising patients' physical and mental health.

A recent selective review of studies of psychopathology associated with isotretinoin[31] provides further insights. It shows that many substantial studies have looked at isotretinoin and antibiotic treatment for acne in relation to depression and suicide. However the present study broadens this brief to accommodate the effects of quality of life in this complex relationship, and these studies are much rarer. In the WHOQOL, positive and negative mood

comprise only two important dimensions of QOL out of 24. A psychopathological model has tended to focus on mood to the exclusion of these many other important aspects in peoples' lives. It is well known that depression is intrinsically linked to poor QOL, and this has been specifically demonstrated using the WHOQOL [23]. The results of the present study show that many other important aspects of QoL improve in addition to mood, which forms part of the psychological domain. It may therefore be worth further examining the broader dimensions of QOL beyond mood in detail in future studies.

Several pharmacological studies have investigated the possibility of a causal link between Isotretinoin (13-*cis*-retinoic acid) and depression. [9, 12-16],Isotretinoin crosses the blood-brain barrier and a depressant effect has been demonstrated in animal models; daily treatment with 13-*cis*-retinoic acid altered aggression behaviour in rats and increased depression-related activity in mice[32] . Retinoids affect several molecules involved in serotonin (5-HT) signalling; *in vitro* studies indicate that 13-*cis*-retinoic acid increases the expression of components of the serotoninergic system, leading to a decrease in bio-availability of 5-HT[33] 5-HT is important in modulation of mood; plasma levels of 5-HT and its metabolite 5-HIAA are decreased in depressed patients[34] . This is suggested to account for the effect of serotonin reuptake inhibitors in some patients with depression.

In a study based on brain imaging, patients taking isotretinoin developed regional changes in brain function that were not observed in patients receiving antibiotics; subtle mood changes were observed, but no patients were clinically depressed[35]. However, a Canadian pharmacy-based case cross-over study indicated that patients taking isotretinoin were more likely to fill prescriptions for antidepressants than in the pre-treatment period (relative risk 2.68)[36].

Our study suggests that the potential depressant effect of isotretinoin may be outweighed by its QoL benefits in many patients with acne. Acne itself is associated with reduced QoL[4,6,7], self esteem and body image[37]. Our results confirm other recent reports from Palestine[38], Korea[39] and Finland[40] , that, at a population level, isotretinoin has no adverse effect on, and may even improve, QoL in patients with acne, especially in those reporting most symptoms of depression. These findings do not exclude the rare individual who is at risk of depression, and even suicidal ideation, due to an idiosyncratic reaction to the drug.

Limitations

Several methodological observations can be made.Our study was limited by a relatively small treatment group, due to the practicalities of running a study as part of a working clinic in a busy district general hospital. This was a particular problem in the latter part of the study, during which we experienced a high rate of non-returning patients. It is common for patients whose condition has improved to default on follow up appointments and our high proportion of students who were only periodically resident locally compounded this problem. However, the rigour of the study was improved
by the matched pairs design, in which the samples we investigated were structured so that there were no significant differences in age, gender group or depression level.. This meant that the control group could be selected from a much wider pool of community participants on the basis of a prescribed set of important characteristics. Self-assessed acne was no higher in the isotretinoin group than the antibiotic group, and both treatment groups had more acne than the community sample indicating that those with the most serious acne are more likely to receive hospital outpatient treatment. Although isotretinoin is sometimes used as a second line agent for tackling more persistent conditions after antibiotic treatment has failed, our results suggest that patients' perceptions of their acne do not appear to influence this physician allocation. However, the samples differed in environmental QoL before treatment where those in the isotretinoin group reported the best QoL, which could be explained in part by better access to quality health care. It seems possible that having access to isotretinoin which some requested, made them feel very positive about health care. The isotretinoin group also reported feeling more physically safe and secure, which could also be linked to the reassurance provided by access to health care. However this might also be linked to other variables that we did not satisfactorily measure, such as socio-economic status.

