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ISOTRETINOIN AND THE RISK OF DEPRESSION IN PATIENTS WITH ACNE VULGARIS

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Isotretinoin and the risk of depression in patients with acne vulgaris

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RÉSUMÉ

L'isotrétinoïne est un médicament efficace dans le traitement de l'acné sévère. Cependant, nombreux sont les cas rapportés signalant possiblement une association entre l'utilisation de cette pharmacothérapie et la dépression, qui mène les médias à lui porter une attention toute particulière.

Plusieurs études observationnelles ont été menées sur le sujet, mais aucune association significative n'a été trouvée. Cependant, la plupart de ces études n'avaient pas de groupe témoin adéquat, ou encore avaient une taille d'échantillon insuffisante, et souffraient donc de problèmes méthodologiques importants.

L'objectif de cette étude se voulait ainsi de déterminer s'il existe une association entre l'utilisation de l'isotrétinoïne et la dépression chez les sujets diagnostiqués d'acné et ayant reçu au moins une prescription d'isotrétinoïne entre le 1er janvier 1984 et le 31 décembre 2003. Afin d'y parvenir, une étude cas-chassé-croisé a été réalisée au sein de cette population. Les données utilisées ont ainsi été obtenues à partir des banques de données administratives de la Régie de l'Assurance Maladie du Québec (RAMQ) et de Med-Écho (hospitalisations) de la province du Québec. Nous avons été en mesure de définir les cas comme des sujets ayant reçu un premier diagnostic de dépression ou une hospitalisation en lien avec la dépression (CIM-9: 296.2, 298.0, 300.4, 309.0, 309.1, et 311.0) durant la période d'étude. Ces derniers devaient également avoir reçu au

moins une prescription d'antidépresseur dans les 30 jours suivant leur diagnostic ou à l'hospitalisation. La date index correspondait au diagnostic ou l'hospitalisation considéré. Par ailleurs, les cas devaient aussi être couverts par le régime médicaments de la RAMQ et avoir reçu au moins un diagnostic d'acné (CIM-9: 706.1) dans les 12 mois précédant la date index. Un cas se voyait donc exclus s'il avait reçu une prescription d'antidépresseur dans les 12 mois précédant la date index. On a pu comparé l'exposition à l'isotrétinoine durant la période à risque (cinq mois immédiatement avant la date index) à la période témoin (cinq mois précédant la période à risque). Les risques relatifs et intervalles de confiance (IC) à 95% ont pu ainsi être estimés en utilisant la régression logistique conditionnelle, tout en ajustant pour les variables confondantes qui variaient dans le temps.

La cohorte initiale était ainsi composée de 30,496 sujets parmi lesquels 126 (0.4%) cas répondaient aux critères de sélection. Le risque relatif non ajusté correspondant à l'exposition à l'isotrétinoïne était de 2.00 (95% IC : 1.03, 3.89). Après avoir ajusté pour les variables confondantes qui variaient dans le temps, le risque relatif était de 2.68 (95% IC : 1.10, 6.48).

Il s'agit de la première étude à avoir démontré une association significative entre l'isotrétinoïne et la dépression. Sachant que la dépression est une maladie pouvant avoir des conséquences non négligeables, une attention particulière devrait être portée aux patients recevant l'isotrétinoïne.

Mots-clés : Acné ; isotrétinoïne ; dépression ; cas-chassé-croisé

ABSTRACT

Isotretinoin is an effective medication for the treatment of severe nodular acne. Over the years however, case reports and adverse reaction databases have signaled a possible association with depression, which led to considerable media attention. Several observational studies have been conducted on the subject, but failed to show an association. However, these studies were either uncontrolled, had small sample sizes, or suffered from other methodological problems.

Thus, the objective of the present study was to determine whether isotretinoin increases the risk of depression in patients with acne vulgaris. A case-crossover study was performed among subjects who received at least one isotretinoin prescription between January 1, 1984 and December 31, 2003. Data were obtained from the Régie de l'Assurance Maladie du Québec (RAMQ) and Quebec's hospital discharge (Med-Écho) administrative databases. Cases were defined as those with a first diagnosis or hospitalization for depression (ICD-9 codes: 296.2, 298.0, 300.4, 309.0, 309.1, and 311.0) during the study period (1984-2003), and who filled a prescription for an antidepressant in the 30 days following their diagnosis or hospitalization. The index date was the calendar date of the diagnosis or hospitalization for depression, whichever came first. Cases were covered by the RAMQ drug plan and had at least one acne diagnosis in the 12 months prior to the index date. Those who received an antidepressant in the 12 months prior to the index date were excluded. Exposure to isotretinoin in a

five-month risk period immediately prior to the index date was compared to a five-month control period that preceded the risk period. Relative risks along with 95% confidence intervals (CI) were estimated using conditional logistic regression.

Of the 30,496 subjects in the initial cohort, 126 (0.4%) cases met inclusion criteria. The crude relative risk was 2.00 (95% CI: 1.03, 3.89). After adjusting for potential time-dependent confounders, the relative risk was 2.68 (95%CI: 1.10, 6.48).

This is the first controlled study to find a statistically significant association between isotretinoin and depression. Because depression could have serious consequences, close monitoring of isotretinoin users is indicated.

