Systemic isotretinoin in the management of acne – a patient questionnaire survey

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Abstract

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Background: The primary aim was to investigate the appropriateness (as outlined in the South African Acne Treatment Guideline[1]) for the prescription of systemic isotretinoin in the management and counselling of acne in the Nelson Mandela Bay Metropole.

Methods: A questionnaire was distributed to patients receiving systemic isotretinoin by 30 community pharmacies. The response rate was 29.2% (57 respondents).

Results: The acne medication history revealed that commercial brands of beauty products were used by 57.9% of respondents, topical benzoyl peroxide by 22.8%, and systemic cotrimoxazole by 19.3%. Only nine females used an oral contraceptive as acne treatment prior to isotretinoin. The average daily dose of isotretinoin was 44.2 (SD=16.9) mg. Half of the respondents received a suboptimal cumulative dosage of isotretinoin. The average prescribed duration of isotretinoin therapy was 6.2 months. Adequate counselling was received by only 57.9% of patients. A third of the patients who were able to fall pregnant received recommendations for contraception. Pregnancy tests were conducted in only two females. Just over 40% of patients reported a complete clearance of acne lesions.

Conclusions: Many prescribers did not follow the recommendations for isotretinoin prescription. The counselling of patients regarding isotretinoin therapy was substandard, especially with respect to pregnancy prevention.

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Introduction

Acne can be defined as a multifactorial, chronic,[2] common disorder of the pilosebaceous unit.[3] The reported incidence of acne among adolescents in Western societies is 79% to 95%,[4] although various forms of this disease can affect people of all ages.[5] Acne has shown to have negative effects on the social functioning and emotions of patients, and can be associated with anxiety, depression and even unemployment.[1,6]

The scientific understanding of the pathogenesis of acne has increased over the past three decades.[7] There has been a shift in the clinical focus of acne treatment away from the resolution of advanced lesions towards the inhibition of the multiple pathogenic processes underlying the earliest acne stages.[7]

In South Africa, the most recent Acne Treatment Guideline was published in 2005.[1] It was based on a consensus document of the Global Alliance to Improve Outcomes in Acne (GAIOA). The GAIOA was created in 2001 as a worldwide effort to assemble a group of experts in the field of acne treatment. After thorough research and meetings, this group prepared a set of recommendations for acne management to be distributed to all countries taking part where the general implementation of these guidelines was to be encouraged. The recommendations and information derived from these meetings were discussed with South African dermatologists, where their contributions were incorporated into the guidelines to make them applicable specifically to South Africa. The recommendations are therefore representative of the current universal approach to acne treatment while also reflecting the thoughts of South African dermatologists.[1]

According to the GAIOA,[1] four grades of acne severity (which were used in this study) should be considered when diagnosing and treating acne patients. These four stages, together with the recommended management of each stage according to the GAIOA,[1] are shown in Table I.

Systemic isotretinoin seldom fails to clear acne and it presents a permanent cure for many patients. The cure rates for patients treated with systemic isotretinoin vary from 38 to 66%, depending on the definition of a cure. Overall, systemic isotretinoin is known to be the most effective agent in the treatment of acne.[1]

Even though effective, systemic isotretinoin can cause a wide range of side-effects. Some of these side-effects are serious, but most of them are more unpleasant than serious.[1] The more dangerous side-effects (for example teratogenicity and the possibility of negative psychological impact) have triggered a continual debate among the medical society and general public worldwide regarding the prescription and use of isotretinoin.[8] Systemic isotretinoin is the drug of choice for severe acne, but the popularity of the prescription of isotretinoin for less severe cases, where other more conservative treatments may have been successful,

Table I: Grading of acne severity according to the GAIOA[1]

Grade of acne	Description of acne	Management guidelines
Grade 1	Comedones only	Topical management. A topical retinoid will suffice in most cases, but addition of benzoyl peroxide or azelaic acid may be necessary in resistant cases.
Grade 2	Inflammatory papules present in addition to comedones	In milder cases with superficial inflammatory papules: the same treatment as for Grade 1 acne. Where papules are more deeply situated, systemic antibiotics are indicated.
Grade 3	Pustules present in addition to any of the above	Systemic antibiotics are necessary. These should always be used in combination with a topical retinoid and, if the systemic treatment needs to go on for longer than three months, a topical anti-resistance agent should be added. Hormonal treatment can be used in female patients who desire contraception or who have other gynaecological indications for this treatment.
Grade 4	Nodules, cysts, conglobate lesions or ulcers present in addition to any of the above	Systemic isotretinoin is the drug of choice. Oral contraceptives combined with anti-androgens can sometimes be effective in females. Systemic antibiotics can bring about excellent improvement, but the improvement is of short duration and systemic antibiotics do not represent a long-term solution for this type of acne and unacceptably long antibiotic courses are usually necessary.

