



## Isotretinoin for acne vulgaris – an update on adverse effects and laboratory monitoring

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# Title page

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# Isotretinoin for acne vulgaris: an update on adverse effects and laboratory monitoring

## ABSTRACT

A significant barrier to the usage of isotretinoin has been concerns regarding its adverse effect profile. The dose-dependent mucocutaneous side effects of isotretinoin are well recognised and easily managed, particularly if a lower dose is used. A possible association with depression has gained widespread media attention and is a source of concern for many patients and their carers, but data from prospective studies and recent meta-analyses has been reassuring. Furthermore, there has been much confusion amongst both patients and physicians regarding a possible association with inflammatory bowel disease, as well the ocular and rheumatological adverse effects of isotretinoin. We provide an update on the evidence surrounding the adverse effects of isotretinoin, and discuss practical strategies to prevent and manage these adverse effects. We also discuss appropriate laboratory monitoring for patients taking isotretinoin.

## MAIN TEXT

The most common adverse effects of isotretinoin are mucocutaneous. Of these, cheilitis is the most common adverse effect and is dose dependent(1), with a degree of actinic aetiology. Table 1 provides a list of the common adverse effects attributed to isotretinoin, as well as some of the less common but important adverse effects that have been reported in patients taking isotretinoin.

### FLARE OF ACNE

A flare of acne may occur in the first few weeks of isotretinoin therapy. Short term exposure of sebocytes to isotretinoin increases intracellular lipid content as well as the expression of sterol-regulatory element binding protein (SREBP)-1 and the eicosanoid synthesising enzyme 5-lipoxygenase (LOX).(2) Both SREBP-1 and 5-LOX are involved in sebum production, and their upregulation may contribute to the flare of acne seen in the first few weeks of therapy.

The presence of multiple macrocomedones appears to be an important risk factor for a flare of acne in the first few weeks of isotretinoin.(3)(4) Macrocomedones can be treated with diathermy or surgically, ideally prior to commencement of isotretinoin.

Commencing isotretinoin at a low dose should reduce the risk of a flare of acne in the first few weeks of treatment. One observational study found that starting at a dose of  $\leq 0.2\text{mg/kg/day}$  was associated with fewer flares of acne compared with patients commenced on  $0.5\text{mg/kg/day}$  ( $p=0.04$ ). (5) If sufficiently severe, a flare of acne in the first few weeks of isotretinoin can be treated by reducing the dose or temporarily ceasing isotretinoin, by adding a non-tetracycline based antibiotic such as erythromycin or trimethoprim, or by commencing a short course of prednisone/prednisolone ( $0.25\text{-}0.5\text{mg/kg/day}$  tapered over 2-6 weeks). These can also be prophylactically co-prescribed at initiation of isotretinoin therapy if risk of scarring is high.

### DEPRESSION

The association between isotretinoin and adverse psychological effects has been clarified over the last decade. Initial concerns regarding an association between isotretinoin and depression arose from case reports. In some of these patients, symptoms of depression settled after cessation of isotretinoin and recurred after rechallenge with isotretinoin.(6)(7)

Biological mechanisms for an association between isotretinoin and acne have been postulated. Retinoids are lipid soluble and can cross the blood brain barrier. It has been suggested that isotretinoin may lead to depressive symptoms by decreasing hippocampal neurogenesis, and/or by altering the expression of components of the serotonergic neurotransmitter system, thereby leading to impaired serotonin signalling.(8) Acne itself is associated with an increased risk of depression and suicidal ideation,(9)(10)(11) although not all studies have found this.(12)

A study by Azoulay and colleagues published in the psychiatry literature in 2008 reported an association between isotretinoin and depression (adjusted relative risk 2.68).(13) The study was retrospective, employing an uncommon study design (case crossover study) in an effort to minimise the effect of confounding. Patients acted both as cases and controls and by definition the control period occurred some time before the period prior to the onset of depression. The observed association between isotretinoin and depression observed in this study could at least partly be explained by the study design which itself could inflate the number of patients prescribed isotretinoin in the risk period compared to the control period.(14)

A retrospective cohort study from Sweden, found an increased risk of attempted suicide was apparent up to 6 months after the end of the treatment with isotretinoin.(15) However the risk of attempted suicide was already rising during the three years prior to treatment, which would be consistent with a relationship between acne itself and mood disturbances.

A recent cohort and nested case-time-control study based on data from the French National Health Insurance database looked at more than 440 000 patients exposed to isotretinoin.(16) It found a significantly lower occurrence of suicide attempts under isotretinoin treatment compared with the French general population (standardised incidence ratio 0.6, 95% confidence interval 0.53-0.67).(16)

Uncontrolled prospective studies show that isotretinoin improve psychological scores,(17)(18)(19)(20)(21) as does a prospective controlled study.(22) Several other prospective controlled studies have demonstrated no association between isotretinoin and depression.(23)(24)(25)(26)(27) The prospective studies examining the association between isotretinoin and depression are summarised in Table 2.

A meta-analysis which pooled the results of 1411 patients from controlled or non-controlled prospective studies, found no positive association between isotretinoin use and depression.(28) In fact, the prevalence of depression fell significantly after isotretinoin use and mean depression scores decreased compared to baseline.