Keywords: Acne; isotretinoin; depression; case-crossover

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LIST OF ABBREVIATIONS

ADERS	Adverse drug event reporting system
AERS	Adverse Event Reporting System
AQOL	Acne Quality of Life Scale
ARIMA	Autoregressive integrated moving average
BDI	Beck Depression Inventory
BHS	Beck Hopelessness Scale
CES	Center for Epidemiologic Studies Depression Scale
CI	Confidence interval
DHPL	Dear Healthcare Professional Letter
DHT	Dihydrotestosterone
DLQI	Dermatology Life Quality Index
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, fourth edition
EQ-5D	EuroQol
FDA	Food and Drug Administration
GPRD	General Practice Research Database
HAD	Hospital Anxiety and Depression Scale
ICD-9	International Classification of Diseases, ninth revision
MCA	Medicines Control Agency
Med-Écho	Maintenance et Exploitation des Données pour l'Etude de la Clientèle Hospitalière
NAMCS	National Ambulatory Medical Care Survey
OR	Odds ratio
P. acnes	Propionibacterium acnes
PPP	Pregnancy Prevention Program
RAMQ	Régie de l'Assurance Maladie du Québec
RR	Relative risk
SD	Standard deviation
SF-36	Short Form-36
SMART	System to Manage Accutane Related Teratogenicity
SSRI	Selective serotonin reuptake inhibitor
UK	United Kingdom
US	United States
VAS	Visual analog scale
WHO	World Health Organization
WHOQOL-BREF	World Health Organization Quality of Life-100- questionnaire

DEDICATION

To my wife, Jessica, for her unconditional love and support

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CHAPTER 1: INTRODUCTION

Acne is a highly prevalent disorder costing over one billion dollars in the United States (US) every year (1). There are a number of medications available for the treatment of acne, several of which are available over-the-counter. However, isotretinoin is the only medication that has been shown to be effective in the treatment of severe recalcitrant nodulocystic acne. It was dubbed a miracle drug by physicians and patients when it was first approved in the US in 1982 and in Canada in 1983.

Isotretinoin's popularity has since been marred by its side effect profile. It is a potent human teratogen if taken during the first trimester of pregnancy (2). This was known at the time of its marketing, but there were no risk management programs in place to prevent isotretinoin-exposed pregnancies. In addition to being a teratogen, isotretinoin has also been associated with mucocutaneous, ophthalmologic, neuromuscular, and gastrointestinal side effects (3). Because of these serious side effects, isotretinoin is considered a second line treatment to patients with severe nodular acne who have not responded to conventional therapy (4).

Over the years, there has been growing concern regarding isotretinoin's possible psychiatric effects. Such side effects have been reported as early as 1983, a year after it was introduced in the US market (5). Case reports

and signals from adverse reaction databases have indicated a possible association between isotretinoin and depression, suicidal ideation, and suicide. However, controlled observational studies failed to find an association between isotretinoin and depression. Because of methodological limitations in these studies and continued concerns that an association may truly exist, several governments have modified the isotretinoin package labeling to better inform physicians and patients of this possible side effect. In 2000, isotretinoin's possible psychiatric effects received considerable media attention after US Congressman Bart Stupak blamed isotretinoin for triggering the suicide of his 17-year old son (6). Thus in view of the growing concerns regarding the use of isotretinoin, its possible association with depression warrants further investigation.

CHAPTER 2: LITERATURE REVIEW

In order to fully appreciate the literature pertaining to isotretinoin, it is essential to provide an overview of the epidemiology and pathogenesis of acne, as well as the available treatments for this condition. Subsequent sections will describe in detail isotretinoin's mechanism of action, its utilization, and its various side effects with a special emphasis on its potential psychiatric effects.

2.1 EPIDEMIOLOGY OF ACNE

Acne vulgaris, or acne, is the most common dermatologic disorder treated by physicians, costing over one billion dollars a year in the US (1). It is a highly prevalent disorder, affecting 85% to 100% of young adults 12 to 24 years of age (7,8). Acne affects males and females equally, and usually develops sooner in females than males because of their earlier onset of puberty (9). This concords with a longitudinal study that followed students for 8 years where females developed acne sooner than males (10). Females reach their peak between ages 16 and 17 and males between ages 17 and 19 (9).

For most affected individuals, acne will usually clear spontaneously by 24 years of age (11). However, acne may persist well beyond puberty. This was demonstrated in a study conducted among 749 adults between 25 and 58 years

of age, where 40% of males and 54% of females had some form of acne (12). In another study, Cunliffe and Gould (13) surveyed 2155 volunteers between 18 and 75 years of age. At 18 years of age, 35% of males and 23% of females had clinical acne (13). By 40 years of age, the prevalence of clinical acne was 1% in males and 10% in females (13). A low prevalence of adolescents and young adults may suffer from acne well into the sixties and seventies (14).

2.2 PATHOGENESIS OF ACNE

2.2.1 PILOSEBACEOUS UNIT

Acne occurs at the pilosebaceous unit (15). The pilosebaceous unit is composed of the hair follicle, sebaceous gland, and the infundibulum which is a duct connected to the surface of the skin. The epithelial cells that line the infundibulum are an extension of the epidermis (15). Four factors have been found to be implicated in the pathogenesis of acne. They are 1) increased sebum secretion, 2) abnormal follicular differentiation, 3) propionibacterium acnes (P. acnes), and 4) inflammation. The following sections will detail the role of each of these factors in the pathogenesis of acne.

2.2.2 INCREASED SEBUM PRODUCTION

Sebaceous glands secrete sebum, which consists of lipid, cellular debris, keratin and bacteria in a complex mixture of triglycerides, fatty acids, wax esters, squalene and cholesterol (11). Sebum has lubricating and antimicrobial action to the skin, and helps prevent water loss to maintain 10% hydration of skin and hair (16). However, acne is present in areas with large concentrations of sebaceous glands. In fact, it has been shown that sebum production is greatest in persons with acne, where the rate of its production is directly proportional to the severity of the condition (9,17,18). Excessive amounts of sebum contribute to the obstruction of the pilosebaceous unit (19), and provides an ideal growth environment for P. acnes (9).