has increased. Prescribers should adhere to the recommended indications for the use of this agent.[1] According to the GAIOA, systemic isotretinoin is indicated in[1]:

- Severe nodulocystic acne and its variants
- Inflammatory acne with scarring
- Moderate to severe acne unresponsive to treatment with:
  - three months of combination treatment including systemic tetracyclines, and/or
  - four cycles of anti-androgen-containing hormonal treatment
- Acne with severe psychological distress (dysmorphophobic patients)
- Gram-negative folliculitis, and/or
- Frequently relapsing acne where repeated or prolonged courses of systemic antibiotics are needed.

The South African Acne Treatment Guideline (SAATG)[1] is available to aid South African health care professionals in prescribing acne medication optimally, in providing necessary counselling, in conducting required monitoring procedures and in the overall care of acne patients, especially pertaining to isotretinoin. The extent to which this guideline (and additional recommendations regarding acne treatment derived from the literature) is followed by health care professionals is questionable.

Aim and objectives

The primary aim of this study was to investigate the appropriateness (as optimally outlined in the SAATG)[1] of the prescription of systemic isotretinoin in the management of acne in the Nelson Mandela Bay Metropole (NMBM) in South Africa, and to investigate the accompanying counselling and monitoring of systemic isotretinoin patients. The more specific objectives of the study were to investigate:

- The acne treatments utilised by patients prior to initiation of systemic isotretinoin therapy
- The grade of acne experienced by patients just prior to initiation of isotretinoin therapy
- The cumulative dosage of systemic isotretinoin that was prescribed to each patient
- The quality and appropriateness of counselling received by patients prior to and during therapy with isotretinoin
- The appropriateness and presence of patient-monitoring procedures prior to and during isotretinoin therapy
- Presence and severity of side-effects experienced by patients on isotretinoin therapy, and
- Patients' perceived satisfaction regarding the outcomes of isotretinoin treatment and the tolerability of side-effects experienced during treatment

Methodology

After a thorough literature review, a structured questionnaire consisting of open and closed questions was designed. The questionnaire was designed specifically for patients who were on systemic isotretinoin therapy during the time of the study. The sections in the questionnaire included demographic information, patient history of acne and acne treatment, patient history of co-morbid conditions and other medications, details on systemic isotretinoin therapy, details on patient counselling and monitoring, side-effects experienced by patients while on isotretinoin, perceived patient satisfaction or dissatisfaction with isotretinoin and a section specifically regarding pregnancy prevention for females on isotretinoin.

A pilot study was conducted by distributing questionnaires to two pharmacies in the NMBM by means of convenience sampling. The pharmacists were asked to distribute the questionnaires to patients who were currently receiving isotretinoin from the pharmacy. Only minor changes to the questionnaire were required after the pilot study.

A list of all community pharmacies in the NMBM in 2006 was obtained from the South African Pharmacy Council. There were 89 pharmacies on the list, of which one-third (30 pharmacies) were selected for the study by means of a stratified randomised sampling method. Individual discussions were held with each of the responsible pharmacists of the selected pharmacies in order to obtain permission for the inclusion of their pharmacies and their patients using isotretinoin in the study. Envelopes, each containing a patient information letter, a questionnaire, an ethical consent form and an ethical assent form, were personally delivered to each pharmacy. The information letter was directed to the participant, or the parent or guardian of the participant. It served to inform the patient of the voluntary and anonymous nature of participation, as well as to explain the correct procedure of completing both the questionnaire and the ethical forms. It was requested that isotretinoin patients younger than 18 years of age only complete the form under the guidance of a parent, guardian or pharmacist. The consent forms were to be signed by all respondents aged 21 years or older, or by parents or guardians of respondents younger than 21 years of age. The assent forms were to be signed by respondents younger than 21 years of age in order to give permission to their parents or guardians to sign the consent forms

on their behalves. The Nelson Mandela Metropolitan University's Human Ethics Committee granted ethical approval for the study.