Another recent meta-analysis found that isotretinoin led to a significant decrease in depression scores compared to baseline.(29) The pooled data (retrospective and prospective studies) also indicated that there was no association between isotretinoin and the risk of depressive disorders. When the authors considered prospective studies alone, no association between isotretinoin and depressive disorders was apparent. When the authors considered the retrospective studies alone, an association was present. However only one of the three pooled retrospective studies used in the analysis actually found an association between isotretinoin and depression and this was the study by Azoulay et al, which, as mentioned above, has been subject to criticism based on its study design(13)(14)

In summary, the data from prospective studies and recent meta-analyses does not support an association between isotretinoin and depression. Nevertheless, the reports of cases of depression which resolve with de-challenge and recur with re-challenge, suggest that a small subset of patients may be susceptible to mood change from isotretinoin. This possibility should be conveyed to patients and their carers prior to commencing isotretinoin

and the patient advised to report any symptoms of mood disturbance occurring during therapy. There is an anecdotal observation that psychological symptoms occurring during isotretinoin treatment is seen more often in young adult patients exposed to cannabinoids and methamphetamines.

Given the potential for isotretinoin to improve psychological health and quality of life, isotretinoin should actively be considered in patients with a history of a mood disorder; shared follow-up with the patient's family physician and/or mental health care professional, particularly in the first few months of therapy, is recommended.

## **INFLAMMATORY BOWEL DISEASE**

Initial concerns regarding a possible association between isotretinoin and the development of inflammatory bowel disease arose from several case reports and a single case control study indicating that exposure to isotretinoin was associated, in a dose dependent fashion, with an increased risk of ulcerative colitis but not Crohn disease.(30) Interestingly, a subsequent study using the same database found no increased risk for either ulcerative colitis or Crohn disease, in patients taking isotretinoin.(31) The main difference between the two case control studies was that the latter study was a nested study in patients taking the combined oral contraceptive pill, which reduces the effect of possible confounding from the oral contraceptive pill. The authors were able to adjust for the confounder of diagnosis (nodulocystic acne) and prior use of tetracycline antibiotics. This is important as tetracyclines, especially doxycycline, may be associated with the development of inflammatory bowel disease, particularly Crohn disease.(32)(33) While doxycycline has been shown to mediate detrimental long term changes in murine gut microbiota, isotretinoin has no significant effect on faecal microbiota.(34)

There is no obvious biological mechanism for an association between inflammatory bowel disease and isotretinoin, although several possible mechanisms have been speculated.(35) On the other hand the anti-inflammatory properties of all-*trans*-retinoic acid and its ability to enhance gut barrier function would suggest a possible beneficial effect of isotretinoin on inflammatory bowel disease.(35) The studies examining the association between isotretinoin and inflammatory bowel disease are summarised in Table 3. A large French case control study, that included 7593 cases of inflammatory bowel disease and 30 372 controls, found that isotretinoin exposure was not associated with an increased risk for ulcerative colitis, whereas it was associated with a decreased risk for Crohn disease.(36)

A further retrospective cohort study found that inflammatory bowel disease developed less frequently in an isotretinoin-exposed group compared with a nonexposed group ( $p=0.03$ ). (37) A large population based retrospective cohort study also found no association between isotretinoin use and Crohn disease or ulcerative colitis after adjusting for several possible confounders including use of tetracyclines.(38) Pre-specified secondary analyses did find a weak but statistically significant association between isotretinoin use and inflammatory bowel disease among patients aged 12-19 (adjusted rate ratio 1.39, 95% confidence interval 1.03-1.87) and a weak association between previous use of topical acne medications and ulcerative colitis (adjusted rate ratio 1.19, 95% confidence interval 1.00-1.42), suggesting a possible association between acne itself and ulcerative colitis.(38)

In a recent retrospective study of more than 600 000 patients with acne vulgaris, the odds of developing inflammatory bowel disease was 87% higher in patients exposed to isotretinoin (odds ratio 1.87; 95% confidence interval 1.20-2.93) although the absolute difference was small (risk difference 2.6 more cases per 10 000 patients; 95% CI, 0.7-4.5).(39) There was no statistically significant difference in the odds of developing inflammatory bowel disease at 1 year in those exposed to isotretinoin versus those that were not exposed. Furthermore, in the sensitivity analysis of patients with acne vulgaris without prior exposure to tetracycline antibiotics, there was no statistically significant difference in the incidence of inflammatory bowel disease at 6 months or 1 year, suggesting tetracycline exposure may be the confounder.(39)

A meta-analysis published in the gastroenterology literature which pooled the results of six studies, found no increased risk of developing ulcerative colitis, Crohn disease, or inflammatory bowel disease in general in patients exposed to isotretinoin compared to patients who had not been exposed.(40)

In summary, most epidemiological studies do not demonstrate an association between isotretinoin and inflammatory bowel disease and there is no clear evidence of a causal link.(41)

Patients with established inflammatory bowel disease have been treated safely with isotretinoin.(42)(43) In a retrospective chart review of patients with acne and known diagnosis of inflammatory bowel disease prior to treatment with isotretinoin, 100% of the patients on isotretinoin had clinical remission of inflammatory bowel disease compared to 37% of patients who were not on isotretinoin ( $p=0.078$ ).(44) In a subgroup analysis of patients with inflammatory bowel disease in one large retrospective cohort study, those treated with isotretinoin were not at an increased risk of subsequent hospital admission for inflammatory bowel disease (rate ratio 0.75; 95% CI 0.44–1.27) relative to untreated patients.(38)

Patients with established inflammatory bowel disease who have clinically significant acne, should actively be considered for treatment with isotretinoin.