The largest and most abundant sebaceous glands are found on the face, namely, the cheekbones, forehead, and nose (15). A dense concentration is also located over the neck and shoulders, chest, upper back and upper arms (15). They are not present on the palms of the hands or soles of the feet (20).

The sebaceous' gland activity is modulated by androgenic hormones, especially dihydrotestosterone (DHT). Sebaceous glands possess the enzymes 5α-reductase, and 3α- and 17α-hydroxysteroid dehydrogenase that convert weaker

androgens to DHT. DHT binds to androgen receptors in sebaceous glands to stimulate sebum secretion. Before puberty, sebum secretion is relatively dormant but surges after androgens levels increase after the onset of puberty (11). Sebum production reaches its peak in the late teens, and its level remains stable until about 70 years of age in men, and the onset of menopause in women (11).

Some women may notice a flare-up in acne prior to menstruation, while others may experience a flare-up with ovulation and pregnancy (12). Furthermore, oral contraceptives that contain androgenic progestins are sometimes implicated in causing flare-ups. Paradoxically, as will be discussed in section 2.6.2.2, certain oral contraceptives with specific formulations may be used as anti-acne treatments in women (21).

Sebum production has been shown to be high after birth (22). It has also been shown that sebaceous glands respond to maternal androgens delivered through breast milk in infants. Together, this may cause infantile acne. In a case series of 29 infants (24 boys and five girls) with a median age at onset of nine months, 24% had mild, 62% had moderate and 14% severe acne (22). The type of acne was predominantly inflammatory (59%). No child had any clinically obvious endocrinopathy. The authors noted the probable contributory role of testicular androgen (22).

2.2.3 ABNORMAL FOLLICULAR DIFFERENTIATION

In individuals with acne, the keratinocytes that line the lumen of the follicle are not readily excreted (15). This is due to abnormal follicular epithelial differentiation (9). Thus these cells are retained instead of being normally shed off through the follicular opening. This obstruction eventually forms a hyperkeratotic plug in the follicular canal. This plug is known as the microcomedo. The exact mechanism by which this abnormal process occurs is not fully elucidated. However, some evidence suggest a possible follicular deficiency in linoleic acid in subjects with acne (23).

2.2.4 PROPIONIBACTERIUM ACNES AND INFLAMMATION

Cutaneous propionibacteria, such as P. acnes, are pathogens that are implicated in the development of inflamed acne lesions. P. acnes are anaerobic, gram-positive diphtheroids that colonize within pilosebaceous follicles. However, it is unknown whether they are permanent or temporary follicular residents (24). P. acnes produce an extracellular lipase that hydrolyzes sebum triglycerides to glycerol and fatty acids. The glycerol portion is the growth substrate for P. acnes. The free fatty acids that are produced by the hydrolysis are proinflammatory (25). P. acnes also release other proinflammatory substances, such as esterases, proteases, hyaluronidsea and chemotactic factors that attract neutrophils. These in turn release hydrolytic enzymes that damage and weaken the follicular wall

and eventually cause its rupture into the dermis (19). Such an inflammation may result in the formation of a pustule or cyst (25).

2.3 TYPES OF LESIONS

Acne is typically characterized by comedones, a plug of sebum and keratin lodged in the follicular duct (26). Comedones may appear as either black- or whiteheads. A closed comedo or micromedo can cause the follicular wall to rupture, which results in an inflammatory reaction (19). Clinically, the inflammation is associated with papules, pustules, macules, nodules and cysts. Each of these lesions will be described in detail below.

2.3.1 PAPULES

Papules are generally five millimeter or less in size, and elevated slightly above the skin surface. They often appear as small red lumps. A group of papules may nearly be invisible to the naked eye, and may feel like 'sandpaper' on the skin. They are caused by localized cellular reactions (27).

2.3.2 PUSTULES

Pustules are dome-shape, fragile lesions, which contain pus. The pus consists of a mixture of white blood cells, dead skin and bacteria. Pustules form around a hair (i.e. the pilosebaceous unit). There is usually no scarring if the pustule can heal without progressing to a cystic form (27).

2.3.3 MACULES

Macules are temporary red or red-pink spots with well-defined borders left by a healing acne lesion. The presence of numerous macules results in an inflamed 'red-faced' look, as though the face has acne (27).

2.3.4 NODULES

Nodules are similar to papules, but are larger in size. They may appear as domes or have an irregular shape. Inflammation is often present and extends deeper into the skin layers. This can cause tissue damage and scarring (27). Nodules can be extremely painful and do not respond to therapies, other than isotretinoin.

2.3.5 CYSTS

Cysts refer to pus-filled acne lesions greater than five millimeter in diameter, in which the walls are composed of inflammatory cells and scar tissue (26). Cysts are large, sac like lesions containing a liquid or semi-liquid material consisting of white blood cells, dead skin cells and bacteria. They are often severely inflamed, extremely painful and similar to nodules, extend into deeper layers of the skin, causing tissue damage and scarring (27).

2.4 ACNE SEVERITIES

2.4.1 COMEDONAL ACNE

Comedonal acne is the mildest form of this condition and is non-inflammatory. It is characterized by comedones on the forehead, chin, nose and paranasal areas (9). This form of acne is non-inflammatory because P. acnes have not yet colonized the follicle. Comedonal acne is mostly seen in the pre-teenage years and early in adolescence (28).

2.4.2 INFLAMMATORY ACNE

Inflammatory acne develops after an initial phase of comedonal acne. This condition is characterized by the formation of small papules and pustules (19).

The inflammation is due to the proliferation of the P. acnes in the obstructed follicle (28).