Pharmacists were asked to hand an envelope to every patient who was receiving isotretinoin from the pharmacy when they came to the pharmacy for medication. Pharmacists were also asked to explain the procedure of completing the questionnaire and ethical forms to the patient, as well as to emphasise the importance of the study and the return date of the questionnaire and ethical forms. Patients had to complete the forms and return them to their pharmacies. The total time for data collection was 12 weeks. In this time, each pharmacy received three telephone calls as reminders of the study. Altogether, 189 questionnaires were distributed.

The questionnaires were retrospectively analysed using quantitative techniques. Microsoft Office Excel® 2003 was used for the basic differential analysis of the data. Numeric analysis comprised of the mean values, standard deviations, the range of data and minimum and maximum values that were calculated. Inferential tests were employed in order to obtain statistical and practical significance of the results. In obtaining statistical significance based on frequencies, the Pearson's chi-square test was used, while the t-test was used to obtain statistical significance where two groups based on sample means were compared. The Cramér's V statistic was used to confirm practical significance of the chi-square test, and the Cohen's d statistic was employed to confirm the practical significance of the t-test.

Limitations of the study were that it only included pharmacies and patients in the NMBM and that a relatively small number of patients were included in the study.

Results

Demographic information

A total of 57 completed questionnaires were received, accounting for a response rate of 29.2%. Of the 57 patients, 24 (42.1%) were female and 33 were male (57.9%). The age distribution of the patients is outlined in Table II. The average age of the population was 20.2 years (standard deviation (SD) = 7.9 years; n = 57). The average age that acne started to develop in the population was 15.3 years (SD = 4.4 years; n = 56). The youngest age of acne development was eight years, while the highest age was 38 years.

Table II: Age distribution of patient population

Age groups (in years)	Patients		
	Number (n = 57)	Percentage (%)	Cumulative percentage (%)
13–18	31	54.4	54.4
19–24	21	36.8	91.2
25–34	2	3.5	94.7
35–49	2	3.5	98.2
≥ 65	1	1.8	100.0

Acne medication history

The acne medication history represented medications, or any other treatment method, used by patients prior to the initiation of systemic isotretinoin therapy. Commercial brands of beauty products in cream, gel and face wash formulations were used by 33 patients (57.9%). Topical benzoyl peroxide formulations were used by 13 patients (22.8%), while 11 patients (19.3%) used systemic cotrimoxazole. A tetracycline derivative (minocycline, doxycycline or lymecycline) was used by 12 patients (21.1%). Only nine females (37.5%; n = 24) stated to have used an oral contraceptive as acne treatment prior to isotretinoin therapy.

Systemic isotretinoin therapy

The most frequently prescribed isotretinoin dose was 40 mg daily, prescribed to 42.1% of the patients (n = 38). The average daily dose was 44.2 mg (SD = 16.9 mg; n = 38). The average prescribed duration of isotretinoin therapy was 6.2 months (SD = 3.4 months; n = 50). The optimal cumulative dosage for isotretinoin is 120 to 150 mg/kg.[1] Only 34 patients completed all areas of the questionnaire necessary for determining the cumulative isotretinoin dose (dose per day, duration of therapy and weight). It was determined that seven (20.6%) of these patients would have received a cumulative dose within the optimal range, while 10 patients (29.4%) would have received a cumulative dose higher than 150 mg/kg. The other 17 patients (50.0%) would all have received a suboptimal cumulative dosage.

Acne severity

Before isotretinoin therapy, 29 patients (50.9%) had acne on areas of the body other than the face; the most frequently affected body area being the torso. Isotretinoin was prescribed to 3 patients (5.3%) with Grade 1 acne, 17 patients (29.8%) with Grade 2 acne, 21 patients (36.8%) with Grade 3 acne and 16 patients (28.1%) with Grade 4 acne.

Counselling and monitoring procedures

Health care professionals included dermatologists, general practitioners and pharmacists. Dermatologists prescribed isotretinoin to 45 patients (78.9%), while 11 patients (19.3%) received prescriptions from general practitioners. One patient (a pharmacist) self-initiated isotretinoin therapy. Only 33 patients (57.9%) were counselled adequately regarding their isotretinoin therapy course, while 24 patients (42.1%) received partial information, were not requested to sign a consent form or did not receive (or could not remember receiving) any counselling from the prescriber at all. Eight patients (72.7%; n = 11) who received isotretinoin prescriptions from general practitioners and 15 patients (33.3%; n = 45) who received prescriptions from dermatologists did not receive adequate counselling. Pharmacists counselled 78.2% of patients sufficiently. Although more patients claimed to have been counselled by their pharmacists than by their prescribers, there was a higher percentage of counselling by the prescriber reported for individual counselling topics. Three females (12.5%; n = 24) did not receive any counselling regarding the danger of isotretinoin in pregnancy. The ages of these females were 22 years, 16 years and 17 years – all three of childbearing age. Thirteen patients (22.8%) were not weighed prior to isotretinoin therapy prescription. Cholesterol tests were conducted for 36 patients (63.2%) and liver enzyme tests for 38 patients (66.7%).

