New evidence is increasingly suggesting that isotretinoin may be best prescribed using a lower daily dose, with the regimen tailored to the individual patient, the severity of their acne and their response to the medicine.\textsuperscript{1–6} Low-dose isotretinoin appears to be as effective as higher doses for resolving acne, and may present a safer, more patient-centred approach to prescribing a medicine that is associated with significant adverse effects, e.g. photosensitivity, liver abnormalities and eczema.\textsuperscript{3}

Current guidelines recommend that isotretinoin treatment is calculated based on body weight, usually 0.5 – 1 mg/kg per day, prescribed for long enough to reach a cumulative dose of approximately 150 mg/kg.\textsuperscript{7, 8}

Based on this newer evidence, a suggested regimen would be to initiate isotretinoin at a dose of 10 – 20 mg/day, continued until all acne lesions have resolved,\textsuperscript{3} which generally occurs between three to five months.\textsuperscript{2} Treatment would then continue for a further two to four months to reduce the risk of relapse and help with resolution of acne scarring.\textsuperscript{3} This second stage of treatment might be at a further reduced dose, e.g. 5 – 10 mg per day.\textsuperscript{3}

**If what we do now works, why change?**

There are several problems with prescribing isotretinoin based on a high daily dose to reach a cumulative total amount, including:\textsuperscript{3}

- There is no clinical difference in effectiveness between high and low daily doses
- Adverse effects are more significant at higher doses
- There is limited evidence for directing treatment based on a cumulative dose
- Treatment duration is not based on the patient’s response to the medicine
- Cumulative, weight-based dosing can be difficult to calculate and monitor

**How is isotretinoin currently being prescribed in New Zealand?**

Current national dispensing data shows that there are two "peaks" of isotretinoin doses being prescribed. At present, 63% of people taking isotretinoin are dispensed 10 – 20 mg per day, and 22% are dispensed 80 – 90 mg per day, with the remainder prescribed intermediate doses.\textsuperscript{9} It is difficult to conclude whether the 10 – 20 mg peak already represents low dose prescribing or whether it represents the traditional weight-based prescribing, but using lower doses for longer in response to adverse effects. It is likely that the higher dose group represents traditional weight-based prescribing. The current total average daily dose of isotretinoin is 42 mg.\textsuperscript{9}
Low doses are as effective as high doses
Research has shown that isotretinoin at doses of 0.1 mg/kg per day is as effective as doses of 1 mg/kg per day in terms of acne clearance. A recent study found that acne clearance rates were between 92 – 95% in people taking isotretinoin 20 mg per day for six months (equivalent to 0.28 mg/kg per day, with a cumulative dose of 52 mg/kg). This is comparable to the rate of clearance achieved with a traditional regimen of 0.5 – 1 mg/kg per day, with a cumulative dose of 150 mg/kg.

Adverse effects increase with increasing dose
Adverse effects of isotretinoin are dose dependent and become more common, and more severe, with higher doses. At 1 mg/kg per day, 98% of patients report adverse events, such as eczema, impetigo and photosensitivity, while at doses below 0.25 mg/kg per day, 50% of patients report adverse effects, which are generally less severe.

There is little evidence to support cumulative dosing
The duration of treatment with isotretinoin is currently based on the calculated cumulative dose. This method is used because several early studies suggested that relapse one to two years after a single 16-week course of isotretinoin was more common in people treated with 0.1 mg/kg per day than those treated with 1 mg/kg per day. This was interpreted to mean that the strongest long-term response from isotretinoin was obtained if the cumulative dose reached 120 – 140 mg/kg.

Subsequent research, however, has not supported cumulative dosing. Long-term follow-up studies show rates of relapse between 40 – 52% several years after treatment. These studies have concluded that relapse risk is determined by age, severity of acne and seborrhoea after treatment, but not by daily dose, duration of treatment or cumulative dose.

Duration should be based on patient response
There are no studies that have specifically assessed the most appropriate duration of treatment to clear acne. In practice, based on recent research and opinion, isotretinoin is continued until acne has cleared (defined as no active acne lesions), and then for another three to four months to limit recurrence. This approach tends to result in a shorter duration of isotretinoin treatment than with most cumulative dosing regimens, while maximising patient outcomes and minimising adverse reactions.

ACKNOWLEDGEMENT: Thank you to Dr Amanda Oakley, Dermatologist and Clinical Associate Professor, Tristram Clinic, Hamilton for expert review of this article.

Changes to the bestpractice Decision Support module
The current Special Authority criteria for prescribing subsidised isotretinoin recommend that a computer-based decision support tool is used when initiating and renewing the medicine. The bestpractice Decision Support Module for prescribing isotretinoin has recently been updated to reflect the new research which shows that lower doses are appropriate.

The module now recommends that the dose of isotretinoin should be based on the patient’s response to treatment and not on a cumulative dose:

“Use a starting dose of 10 – 20 mg and continue until there is a resolution of active acne lesions. Treatment dosages can then be halved and continued for a further two to four months”.

The default isotretinoin capsule dose in the Decision Support module is now 10 mg.

References