2.4.3 NODULOCYSTIC ACNE

Nodulocystic acne is a degradation of the condition. It is characterized by pustular lesions larger than 0.5 cm (29). This represents the worst form of acne and such Individuals often require aggressive treatment.

2.5 PSYCHOSOCIAL IMPACT OF ACNE

Although acne is a non life-threatening condition, it may have an important psychosocial impact on an individual. Because of its effects on a person's physical appearance, acne could lead to feelings of embarrassment and shame while decreasing one's self-esteem and self-confidence (30,31). Severe acne has also been associated with a high unemployment rate (32).

The section below will describe several observational studies that have been conducted to determine the psychosocial impact of acne. In a study conducted by Yazici et al. (33), the psychosocial impact of acne was assessed in 61 subjects with acne and compared with 38 healthy subjects. Subjects with acne responded to the Acne Quality of Life Scale (AQOL), Dermatology Life Quality Index (DLQI) and Hospital Anxiety and Depression Scale (HAD), while healthy subjects only responded to the HAD. The anxiety (HAD-A) and depression (HAD-D) subscales of the HAD were significantly greater in patients with acne than healthy subjects. Furthermore, there were no correlations between acne severity and the AQOL, DLQI, HAD-A or HAD-D, indicating that subjects with acne were at an increased risk of anxiety and depression irrespective of their acne severity. Finally, there were no statistically significant differences in AQOL, DLQI, HAD-A, HAD-D scores between males and females.

In another study conducted by Gupta et al. (34), the prevalence of depression and suicidal ideation in 480 patients with diverse dermatological conditions was compared. Close to 6% of patients with acne had clinical depression and suicidal ideation, compared with 0% of patients with alopecia areata, 2.1% of patients with atopic dermatitis and mild-to-moderate dermatitis. Patients with severe psoriasis had a prevalence of 7.1% of clinical depression and suicidal ideation, and were thus the only group to have higher rates than the acne group. However, it must be noted that this study used patients with mild-to-moderate acne, and as such, it is possible that patients with severe acne would have had similar or greater rates of depression or suicidal ideation than the severe psoriasis group.

In addition to causing greater depression and suicidal ideation, the quality of life of individuals with acne may also be affected. Quality of life, a measure of the degree of enjoyment or satisfaction experienced in everyday life, was determined in a study of 130 patients with acne referred for specialist care (35). Three measures were used, which included two generic questionnaires (EuroQol (EQ-5D), Short Form-36 (SF-36)) and one disease-specific questionnaire (Dermatology Life Quality Index (DLQI)). The questionnaires were administered two to three weeks before the outpatient appointment, and at four and 12 months after the treatment began. Before the outpatient visit, when compared to population norms, acne patients reported more pain/discomfort (42.1% versus 17.7%) and anxiety/depression (52.8%

versus 15.5%) on the EQ-5D. The mean score for the DLQI varied from 9.2 at baseline to 2.2 at 12 months, compared to 0.82 and 0.93 for the EQ-5D and SF-36 physical and mental component scales 49.7 and 44.1 (at baseline) to 53.4 and 50.9 (at 12 months), respectively. Therefore, DLQI demonstrated greater responsiveness to change in health status at four and 12 months than did the other two generics. However, this study had considerable loss to follow-up; out the 130 patients recruited, only 60 (46%) completed the questionnaires by 12 months. In an another study, 111 patients with acne referred to a dermatologist were found to have a mean DLQI score of 7.5 (range 0-29), which is similar in deficits in quality of life in patients suffering from other chronic conditions like asthma, epilepsy, diabetes, back pain, arthritis, coronary artery disease (36).

Table 1 displays a summary of the observational studies conducted on the psychosocial impact of acne. These studies concluded that acne can have important psychiatric consequences on those who suffer from it. Fortunately, therapeutic treatments are effective at improving the mental state of those individuals (30,31,35,37). Interestingly, some studies found no correlation between acne severity and level of depressive symptoms (33,36). In fact, patients with mild-to-moderate acne have also been found to have depression, suicidal ideation (34), and some have even committed suicide (38). This indicates that acne severity is perceived differently from one individual to another.

Table 1. Observational studies on the psychosocial impact of acne

Authors	Number of subjects with acne	Questionnaires	Reference group(s)	Before treatment	After treatment
Yazici et al. (2004) (33)	61	Acne Quality of Life Scale, Dermatology Life Quality Index, Hospital Anxiety and Depression Scale	Healthy volunteers	Higher rates of anxiety and depression in the acne group	n/a
Klassen et al. (2000) (35)	130	Dermatology Life Quality Index, EuroQoL, Short-Form 36	Population sample	More pain/discomfort, anxiety/depression	Improvement on all measures
Kellet et al. (1999) (30)	33	Hospital Anxiety Depression Scale	Normal population, general dermatology outpatients, psoriasis, oncology, and psychiatric patients	Patients with acne had greater depression and anxiety scores than all other groups	Improvement on measures related to self-image
Mallon et al. (1999) (36)	111	Dermatology Life Quality Index, Rosenberg measure of self-esteem, General Health Questionnaire 28, Short-Form 36	Population sample	Patients with acne had similar deficits as those with asthma, epilepsy, diabetes, back pain, arthritis, coronary artery disease	n/a
Gupta et al. (1998) (34)	72	Carroll Rating Scale for Depression	Patients with alopecia areata, atopic dermatitis, psoriasis	Patients with acne had greater rates of clinical depression and suicidal ideation than those with alopecia areata, atopic dermatitis, and mild-to-moderate dermatitis	n/a
Lasek et al. (1998) (37)	60	Skindex questionnaire	Healthy volunteers, patients with psoriasis, benign skin lesions,	Inverse relationship between quality of life and severity of acne	Improvement on all measures
Krowchuk et al. (1991) (31)	39	Piers-Harris self-concept scale	Compared with normative data	Dissatisfaction with facial appearance, embarrassment, social inhibition	Improvement for the majority of patients

Abbreviations: n/a; not applicable.