Reported side-effects

The frequency of the occurrence of side-effects, as reported by the patient population, is outlined in Table III. Cheilitis was the most frequently experienced side-effect, reported by 56 patients (98.2%). Dry skin was reported by 50 patients (87.7%), while an initial worsening of acne (flare-

Table III: Frequency of side-effects reported most by patient population*

Rank	Side-effects	Patients	
		Number (n = 57)	Percentage (%)
1	Dry lips	56	98.2
2	Dry skin	50	87.7
3	Initial acne flare-up	36	63.2
4	Dry eyes	32	56.1
5	Nose bleeding	31	54.4
6	Sunburn	30	52.6
7	Backache	25	43.9
8	Depression	24	42.1
8	Fatigue	24	42.1
9	Muscle pains	23	40.4
10	Dizziness	22	38.6
10	Headache	22	38.6
10	Slow healing wounds	22	38.6
10	Joint pains	22	38.6
11	Neck stiffness	18	31.6
12	Sudden urges to fall asleep	17	29.8
12	Constipation	17	29.8
13	Loss of appetite	14	24.6
14	Blurred vision	13	22.8
14	Hair loss	13	22.8
15	Anxiety	11	19.3
16	Ingrown nails	10	17.5
16	Weight loss	10	17.5

* Only side-effects with a frequency of 10 or more are reported in Table III.

up) was experienced by 36 patients (63.2%). The recommended short course of prednisone, which serves to alleviate this side-effect,[9] was prescribed to only 11 of these patients (30.6%; n = 36).

Depression was reported by 24 patients (42.1%) and 8 patients (14.0%) experienced suicidal thoughts while on isotretinoin therapy. Also of note was that 17 patients (29.8%) reported sudden urges to fall asleep while on the medication. Fourteen patients had a decreased appetite and weight loss occurred in 10 patients. Contradictory to this, nine patients reported noticeable weight gain.

Isotretinoin and pregnancy prevention

Of the 24 female patients, 16 (66.7%) stated that they possessed childbearing potential. Three patients reported that they were not able to fall pregnant, while five females chose not to answer this question in the questionnaire. Fourteen females reported on their contraceptive measures prior to and during isotretinoin therapy. The results are shown in Table IV. After commencement of therapy, no changes occurred in the contraceptive methods utilised by patients, except for one patient who ceased taking her oral contraceptives and started practising abstinence. Only one female used two contraceptive measures. Contraception was recommended to only five of the sixteen females who were able to fall pregnant (31.3%), while not one patient between 13 and 18 years of age received recommendations from their prescribers regarding contraception. Only four females (21.1%; n = 19) received correct information from their health care professionals regarding the

Table IV: Contraceptive measures taken before and during isotretinoin therapy

Contraceptive measure	Prior to isotretinoin therapy		During isotretinoin therapy	
	Number of females (n = 14)	Percentage (%)	Number of females (n = 14)	Percentage (%)
Oral contraceptive	6	42.9	5	35.7
Abstinence	5	35.7	6	42.9
Injectable contraceptive	1	7.1	1	7.1
Vasectomy of husband	1	7.1	1	7.1
Hysterectomy	1	7.1	1	7.1
None	1	7.1	1	7.1

teratogenicity of isotretinoin and the procedure that must be followed should pregnancy occur while on treatment. Pregnancy tests were conducted in two females (8.3%; n = 24).

Efficacy of isotretinoin

There was a noticeable improvement in the patients' acne severity since initiation of therapy. This was confirmed by the smaller number of patients who suffered grades 2, 3 and 4 acne after starting with isotretinoin when compared to prior to isotretinoin therapy initiation. This difference was significant ($chi^2(4) = 46.67$; $p < 0.0005$; V = 0.64 Large). Just over 40% of patients reported a complete clearance of acne lesions during their isotretinoin therapy course. A significantly lower number of patients reported to have acne on the torso area, neck, shoulders, arms, scalp and legs after the initiation of isotretinoin ($chi^2(1) = 14.88$; $p < 0.0005$; V = 0.55 Large). More than 80% of patients felt either very satisfied or satisfied with the perceived efficacy of isotretinoin. Although many side-effects were reported, 71.9% of patients felt that their quality of life was not negatively affected or only affected negatively to a small degree. The questionnaire posed a hypothetical scenario to the patients: If they were able to return to the moment when isotretinoin was prescribed to them, would they have chosen to use isotretinoin again? Eight patients (14.0%) reported that they would have chosen not to use isotretinoin, while the other patients all stated that they would have made the same decision.