## **BENIGN INTRACRANIAL HYPERTENSION**

An important reported adverse effect of isotretinoin is benign intracranial hypertension, which can lead to permanent visual impairment. A review of 179 cases of benign intracranial hypertension associated with isotretinoin use found that the mean time from drug exposure to diagnosis of benign intracranial hypertension was 2.3 months.(45) Six of these patients had a positive rechallenge; unfortunately the dose of isotretinoin was only recorded in one young patient, who was on 120mg/day. Benign intracranial hypertension has also been associated in various case reports with the tetracycline group of antibiotics, in particular tetracycline and minocycline, resulting in co-prescribing with isotretinoin being a listed contraindication. Safe co-prescribing of isotretinoin and tetracyclines has been described, but concomitant use of these medications should only occur when the potential benefits

outweigh the risks, the dose of both drugs kept as low as possible, and the patient monitored carefully.(46)

Benign intracranial hypertension should be considered in the case of a new headache or a headache that is different to the patient's usual headache disorder,(47) especially when accompanied by other symptoms such as visual disturbances or tinnitus. Isotretinoin has been used safely in patients with a previous history of drug-induced benign intracranial hypertension,(48) but it would be sensible to use low dosages of isotretinoin (e.g. 10 mg/day) and to monitor the patient closely for symptoms and signs of raised intracranial pressure in liaison with the patient's neurologist/ophthalmologist.

## **OCULAR EFFECTS**

A number of dose dependent ocular side effects have been attributed to isotretinoin. In a study that reviewed 1741 spontaneous reports, the authors categorised the ocular side effects into "certain", "probable/likely" and "possible", based on a World Health Organization classification system. Adverse effects due to isotretinoin that were deemed to be "certain" included abnormal Meibomian gland secretion, blepharoconjunctivitis, corneal opacities, decreased dark adaptation, decreased tolerance to contact lens, decreased vision, increased tear osmolarity, keratitis, meibomian gland atrophy, myopia, ocular discomfort, ocular sicca, photophobia, and teratogenic ocular abnormalities.(49) Those that were deemed to be "probable/likely" were decreased colour vision (reversible) and permanent loss of dark adaptation.(49) As there were no usage figures, it was not possible to determine the risk of developing ocular adverse effects. However, a large retrospective cohort study of 14 682 new users of isotretinoin found the incidence of any ocular disease within 1 year of starting isotretinoin was 13.8%, compared to 9.6% of age matched isotretinoin-naïve patients and 7.1% of age matched acne-free patients.(50) The most common reported ocular effects were conjunctivitis, hordeolum, chalazion, blepharitis, eye pain and dry eyes, with the peak risk at 4 months after first prescription of isotretinoin.(50) The dose and duration of isotretinoin was not recorded, but the adverse effects were likely dose-related.

The ocular adverse effect that has generated the most concern is the loss of dark adaptation, with concerns regarding its potential irreversibility. Maclean reported a case in which subjective symptoms of decreased night vision persisted 9 months after cessation of isotretinoin (70mg/day), although electro-retinogram (ERG) and electro-oculogram (EOG) were only performed at the 3 month mark.(51)

In a retrospective observational study of 47 pilots who had taken isotretinoin and undergone ocular electrophysiological testing, 2 pilots had abnormal dark adaptation testing and 13 had abnormal ERG parameters.(52) Among patients with abnormal parameters, the mean time interval between cessation of isotretinoin and testing was 37.6 months with a range of 6-96 months. One subject had subclinical changes persisting in the electroretinogram 8 years after cessation of isotretinoin. The dosages of isotretinoin used were not reported, and no pre-isotretinoin testing had been performed.

There are several small prospective studies relating to dark adaptation; Brown and Grattan were able to demonstrate a significant reduction in a-wave ERG values in the seven patients



taking isotretinoin in which they had pretreatment and three month data (dosage and indication not stated).(53) In a prospective study of six patients taking isotretinoin published by the same authors, two patients displayed definite deterioration in scotopic (dark adapted) ERG during treatment compared to baseline and one patient displayed borderline changes.(54) None of the patients were aware of reduced night vision. Once again, the dose and duration of therapy were not stated.

In a prospective study of 50 patients on isotretinoin (1mg/kg/day) for cystic acne, 6% reported abnormal night vision.(55) Subjectively their vision returned to normal after cessation of isotretinoin. Two of the patients had abnormal ERGs: in one patient the ERG was normal when retested at 1 year, but in the other the ERG was still abnormal, although improving, at 25 months. Dark-adaptation curves were normal for one patient several months after isotretinoin therapy was stopped but two patients had elevated cone thresholds at least one year later.

In summary, night vision impairment may occur in patients being treated with isotretinoin. Subclinical impairments in electrophysiological examination findings in the absence of any patient reported changes in night vision may not be infrequent. Decline in night vision appears to be in most cases reversible upon cessation of isotretinoin, although subclinical abnormalities in electrophysiological tests may last longer than initially thought. Isotretinoin is thought to cause night vision impairment by inhibiting ocular retinol dehydrogenases, leading to a reduction in the formation of the visual chromophore 11-*cis*-retinal.(56) Therefore, the use of lower dosages of isotretinoin (10-20 mg/day) may reduce the likelihood of clinical or subclinical abnormalities in night vision, although data to confirm this is lacking.

It is important to counsel prospective pilots (and long distance truck drivers) appropriately, and if isotretinoin is to be used, the dosage kept low, after discussion with their aviation medical specialist.