2.6 ANTI-ACNE TREATMENTS

2.6.1 TOPICAL TREATMENTS

When topical treatments for acne are appropriate, they offer a number of advantages over systemic treatments. In fact, the current trend is to favor topical treatments over the long-term use of systemic antibiotics (39). Since the skin is the largest organ of the body and is thus readily available, direct application of a topical agent would offer better monitoring of the therapy (40). Another major advantage is that topical agents do not cause as many side effects as systemic agents (40). Drug-drug interactions with topical agents are also uncommon for this same reason (41,42). Another concern is that many systemic agents, such as systemic antibiotics, do not readily penetrate the environment inhabited by P. acnes. This is due to the fact that the micromedo is highly lipid and therefore is poorly penetrated by hydrophilic antibiotics (41). Therefore, applying high concentrations of a drug directly upon its intended site of action can maximize the chance of penetration and a beneficial outcome. However, it should be noted that topical treatments are indicated for patients with non-inflammatory or mild to moderate inflammatory acne (9). Systemic treatments, on the other hand, are preferred when the condition is resistant to topical therapy, covers large areas of the body, causes significant psychological distress, or requires rapid improvement (41).

There are a number of topical treatments available for the treatment of acne. Their indication for use primarily depends on the severity of the acne and patient tolerability. A description of the main topical treatment is presented below.

2.6.1.1 TOPICAL ANTIBIOTICS

Topical antibiotics are effective treatments for mild-to-moderate inflammatory acne. They work by reducing the population of P. acnes in sebaceous follicles and by suppressing neutrophil chemotaxis (43). One of the main advantages of topical antibiotics over other topical treatments is their low irritative profile (44). Despite this advantage, there has been growing concern regarding P. acnes resistance to these agents (24,44). Erythromycin and clindamycin are the most commonly used topical antibiotics.

2.6.1.1.1 ERYTHROMYCIN AND CLINDAMYCIN

In a randomized, double-blind clinical trial of 60 patients with moderate acne, topical erythromycin and clindamycin were found to be therapeutically equivalent (45). In fact, in several large randomized controlled trials, topical erythromycin and clindamycin when applied twice daily were superior in reducing the number of papules and pustules in patients with moderate-to-severe acne compared to placebo (46-48). However, because of growing

concerns of P. acnes resistance, erythromycin and clindamycin concentrations have been increased from one to four percent (24).

Current recommendations are that topical antibiotics should be given in combination with other topical agents like benzoyl peroxide or tretinoin (44). Such combination therapies result in a superior therapeutic effect than if each component was used alone. This was demonstrated in two double-blind, randomized clinical trials involving 334 patients (49). The results of these trials were that a combination gel containing clindamycin one percent and benzoyl peroxide five percent was superior in reducing inflammatory lesions as compared to each component alone, and superior to the clindamycin-only gel in reducing non-inflammatory lesions (49).

2.6.1.2 TOPICAL RETINOIDS

2.6.1.2.1 TRETINOIN

Tropical tretinoin, a vitamin A derivative, was the first topical retinoid to be introduced in the US market in 1971 (26). Tretinoin prevents micromedo formation by reversing the process of abnormal follicular differentiation (9). A meta-analysis of randomized controlled trials involving 900 patients showed that tretinoin 0.05% gel may induce up to a 53% reduction in comedones and papules (50). Despite its efficacy, tretinoin may be photoirritant (28), and has

been associated with erythema and peeling which have often limited its use in clinical practice (26).

2.6.1.2.2 ADAPALENE

Adapalene is a synthetic retinoid used to treat mild to moderate acne. As with tretinoin, adapalene inhibits comedo formation but also has anti-inflammatory activity (51). In a comparative trial of adapalene and tretinoin, adapalene was shown to produce a 49% reduction in inflammatory and non-inflammatory lesions compared to 37% for tretinoin by week 12 of the treatments (52). In other trials, adapalene was also shown to be better tolerated than tretinoin and caused less erythema, scaling and dryness of the skin (53-55).

2.6.1.2.3 TAZAROTENE

Tazarotene is the first of a family of receptor-selective acetylenic retinoids. In a review of anti-acne treatments, tazarotene induced reductions in total lesions of up to 71% compared to tretinoin at 37% and adapalene at 49% by week 12 (56). This increased effectiveness has been attributed to its increased specificity for certain retinoic acid receptors (28). However, it must be noted that tazarotene may cause greater skin irritation than other topical retinoids, and is therefore considered a second-line option to patients who have not responded to topical tretinoin or adapalene (29).

2.6.1.3 OTHER TOPICAL TREATMENTS

2.6.1.3.1 BENZOYL PEROXIDE

Benzoyl peroxide has been labeled the gold standard for mild-to-moderate acne (44). It is a potent bactericidal agent that inhibits the growth of P. acnes more effectively than topical antibiotics (erythromycin and clindamycin) (19). In addition, no bacterial resistance to benzoyl peroxide has been detected (44).

Benzoyl peroxide is available in 1%, 2.5%, 5%, and 10% gels and lotions (19). In two trials of 153 patients with mild to moderate acne, Mills et al. (57) compared the efficacy of topical benzoyl peroxide at different concentrations (2.5% vs. 5% and 2.5% vs. 10% used twice daily). Based on lesion counts, there were no differences in efficacy among the different concentrations. However, erythema and scaling occurred most often with the 10% concentration formulation. Their conclusion was that the 2.5% and 5% concentrations were preferable becaused they caused less side effects than the 10% formulation.