Discussion

The results of this study indicated that the recommendations for the prescription of isotretinoin are not always followed by prescribers. For example, in South Africa, the use of an effective contraceptive measure one month prior to, during and for one month after isotretinoin therapy is recommended.[1] In the United States of America (USA), the use of two contraceptive measures is required for females on isotretinoin therapy,[10] while two complementary contraceptives are recommended in the United Kingdom.[11] Of the 16 patients who stated that they were able to fall pregnant, only 5 (31.3%) received recommendations for contraception from their health care professionals. Even though females must be fully aware of the teratogenicity of isotretinoin and should sign consent forms indicating their understanding of the fact that a therapeutic abortion would be compulsory if pregnancy occurred during isotretinoin therapy,[1] only four females (21.1%; n = 19) received correct information from their health care professionals regarding this fact. A negative pregnancy test prior to initiation of isotretinoin therapy and monthly thereafter is

highly recommended in the SAATG[1] and is compulsory in the USA,[9] but pregnancy tests were only conducted in two females (8.3%; n = 24). There was a significant improvement in the patients' acne severity since initiation of therapy and just over 40% of patients reported a complete clearance of acne lesions during their isotretinoin therapy course.

The response rate to the questionnaire survey was low and thereby limited the validity of the results and of the statistical tests that could be performed. A nationwide survey will allow for results more accurately representative of the South African population. The low response rate could have been caused by a variety of factors, including the lack of personal communication with the respondents, the dependence of the researcher on the goodwill and responsible participation of pharmacists and patients, the lack of cooperation by many pharmacists, the complicated ethical forms that had to be completed by patients and the length of the questionnaire. Even though the questionnaire contained mainly multiple choice or open-ended questions and was designed to be as direct, patient-friendly and concise as possible, some patients might have found it time-consuming. In review of the study, it was observed that it would have been more appropriate to target a patient population who had already completed treatment courses with systemic isotretinoin, instead of patients who were currently on isotretinoin. The reason for this retrospective discovery was that patients who already completed their isotretinoin courses would have been able to give more consistent and valid feedback regarding the outcomes of therapy. Patients could have been at any stage of therapy during completion of the questionnaire, which could have affected factors like side-effects experienced, levels of acne clearance and patients' satisfaction with the effectiveness of isotretinoin.

Conclusion and recommendations

Many prescribers did not follow the recommendations for isotretinoin prescription as stipulated in the SAATG.[1] Isotretinoin was prescribed to many patients who did not have Grade 4 acne and who had not received previous prescriptions for systemic antibiotic therapy or hormone therapy, which might have been effective if tried before resorting to isotretinoin. However, the psychological aspects and scarring potential of the patients were not investigated and could have contributed to the prescribers' decisions. A majority of patients received inappropriate cumulative doses, which, if too low could lead to recurrent acne, or if too high could have led to severe (unnecessary) side-effects. The effectiveness of isotretinoin were proven once again, as just over 40% of patients (who were still on isotretinoin) reported a complete clearing of acne, while over 80% of patients felt satisfied or very satisfied with the perceived efficacy of isotretinoin. Counselling of patients regarding isotretinoin therapy was substandard by all health care professionals. Monitoring procedures as recommended in the SAATG[1] were largely insufficient and not conducted in accordance with recommendations. Special emphasis is placed on the unacceptable lack of compliance of health care professionals in implementing pregnancy prevention measures among female isotretinoin users and counselling females in this regard. The reservation of the prescription of systemic isotretinoin to dermatologists only should be considered, as well as the implementation of a stringent national Pregnancy Prevention Programme in South Africa. The implementation of this programme should be compulsory for all females on isotretinoin therapy and all health care professionals involved in the care of females on isotretinoin therapy. Although guidelines for isotretinoin prescription are available in South Africa, a national consensus flowchart or protocol for the prescription of isotretinoin therapy should be designed and implemented.

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