## **HYPEROSTOSES**

There are several non-controlled case series which document the development of hyperostoses or bony spurs on radiological examinations of patients treated with high dose isotretinoin (1mg/kg/day or greater).(57)(58)(59)(60). However, in each of these studies the radiological findings did not correlate well with musculoskeletal symptoms. Diffuse idiopathic skeletal hyperostosis (DISH) is characterised by etheseal ossification and/or calcification mainly involving the thoracic spine.(61) It is a relatively common condition, especially in older individuals, making case reports of a possible association between isotretinoin and DISH difficult to interpret. In one study, the overall prevalence of DISH in the healthy population over the age of 50 years was 15% in women and 25% in men.(62) DISH is more prevalent in developed nations and has been linked to the metabolic syndrome.(61)

Gerber et al. performed a retrospective study of patients on high dose isotretinoin (2 mg/kg/day for at least 2 years) that included a control group.(63) Compared to age and sex

matched controls there was no statistically significant increased risk of vertebral abnormalities in patients on isotretinoin.(63)

Studies examining whether lower doses of isotretinoin can induce hyperostotic changes at a higher rate than placebo, have shown mixed results. Carey et al examined 120 patients treated with a four month course of isotretinoin at a dosage of either 0.1, 0.5 or 1mg/kg/day.(64) Patients were radiographed within 1 year of treatment; 12% of patients had some radiographic abnormality, mostly subtle and consisted of small hyperostoses at the insertion of the anterior spinal ligament, plantar fascia or Achilles tendon. No patient had abnormalities at more than one site. Five of the patients with skeletal changes had arthralgias but only one of these had pain at the site of the abnormality. A sex and age match control group was obtained and 7% of this group had hyperostoses on X-rays, which was not significantly different from the isotretinoin group. Eleven of the 14 (79%) isotretinoin patients who had radiological abnormalities had follow-up 18 months after the original radiological examination. Only one patient showed radiological deterioration at one site, and none were clinically symptomatic. In six patients there was a definite clinical improvement and in four, the X ray appearances were unchanged.

Tangrea et al. examined the effect of long term low dose isotretinoin (10mg daily for 3 years) on DISH in 269 patients enrolled in a randomised controlled trial for chemoprevention of non melanoma skin cancer;(65) they had X-rays performed at baseline and at 3 years. The patients were aged between 40-75, significantly older than the age group in which isotretinoin is commonly prescribed. Compared with patients who were assigned to placebo, patients who were assigned to isotretinoin were more likely to exhibit progression of existing hyperostotic abnormalities (40% versus 18%,  $p<0.001$ ) and new hyperostotic involvement at previous unaffected levels (8% vs 1%,  $p=0.015$ ). There were, however, no significant group differences in self reports of back pain or stiffness.

In summary, the data regarding an association between isotretinoin and DISH has been conflicting. The most methodologically robust study, a randomised controlled trial, shows a possible association, although the participants were not acne patients and were significantly older. However, several studies demonstrate that isotretinoin-associated hyperostotic changes do not appear to correlate with additional symptoms of pain or stiffness.

## **PREMATURE EPIPHYSEAL CLOSURE**

Another issue that has been a source of concern has been the possible association between isotretinoin and premature epiphyseal closure. Milstone et al reported a case of premature epiphyseal closure in the right knee of a 10 year old patient taking isotretinoin for four and a half years for epidermolytic hyperkeratosis.(66) During the last two and half years of treatment the dose of isotretinoin averaged 3.5mg/kg/day. The patient was also taking vitamin A supplements. Marini reported the development of dense metaphyseal bands and growth arrest in a 9 year old boy with fibrodysplasia ossificans progressiva after five months treatment with very high dose isotretinoin (4-5mg/kg).(67) Cessation of isotretinoin led to gradual decrease of the bands and resumption of clinical growth.

There have been rare reports of premature epiphyseal closure occurring in patients treated for acne. These include a case in a 14 year old male who had taken a six month course of isotretinoin 12 months earlier, at a dose of 0.75mg/kg,(68) and a 15 year old male who was found to have irreversible closure of the epiphyseal growth plate on his knee radiograph 4.5 months after starting isotretinoin (1mg/kg/day).(69) In the latter case, an X-ray was performed at around the beginning of treatment, and epiphyseal closure was not evident at the time.

After developing bilateral knee pain, a 16 year old male was found to have evidence of irregular epiphyseal cartilage and marked metaphyseal-epiphyseal oedema on MRI of the knee.(70) He had commenced isotretinoin (0.5mg/kg/day) approximately 9 months earlier. Isotretinoin was stopped, and his symptoms resolved; a follow-up MRI seven months later revealed a persistent small sequellar lesion of irregular epiphyseal cartilage but reduction in metaphyseal-epiphyseal oedema.

The biologic mechanism of a retinoid effect on epiphyses may involve specific retinoid receptors. Animal studies have shown that guinea pigs treated with all-*trans*-retinoic acid and a retinoic acid receptor (RAR) selective agonist developed dose-dependent closure of the proximal tibial epiphyseal plate.(71) It would therefore be sensible to use lower dosages of isotretinoin in pre-pubertal children (e.g. 0.1 mg/kg/day), even though the risk is undetermined.