2.6.1.3.2 SALICYLIC ACID

Salicylic acid is used to treat comedonal acne (28). It has keratolytic effects by shedding off the epithelial cells in the lining of the follicle (28,44). It is available over-the-counter in either solutions, cleansers, and soaps (28). It is

considered an alternative for patients who cannot tolerate the side effects of topical retinoids (9).

2.6.1.3.3 AZELAIC ACID

Azelaic acid is a naturally occurring dicarboxylic acid that works by normalizing keratinization and reducing the proliferation of P. acnes (58). In an randomized controlled trial of 92 patients with moderate acne, treatment with azelaic acid 20% resulted in a 72% in total lesion reductions compared to 47% for placebo (59). In another randomized controlled trial, azelaic acid 20% was shown to have a similar efficacy as tretinoin 0.05%, benzoyl peroxide 5%, and topical erythromycin 2% (60). In comparison to other topical treatments, azelaic acid poses no teratogenic risks, exhibits excellent local tolerability, and does not induce P. acnes resistance as with topical antibiotics (60). A summary of the main topical treatments for acne is presented in Table 2.

Table 2. Topical treatments for acne vulgaris

Topical agent	Mechanism of action	Side effects
Topical antibiotics		
Erythromycin	Reduction of P. acnes population	Irritation P. acnes resistance
Clindamycin	Reduction of P. acnes population	Irritation P. acnes resistance
Topical retinoids		
Tretinoin	Prevents microcomedo formation	Photoirritant Erythema Peeling
Adapalene	Prevents microcomedo formation Anti-inflammatory activity	Same as tretinoin, but less severe
Tazarotene	High specificity for retinoic receptors	Same as tretinoin, but more severe
Other topical agents		
Benzoyl peroxide	Inhibits growth of P. acnes Mild keratolytic effects	Erythema Peeling
Salicylic acid	Keratolytic effects	Dryness Irritation
Azelaic acid	Normalizes keratinization Inhibits proliferation of P. acnes	Dryness Peeling Erythema Irritation

2.6.2 SYSTEMIC TREATMENTS

Section 2.6.1 described the different topical treatments available for the treatment of mild acne. However, these treatments are not as effective for moderate to severe acne. The following sections will describe all available systemic treatments, as well as describe their mechanism of action, their efficacies, and side effects. A summary of the main systemic treatments is presented in Table 4.

2.6.2.1 SYSTEMIC ANTIBIOTICS

Systemic antibiotics have been used in the treatment of moderate to severe acne for many years. They work in several ways. First, they suppress the growth of P. acnes, and thus prevent the release of its inflammatory mediators (61). Second, certain systemic antibiotics, such as tetracycline and erythromycin, have anti-inflammatory properties which work by preventing neutrophil chemotaxis (43). Third, systemic antibiotics reduce comedone formation by suppressing the infiltration of perifollicular lymphocytes (62). Because they are systemic agents, oral antibiotics cause more side effects than topical agents (40). As with topical antibiotics, there is concern of increased P. acnes resistance to systemic antibiotics (40).

2.6.2.1.1 TETRACYCLINE, MINOCYCLINE AND DOXYCYCLINE

Tetracycline and its lipophilic derivatives, minocycline and doxycycline, are the most commonly prescribed oral agents for acne vulgaris (63). A six-week treatment with tetracycline reduces the number of lesions by 50% (64). Therapy usually starts at 500 mg twice daily for three to six weeks, and then reduced to 250 mg twice daily (28). Side effects associated with tetracycline use include nausea, vomiting, diarrhea, vaginal candidiasis, photosensitivity, and hypersensitivity reactions (28,63). Permanent tooth discoloration may occur in children under the age of nine (28). In addition, tetracycline should not be prescribed to pregnant women because of possible neural tube, cleft palate, and cardiovascular malformations (65).

If tetracycline therapy fails, doxycycline and minocycline may be indicated. Both are prescribed at a dosage of 50 mg to 100 mg twice daily, which is reduced after three to six weeks if improvement is observed (28). Because minocycline is more lipophilic than tetracycline and doxycycline, it can cross the blood-brain barrier and cause headaches, vertigo, ataxia, and light-headedness (28). Minocycline has also been associated with serum-sickness-like reactions, drug-induced lupus, and hypersensitivity reactions (66).

2.6.2.1.2 ERYTHROMYCIN

Erythromycin is not as effective as tetracycline in the treatment of moderate to severe acne. This was shown in a trial of 200 patients randomly assigned to either erythromycin or tetracycline. Seventy percent of those who got erythromycin and 89% of those who got tetracycline stated that their acne got better by week 12 (67). However, the erythromycin group reported a greater number of gastrointestinal side effects (nausea, vomiting, abdominal cramping, diarrhea) than the tetracycline group (67). Others have found that P. acnes exhibits greater resistance to erythromycin than to tetracycline (68). These side effects have limited the use of erythromycin in clinical practice (28).

2.6.2.1.3 CLINDAMYCIN

Clindamycin has been shown to have a similar efficacy as tetracycline in the treatment of inflammatory acne (69). However, its use has been associated with pseudomembranous colitis, affecting between two and 30% of patients (70). Because of this important side effect, clindamycin is rarely used as an acne treatment (9).

2.6.2.2 HORMONAL THERAPY

As was discussed in section 2.2.2, there is a direct correlation between androgen levels and acne (71). It has been proposed that androgens

increase sebaceous gland activity, and may also cause hyperkeratosis of the pilosebaceous gland (72). This is especially true in acne patients, where their sebaceous glands are thought to be hyperresponsive to normal serum androgen levels (73).