We did not find that the consecutive patients recruited to the isotretinoin sample were significantly more depressed than the other treatment group. Although the dermatologists did not identify any participant who could be diagnosed with severe clinical depression, it is possible that given that the two hospital samples were not randomised to treatment, there may have been subtle biases in the way acne outpatients were allocated to the treatment groups; in particular, that those who seemed mildly depressed were not prescribed isotretinoin.

The data presented here is original, being the first to be published on the QoL of adolescents under 18 years using the WHOQoL-BREF in Britain. The measure was found to be appropriate and acceptable for this age group as there was little missing data or adverse comments. However, although the WHOQOL–BREF inquires about the highest educational level completed, which is an acceptable proxy for social class and wealth in adults, replies to

this question do not easily distinguish these groups in younger adults who are still largely in education and cannot yet say what is the highest level they will attain**.** This question should therefore be changed in any young adults version of the WHOQOL in the future.

This study adds to an increasing body of evidence that successful treatment of acne significantly improves quality of life. This seems to be particularly true for those with more depressive symptoms at the outset. It also supports previous studies that have failed to find a deleterious effect on mood during isotretinoin treatment, although subtle mood changes may have gone undetected either due to sample size or sensitivity of the depression scale. . This study also provides a further example of the successful use of the WHO-QoL BREF, significantly adding to evidence for its use in adolescent populations.

Table 1: Descriptive statistics of groups at baseline

	Community (N=94)	Isotretinoin (N=65)	Antibiotics (N=31)	F
Age	19.7	19.8	19.3	.21
Depression score	13.1	10.5	11.2	1.93
Male	53%	60%	51%	.92[a]
Perceived acne severity (VAS)[b]	1.7	3.3	2.9	65.15**
Overall QoL	4.3	4.1	4.3	1.35
Physical domain	79.6	80.5	78.8	.20
Psychological domain	70.9	66.5	65.9	1.95
Social domain	74.3	69.4	70.4	1.51
Environmental domain	71.7	77.7	75.8	3.91*

Notes: *p<0.05, **p<0.001; a = chi2 statistic, b – difference lies between control group and both treatment groups

Table 2: Changes in QoL, depression and acne ratings over time for treatment groups

		Time 1			Time 2		
		N	Mean	Std. Deviation	N	Mean	Std. Deviation
Isotretinoin	Physical QoL	65	80.49	11.20	51	80.73	11.01
	Psychological QoL	65	66.51	12.91	51	73.06	9.68
	Social relationships QoL	65	69.42	19.82	51	75.27	17.10
	Environmental QoL	65	77.72	11.42	51	79.16	11.43
	Depression score	63	10.46	8.56	48	8.08	7.06
	Perceived acne rating	62	3.33	0.87	47	1.85	1.04
	Objective acne: Leeds score	49	9.18	4.98	24	2.55	2.63
Antibiotics	Physical QoL	31	78.77	12.30	23	78.52	12.09
	Psychological QoL	31	65.90	19.59	23	70.48	16.56
	Social relationships QoL	30	70.43	15.77	23	68.52	16.57
	Environmental QoL	30	75.80	18.31	23	75.17	13.77
	Depression score	31	11.16	9.15	19	7.89	7.42
	Perceived acne rating	31	2.90	1.00	18	1.90	0.63
	Objective acne: Leeds score	27	8.85	4.546	9	4.11	3.92

Table 3: ANCOVA (repeated-measures) of the quality of life of before the commencement of treatment and three months later, controlling for depression.

Domain	Effect	F (df)	Significance (p value).
Overall QoL	Time	.06 (1,70)	NS
	Time x depression	.43 (1,70)	NS
Physical QoL	Time	11.34 (1, 70)	<.005
	Time x depression	20.63 (1, 70)	<.001
Psychological QoL	Time	1.11 (1, 70)	NS
	Time x depression	22.01 (1, 70)	<.001
Social QoL	Time	4,27 (1, 69)	<.05
	Time x depression	13.43 (1, 70)	<0.001
	Time x treatment group	4.36 (1, 70)	<0.05
Environmental QoL	Time	0.14 (1, 69)	NS
	Time x depression	0.002 (1, 70)	NS

Notes: NS – not significant

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