## **MUSCULAR EFFECTS**

Myalgia is a common dose-dependent adverse effect of isotretinoin. In general symptoms of myalgia and muscle tenderness are mild, and quickly reversible on discontinuation of therapy.(72)

Elevations of creatine kinase (CK) levels may occur in patients on isotretinoin and are frequently asymptomatic. In one study of 442 patients with acne who were commenced on isotretinoin at a dose of 20-60mg daily, gradually increased to 0.75-1mg/kg/day, elevated CK levels (>167 IU/L) occurred at least once in 37.3% of patients.(73) Values above 5000 IU/L were found in 7 patients (1.6%). Only two of these seven patients had mild muscle cramps; the others were asymptomatic. Five patients reported strenuous physical activity, while one patient had recently received an intramuscular steroid injection. In response to the high CK levels the patients were instructed to avoid vigorous physical activity. In five patients the isotretinoin was temporarily or permanently discontinued, in two patients the dose was simply reduced and in one patient the dose was unadjusted. CK levels returned to normal in all patients within 2 weeks of the maximal CK being detected.

Although in most cases elevation of CK is a benign phenomenon, there are rare reports of rhabdomyolysis occurring in patients treated with isotretinoin, including a case with a fatal outcome.(74) Furthermore, cases of true myopathy confirmed by electromyography with or without elevated CK levels have rarely been reported, and have generally been characterized by full recovery after discontinuation of isotretinoin.(72)

In patients who develop myalgia or increased CK levels while on isotretinoin, the dose of isotretinoin may be reduced or the drug temporarily discontinued until these findings resolve.(75) These patients should be encouraged to reduce strenuous physical activity or contact sports while on isotretinoin, and to avoid any medications that may also lead to myopathy. CK levels, electrolytes and urinalysis (including testing for myoglobinuria) should be performed in patients presenting with severe muscle pain or weakness or change in the colour of urine. There is no evidence to support regular monitoring of CK (or recommending reduced exercise) in physically active patients who are asymptomatic.

## **TERATOGENICITY**

Isotretinoin is a known teratogen. The precise molecular basis of retinoid embryopathy remains unknown, but it has recently been hypothesized that isotretinoin exaggerates neural crest cell apoptosis via upregulation of the pro-apoptotic transcription factor p53.(76) Retinoic acid embryopathy produces malformations particularly affecting craniofacial, cardiac, thymic, and central nervous system structures.(77) In one study of 94 prospectively ascertained pregnancies exposed to isotretinoin which ended in birth, 28% resulted in congenital malformation.(78) Several other prospectively reported cases of exposure to isotretinoin appeared to have had normal outcomes at birth, but were later found to have impairment of the central nervous system, hearing, or vision (i.e. neurodevelopmental delay).(79) Exposure to isotretinoin during pregnancy also appears to increase the risk of spontaneous abortion.(80)

In an effort to reduce the number of pregnancies in patients on isotretinoin therapy, the iPLEDGE program, a computerised risk management program, was launched in the USA in 2006. The iPLEDGE program requires the registration of all wholesalers distributing isotretinoin, all healthcare professionals prescribing isotretinoin, all pharmacies dispensing isotretinoin and all patients prescribed isotretinoin.(81) Amongst the requirements of the program are two negative pregnancy tests prior to the commencement of isotretinoin and monthly negative pregnancy tests prior to issuing each monthly prescription. Most other countries have not adopted such a stringent pregnancy prevention program, but simply recommend that the possibility of pregnancy be excluded prior to the commencement of isotretinoin and that patients are advised to avoid falling pregnant during the treatment and for 1 month after completion of the treatment,(82) using two reliable methods of contraception. There is little evidence that stringent pregnancy prevention programmes such as iPLEDGE are more effective, but they do significantly reduce access to isotretinoin, particularly amongst socio-economically disadvantaged patients.(83)

Should a patient become pregnant on isotretinoin, isotretinoin should be immediately discontinued, and advice sought from a perinatal specialist. There is currently no evidence that very low doses of isotretinoin (e.g. 5 mg/day) are safe in pregnancy, although up to 10,000 IU vitamin A daily does appear to be safe.(84)

## **MALE AND FEMALE FERTILITY**

Despite some initial concerns, male fertility is not adversely affected by isotretinoin.(85) A study of 81 patients found positive effects of low dose isotretinoin on all sperminogram

parameters, and no effects on the total testosterone, FSH and LH levels.(85) In another study, 19 men with infertility from oligoasthenozoospermia were treated with isotretinoin (20 mg, twice daily for 20 weeks).(86) By the end of treatment, there was a statistically significant improvement in sperm concentration and a trend toward improvement in sperm morphology.(86) Six pregnancies and five births occurred during the study.

Although in one study of females taking isotretinoin for acne, the levels of anti-Mullerian hormone, ovarian volume and antral follicle counts were decreased at the end of six months treatment with isotretinoin, these levels improved with time and were statistically similar to baseline at 18 months post treatment.(87)

Male sexual dysfunction in association with isotretinoin was first reported in 1994, at which time Roche had received 150 reports of male sexual dysfunction over the previous 10 years, including 32 potency disorders and two reports of ejaculatory failure.(88) To put this in context, this was 0.008% of the 18,000 reports of adverse reactions. Using disproportionality statistics, the Dutch Pharmacovigilance Center Lareb noted a possible signal between isotretinoin and sexual dysfunction based on 7 spontaneous reports over a 14 year period.(89) They suggested a reduction in the circulating levels of testosterone might be responsible but this is unlikely as the reduction, whilst statistically significant in some studies, is quite small; in one study the mean testosterone level fell from 1.9 +/-0.3 nmol/L at baseline to 1.3 +/-0.1 nmol/L at 16 weeks but remained within the normal reference range (1-3.2nmol/L) (90)