Over the last few years, oral contraceptives (OC) have been proposed as another therapeutic option for women with acne. This is because OCs have been shown to reduce the amount of circulating androgens, thereby decreasing the severity of acne (71). There are currently two hormonal preparations indicated for the treatment of acne; those containing norgestimate and those containing cyproterone acetate (74).

Two randomized, double-blind placebo-controlled clinical trials were performed to assess the efficacy of the ethinyl estradiol/norgestimate combination in the treatment of moderate acne (21,75). In the first, Lucky et al. (21) randomized 257 patients to receive either the OC or placebo. The OC group experienced a 53% reduction in total lesion counts at 26 weeks, compared with a 27% reduction in the placebo group. The main adverse effect was nausea. The OC treatment was protective of pregnancy and alleviated dysmenorrhoea (21). These results concord with those of a second study that randomized 250 patients to either OC or placebo (75). The OC group experienced a 46.4% reduction in total lesion counts at 24 weeks, compared with a 33.9% reduction in the placebo group. The authors attribute

the rather large reduction in lesion counts in the placebo group to the study protocol itself, since the frequent office visits may have increased patient awareness and led to better skin care in some patients (75).

Cyproterone acetate, a progestin, works by acting as a competitive inhibitor to testosterone and DHT on androgen binding sites, and also inhibits gonadotropin secretion (74). Studies conducted on cyproterone acetate have been of poor quality. Only one study was a randomized trial, but used subjective dermatological measurements, such as "complete healing" and "definitive healing" to assess treatment efficacy (76). Other studies were not randomized trials (77,78) and only one used an objective dermatological measure such as lesion count to assess treatment efficacy (78). In all, these studies reported 60% to 73% in improvement compared to baseline (76-78).

In Canada, the use of cyproterone acetate has been a controversial issue since it was first licensed for sale in 1998. The Food and Drug Administration (FDA) has never approved the licensing of this agent. This is because of concerns over a possible association with liver cancer. In 1994, German regulatory authorities commissioned a safety review after a woman died from liver cancer after she had used the ethinyl estradiol/cyproterone acetate combination as a birth control method for 14 years (79). Supporting this association are laboratory studies showing abnormal liver cell growth in animal and human tissue exposed to cyproterone (80). This evidence led

German regulatory authorities to restrict the use of cyproterone acetate to women suffering from severe acne with hormonal imbalances.

The risks associated with the use of cyproterone acetate prompted Health Canada to issue an advisory in May 2005 (81). The Product Monograph now states that ethinyl estradiol/cyproterone acetate combination pills should not be used as a means for birth control, and should be discontinued three to four months after signs of acne have resolved (81).

2.6.2.3 ISOTRETINOIN

Isotretinoin (13-cis-retinoic acid) is a systemic retinoid that represented a major breakthrough in the treatment of severe nodular acne. Because isotretinoin is the focus of this thesis, section 2.8 will be dedicated to describing all aspects related to this medication. They include its mechanism of action, its utilization since its marketing, its effectiveness at preventing acne relapse, its cost, as well as its documented side effects.

2.6.3 ADJUNCTIVE THERAPIES

Sections 2.6.1 and 2.6.2 listed all currently available pharmacologic treatments for acne. There are however, non-pharmacological treatments that have seen some success in the treatment of acne. The following sections will describe the effectiveness of chemical peels, photodynamic therapy, corticosteroids as well as other adjunctive therapies.

2.6.3.1 COMEDONE EXTRACTION

Comedone extraction is performed using a comedone extractor by an experienced operator (28). This procedure is believed to provide faster improvement that topical therapy (28). However, patients are usually advised not to perform this procedure themselves since the inflammatory material

may be pushed deeper in the skin and result in a deterioration of the condition (15).

2.6.3.2 CHEMICAL PEELS

Chemical peels help correct the surface of scarred and hyperpigmented skin (82). Peeling agents include alpha-hydroxy acids, salicylic acid (28,44), and trichloroacetic acid (15). Chemical peeling should only be performed once the acne is deemed to be under control (15).

2.6.3.3 PHOTODYNAMIC THERAPY

Photodynamic therapy, usually performed in patients with mild or moderate acne, uses ultraviolet light to target P. acnes in the pilosebaceous unit (83,84). Significant reductions in acne lesions are possible after four to 12 weeks of photodynamic therapy (using blue light and mixed blue and red light) (84). However, photodynamic therapy should not be performed for long periods of time because it might enhance comedogenesis and damage the skin (15).

2.6.3.4 CORTICOSTEROIDS

Corticosteroid injections are indicated for large pustular nodulocystic lesions. They have the ability of rapidly reducing the size and inflammation of lesions

(9,28). Corticosteroid injections have possible side effects, which include skin depression (28) and atrophic scars (15). Therapy is usually repeated every two to three weeks (28).

2.6.3.5 OTHER THERAPIES

A number of other therapies are available for patients with acne, especially for those with scarring acne. They include dermabrasion, laser resurfacing, punch grafts, and collagen injections (28).

2.7 CANADIAN ACNE TREATMENT GUIDELINES

Two Canadian acne treatment guidelines were published over the years. Both sets of guidelines primarily focused on the treatment of severe acne. The first Canadian acne treatment guidelines were published in 1995 (85). In these guidelines, severe acne was defined as having numerous comedones, papules, nodules and scars. In the more recent Canadian acne treatment guidelines published in 2000, severe acne was defined as having either persistent inflammatory papules, papulopustular disease, scarring, presence of sinus tracts, or inadequate therapeutic response (86). The difference in these definitions has thus implications on how to treat severe acne. According to the 2000 guidelines, the presence of scars and the severity of inflammatory lesions are deemed independent indicators of severe acne.