## LABORATORY MONITORING

Isotretinoin medicine data sheets recommend baseline investigations (complete blood count, renal and liver function), repeated regularly during treatment, in addition to appropriate pregnancy screening. A meta-analysis has shown that while isotretinoin was associated with statistically significant changes in the mean value of white blood cell counts, hepatic and lipid panels, the mean changes did not meet *a priori* criteria for high risk and the proportion of patients with laboratory abnormalities was low.(91)

Leukopenia and thrombocytopenia may occur in patients taking isotretinoin. However in the absence of any risk factors, routine monitoring of complete blood count is not warranted given that abnormal results tend to remain stable or resolve despite continued therapy.(92) In a recent retrospective study of 704 acne patients treated with isotretinoin, abnormalities in the complete blood count were observed in 8.2% of patients, the most common being leukopenia observed in 3.7% of patients.(93) The severity of all changes were grade 1 and changes in the complete blood count were not related to decrease, increased or stable dosages (p=0.72).(93) In a recent cohort study by Barbierie and colleagues of 1863 patients treated with isotretinoin, there were no instances of Grade 3 or Grade 4 abnormalities in complete blood count except for one likely spurious platelet count.(94)

In the aforementioned retrospective study of 704 patients, abnormal liver function was observed in 7.2% of patients and all were Grade 1.(93) Alterations of liver function (recovery or increase) were not related to dose increase or decrease (p=0.57).(93) In the cohort study by Barbierie and colleagues, Grade 3 abnormalities of liver function tests occurred in less

than 0.5% of patients and were not more common than baseline; there were no Grade 4 abnormalities.(94) In another large retrospective cohort study of 13 772 patients, the cumulative incidence of new transaminase abnormalities during the treatment period was 11%, with 1% being grade 2 or higher.(95) Moderate to severe abnormalities were generally transient and reversible. Elevations of AST and ALT are commonly accompanied by elevations in creatine kinase, indicating that a muscle cause for these elevations is sometimes responsible, rather than true liver toxicity.(96) The ingestion of concurrent dietary supplements may also be an important cause of transaminitis.(97) In our experience, mild elevations of transaminases (<3 times the upper limit of normal), are often transient and do not usually necessitate interruption of isotretinoin treatment. However, in such instances, more frequent monitoring of liver function tests may be warranted and consideration should be given to other factors that may be contributing to the transaminitis such as muscular causes (including strenuous activity), other medications or supplements, and viral illnesses.

Lipid abnormalities are the most common laboratory abnormalities seen in patients on isotretinoin.(95) In the aforementioned retrospective cohort study of 13 772 patients treated with isotretinoin for acne, the cumulative incidence of new abnormalities in patients with normal values at baseline was 44% for triglyceride level and 31% for total cholesterol level.(95) The mean daily dosage of isotretinoin used was 65mg. In the cohort study by Barbieri and colleagues, Grade 3 abnormalities in triglycerides occurred in fewer than 1% of patients and there were no Grade 3 abnormalities in total cholesterol or Grade 4 abnormalities in either cholesterol or triglycerides.(94) Although reported, cases of hyperlipidaemia induced pancreatitis in patients on isotretinoin are exceedingly rare. A systematic review of the literature over a 35 year period to January 2016 found only 4 cases of hypertriglyceridemia induced pancreatitis in patients on isotretinoin, with most cases of isotretinoin associated pancreatitis thought to be idiosyncratic.(98) In our experience, the occurrence of very high hypertriglyceridemia (>500 mg/dL or 5.6 mmol/L) in patients on low dose isotretinoin (0.1-0.25mg/kg/day) with normal baseline lipids is rare. Most cases of hypertriglyceridemia are mild (<300 mg/dL or 3.4 mmol/L) and can be managed through lifestyle/dietary modification without the need to interrupt isotretinoin treatment.

#### *Timing and frequency of monitoring*

In a large meta-analysis, the changes in total cholesterol and triglycerides between 0 weeks and 8 weeks were similar to the changes in total cholesterol and triglycerides between 0 and 20 weeks, indicating no substantial late effect of therapy on these parameters.(91) In a retrospective review, mean duration of treatment before abnormalities were detected was 56.3 days for hypertriglyceridemia, 61.9 days for alanine transaminitis, and 50.1 days for hypercholesterolemia.(92) On the basis of this, the authors of that review suggest that in healthy patients checking liver function tests and lipids two months after the peak dose (they used 0.5 to 1 mg/kg/day) is attained is sufficient with no further testing required if the results are normal.(92) Ongoing monitoring may be required for patients with known lipid abnormalities, those with risk factors for hyperlipidaemia or liver abnormalities, including those who have commenced new medications or supplements, or patients with abdominal pain. Women of childbearing potential should have regular pregnancy tests while on isotretinoin.

## **OTHER ADVERSE REPORTS**

With a medication that has been used in millions of patients over almost 40 years, it is not surprising that there have been many case reports of treatment emergent adverse effects. Most of these have not been substantiated with larger cohort studies.

## **CONCLUSION**

With almost 40 years of experience using isotretinoin in the management of acne vulgaris, our understanding of its mechanism of action, and the optimal way in which it should be prescribed continues to evolve.<sup>(99)</sup> Isotretinoin has been associated with numerous adverse effects, although the risk of many of these can be substantially reduced by using lower dosages. Recent meta-analyses examining the association between isotretinoin and depression and inflammatory bowel disease have been reassuring.

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**TABLE 1: REPORTED ADVERSE EFFECTS OF ISOTRETINOIN (including reports where causality has not been proven)**

| <b><u>1.1 Common adverse effects</u></b>                          |  |
|---|--|
| <i>Mucocutaneous</i>  | Xerosis<br>Cheilitis<br>Facial erythema<br>Photosensitivity<br>Pruritus<br>Flare of acne<br>Skin fragility, delayed healing<br>Dermatitis<br>Palmoplantar desquamation<br>Nasal mucosal dryness<br>Epistaxis<br>Alopecia<br>Nail dystrophy<br>Paronychia<br>Staphylococcus aureus infections |
| <i>Ocular</i>   | Dry eyes<br>Ocular discomfort<br>Blepharoconjunctivitis<br>Hordeolum<br>Chalazion  |
| <i>Musculoskeletal</i>  | Myalgia<br>Arthralgia  |
| <i>Biochemical</i>  | Increases in liver transaminases<br>Leucopenia, neutropenia<br>Elevated cholesterol and triglycerides  |
| <i>Other</i>  | Headache<br>Fatigue  |
| <b><u>1.2 Uncommon but important reported adverse effects</u></b> |  |
| <i>Mucocutaneous</i>  | Hyperhidrosis<br>Pyogenic granuloma<br>Steven Johnson Syndrome/Toxic epidermal necrolysis<br>Urticaria/angioedema/anaphylaxis  |
| <i>Ocular</i>   | Corneal opacities<br>Decreased dark adaptation<br>Keratitis<br>Decreased vision<br>Myopia<br>Photophobia<br>Decreased colour vision  |
| <i>Musculoskeletal</i>  | Uni-, oligo- or poly-arthritis<br>Enthesopathy<br>Sacroilitis  |

|                         |   |
|-------------------------|---|
|                         | Lower back pain<br>Hyperostoses<br>Myopathy<br>Rhabdomyolysis<br>Premature epiphyseal closure   |
| <i>Gastrointestinal</i> | Diarrhoea<br>Abdominal pain<br>Pancreatitis<br>Inflammatory bowel disease*                      |
| <i>Psychiatric</i>      | Affective disorders, particularly depression*<br>Suicidal ideation*<br>Behavioural disturbances |
| <i>Neurological</i>     | Benign intracranial hypertension<br>Impaired hearing (rare reports)<br>Tinnitus                 |
| <i>Biochemical</i>      | Thrombocytopenia<br>Hyperuricaemia  |

\*Although cases of these conditions, have been reported, a definite association between isotretinoin and these conditions is yet to be established. See main text for further details



**TABLE 2: PROSPECTIVE STUDIES OF ISOTRETINOIN AND DEPRESSION**

| Reference                  | Study type   | Subjects | Endpoint  | Result  |
|----------------------------|--|----------|---|---|
| Luvizotto et al 2020(100)  | Prospective, non-controlled  | N=42     | BDI   | Statistically significant improvement in depression scores after 3, 6, 9 and 12 months from start of treatment                      |
| Bray et al J 2019(101)     | Prospective non-controlled   | N=56     | LOT-R, MAACL-R  | LOT-R scores improved significantly with isotretinoin; Depression trait scores of MAACL-R remained stable                           |
| Metekoglu et al 2019(18)   | Prospective, non-controlled  | N=112    | HAD   | Statistically significant improvement in HAD-D score at end of treatment  |
| Erdogan et al(27)          | Prospective, controlled (control – oral antibiotics)                                     | N=102    | HAD, SPS  | No changes in HAD, SPS after 3 months of treatment  |
| Suarez et al 2016(25)      | Prospective controlled (control group = oral antibiotic/topical therapy, non-randomized) | N=60     | Zung depression scale, locally developed scale (GeDepr) | No significant difference in frequency of depression between treatment and control groups   |
| Gnanaraj P et al 2015(102) | Prospective non controlled   | N=150    | Hamilton Rating Scale for Depression                    | Statically significant improvement in depression scores at end of treatment (3 months)  |
| Fakour et al 2014(103)     | Prospective non-controlled   | N=98     | BDI   | Worsening of BDI scores by end of treatment (statistically significant); 49% had evidence of depression at baseline (BDI score >13) |
| Marron et al. 2013(21)     | Prospective, non-controlled  | N=346    | HADS  | Statistically significant reduction in depression scores at and of treatment  |
| Nevoralova et al 2013(20)  | Prospective non controlled   | N=100    | BDI   | Statistically significant improvement in BDI scores at end of treatment   |
| Yesilova et al 2012(104)   | Prospective non controlled   | N=43     | HADS  | HADS scores (depression subset and total) improved significantly by end of treatment  |
| Ergun et al 2012(105)      | Prospective non-controlled   | N=63     | HAD-D   | Statistically significant improvement in HAD-D scores during treatment  |

|                        |   |       |  |  |
|------------------------|---|-------|--|--|
| McGrath et al 2010(26) | Prospective, controlled (comparison group 1 = oral antibiotic/topical adapalene; comparison group 2= matched community samples) | N=190 | CES-D                                      | No deterioration in depression scores with time in isotretinoin group  |
| Bozdag et al 2009(17)  | Prospective, non-controlled   | N=50  | BDI  | Statistically significant improvement in depression scores at end of treatment   |
| Rehn et al 2009(19)    | Prospective non-controlled  | N=135 | BDI  | Statistically significant improvement in BDI scores, non-statistically significant reduction in patients with clinically significant depressive symptoms (BDI $\geq$ 10), and suicidal ideation  |
| Hahm et al. 2009(106)  | Prospective non-controlled  | N=38  | BDI  | Statistically significant improvement in BDI scores after 8 weeks of treatment (not assessed beyond 8 weeks)   |
| Kaymak et al 2009 (22) | Prospective controlled (control =topical arm)   | N=78  | BDI, HAD                                   | Statistically significant improvement in BDI and HAD scores in isotretinoin group with time<br>All scores in isotretinoin group had improved significantly more compared with control group at end of 4 months   |
| Cohen et al 2007(24)   | Prospective controlled (control group = oral antibiotic/topical therapy, non randomised)  | N=200 | Zung depression status inventory and CES-D | No statistically significant difference in Zung depression status inventory at follow-up compared with baseline. Based on a CES-D $>15$ indicating depression, two patient in isotretinoin group developed depression (zero in control group) but difference not statistically significant |
| Kaymak et al 2006(107) | Prospective non-controlled  | N=100 | Hamilton Depression Rating Scale           | Statistically significant worsening of scores at 3 months but returned to baseline at 6 months (end of treatment)  |

|                                  |  |       |   |  |
|----------------------------------|--|-------|---|--|
| Chia et al<br>2005(108)          | Prospective<br>controlled (control<br>= oral antibiotic<br>and/or topical<br>therapy; no<br>randomisation) | N=132 | CES-D   | At 3-4 months follow-up, CES-D scores<br>suggestive of clinically significant<br>depression no more prevalent in<br>isotretinoin group than in the<br>conservative therapy group. Similarly,<br>the incidence (new onset) of CES-D<br>scores suggesting clinically significant<br>depression was not significantly<br>different between the treatment<br>groups. |
| Ferahbas A<br>et al<br>2004(109) | Prospective non-<br>controlled   | N=45  | Montgomery-<br>Asberg<br>Depression<br>Rating Scale | Non-statistically significant decrease in<br>depression score at 16 weeks  |
| Ng et al<br>2002(23)             | Prospective<br>controlled (control<br>group =oral<br>antibiotic/topical<br>therapy; no<br>randomization)   | N=215 | BDI   | No difference between change in mean<br>BDI score over treatment course<br>between isotretinoin and control group  |

Abbreviations: HAD = Hospital anxiety and depression scale; HAD-D = Hospital anxiety and depression scale – Depression; SPS = Suicide probability scale; CES-D = Centre of Epidemiological Studies Depression Scale; BDI = Beck Depression Inventory; LOT-R = Life Orientation Test – Revised; MAACL-R=Multiple Affect Adjective Checklist Revised

**TABLE 3: COHORT AND CASE CONTROL STUDIES OF DEPRESSION AND INFLAMMATORY BOWEL DISEASE**

| Reference                 | Study Type                | Subjects  | Methods  | Results   |
|---------------------------|---------------------------|---|--|---|
| Wright et al 2021(39)     | Retrospective cohort      | Exposed group = 27230<br>Non-exposed group = 631089 | Search of American database  | Odds of developing IBD within 6 months were 87% higher among isotretinoin-exposed patients compared to unexposed (adjusted odds ratio, 1.87; 95% confidence interval, 1.20-2.93), although the absolute difference was small (risk difference, 2.6 more cases per 10,000 patients; 95% CI, 0.7-4.5). No significant difference in the odds of developing IBD at 1 year between isotretinoin-exposed and non-exposed |
| Rashtak et al 2014(37)    | Retrospective cohort      | Exposed group = 576<br>Non-exposed group = 502      | Review of medical records in single centre (Mayo Clinic)                 | Isotretinoin associated with reduced risk of IBD [odds ratio 0.33; 95% CI, 0.12-0.93; p = .04]  |
| Racine et al 2014(36)     | Case control              | Cases = 7593<br>Controls = 30372                    | Search of French database  | Isotretinoin not associated with increased risk of UC but was associated with decreased risk of CD [OR = 0.45 (95 % CI: 0.24, 0.85)]  |
| Alhusayen et al 2013(38)  | Retrospective cohort      | Exposed group = 46922<br>Non-exposed group=1526946  | Search of population based health records in British Columbia, Canada    | No increased risk of IBD, UC or CD in those exposed to isotretinoin.<br>Increased risk of IBD in patients aged 12-19 [adjusted rate ratio 1.39 (95% CI 1.03-1.87)]<br>Increased risk of IBD in patients aged 12-19 who had taken topical medications [adjusted rate ratio 1.15 (95% CI; 0.98-1.36)]   |
| Etminan et al 2013(31)    | Nested case control study | Cases =2159<br>Controls=43180                       | Search of American insurance database; nested (oral contraceptive users) | IBD, UC, CD not associated with isotretinoin exposure   |
| Crockett et al 2010(30)   | Case control study        | Cases = 8189<br>Controls = 21832                    | Search of American insurance database                                    | UC associated with isotretinoin exposure [OR 4.36 (95%CI 1.97-9.66); no association with CD]  |
| Bernstein et al 2009(110) | Case control study        | Cases=2008<br>Controls=19814                        | Search of American health database                                       | IBD, CD, UC not associated with isotretinoin exposure   |

Abbreviations: IBD=Inflammatory bowel disease; UC= ulcerative colitis; CD=Crohn disease