Therefore, these guidelines put a higher emphasis on the presence of scarring than did the 1995 guidelines.

There are three major differences between the 1995 and 2000 guidelines. The first is that the 1995 guidelines proposed up to three courses of systemic antibiotics, each lasting four to six months, before considering isotretinoin therapy. In contrast, the 2000 guidelines propose initiating an isotretinoin treatment after failure of a four-month therapy of a single course of systemic antibiotics or hormonal therapy. The second is that the 2000 guidelines emphasize scarring as a primary decision criterion for prescribing isotretinoin. Finally, the 2000 guidelines propose initiating an isotretinoin therapy in the presence of scars, irrespective of the severity of acne.

Table 3. Systemic treatments for acne vulgaris		
Medication	**Acne severity**	**Frequency of use in clinical practice**
Systemic antibiotics		
Tetracycline	Moderate-to-severe	Very often
Minocycline	Moderate-to-severe	Very often
Doxycycline	Moderate-to-severe	Often
Erythromycin	Moderate-to-severe	Less often
Azithromycin	Moderate-to-severe	Less often
Clindamycin	Moderate-to-severe	Rarely
Hormonal therapy		
Norgestimate	Moderate-to-severe	Less often
Cyproterone acetate	Moderate-to-severe with concomitant hormonal imbalances	Less often
Systemic retinoids		
Isotretinoin	Severe nodular acne	Very often

2.8 ISOTRETINOIN

Isotretinoin is an effective medication for the treatment of severe nodular acne. It has been labeled a miracle drug by many physicians and patients. This is because it is the only anti-acne agent able to target the various etiological factors associated with acne (3). However, since its release in the market it has been associated with some serious side effects. As a result, several guidelines and programs have been implemented to better prescribe this medication. The present section will describe isotretinoin's mechanism of action, its utilization, its effectiveness at maintaining long-term remissions, its relative cost compared to other anti-acne treatments, as well as its side effects.

2.8.1 MECHANISM OF ACTION

Isotretinoin is a systemic retinoid. Retinoids, which could either be synthetic or natural, are a family of compounds possessing functional properties of vitamin A. Retinoids are known to affect cellular growth (87,88), immune functions, tumor promotion, and malignant potential of cells (89).

Isotretinoin is actually a natural compound that circulates in the blood after a meal rich in vitamin A (90). It is administered orally and is usually absorbed in two to four hours, and is primarily transported by albumin in the plasma

(91). It has an elimination half-life of 10.4 to 29.5 hours (91). To date, the exact mechanisms through which isotretinoin mediates its therapeutic effects are unknown. However, it has been shown to induce a dramatic reduction in the size of the sebaceous glands, while being able to inhibit the production of sebum (3). It also has the ability to reduce the formation of comedones, and decrease the inflammation associated with acne (3).

2.8.2 ISOTRETINOIN UTILIZATION

According to the product monograph, isotretinoin is indicated for severe nodular acne (92). The recommended duration of an isotretinoin treatment is between 15 to 20 weeks (92,93).

Since its introduction in the market, isotretinoin's popularity in the treatment of dermatologic conditions has increased significantly. Fleischer et al. (94) used the National Ambulatory Medical Care Survey (NAMCS) to determine the demographics of patients with acne using isotretinoin, minocycline and tetracycline between 1990 and 1997. Out of the 35 million visits to the physician, isotretinoin was prescribed 5.8 million times (17% of the visits). Whites were 2.3 times more likely to being prescribed isotretinoin than blacks. It was suggested that this difference was due to the socioeconomic situation of blacks in the US. Interestingly, although women consulted 1.4 times more than men, men were 1.7 times more likely than women to receive

isotretinoin. This difference was not associated with the expense of the medication, but rather to the teratogenecity of the medication.

The results of the study above are likely to be different in countries with medication reimbursement programs, such as Canada. In such systems, the expense of the medication is no longer an issue. Thus, we would not expect to observe racial differences solely because of the cost of the medication. If differences did appear, then they would most likely be associated with cultural perceptions of the risk benefit ratio of treatment as well as perceptions of trust in physicians and the medical care system (95). Sex differences in the use of isotretinoin may be related to the teratogenecity of the medication. Therefore, physicians may be more reluctant to prescribe isotretinoin to women.

In a second study, Wysowski et al. (96) used two US pharmaceutical marketing research databases, the National Prescription Audit Plus and the National Disease and Therapeutic Index, as well as two health plan networks. A total of 19.8 million isotretinoin prescriptions were dispensed between 1982 and 2000. From 1983 through 1993, the median number of prescriptions was just over 800,000. Interestingly, between 1992 and 2000 there was a 2.5-fold increase in the median number of prescriptions dispensed. During the same period, the proportion of patients with severe

acne receiving isotretinoin declined from 63% to 46%. In contrast, the proportion of patients with mild and moderate acne increased from 31% to 49%. The authors interpreted this as a red flag, given that it is increasingly being prescribed outside of its intended severity. Others have become concerned over the use of isotretinoin for new off-label indications such as gram-negative folliculitis, recalcitrant rosacea, pyoderma faciale, generalized lichen planus, psoriasis, cutaneous lupus erythematosus and acne fulminans (97).

Isotretinoin is intended for patients with severe nodular acne or for those who have not responded to conventional therapy. However, Chen et al. (98) found that 39% of patients had not received any anti-acne medication in the six months prior to the first isotretinoin prescription as recommended by product guidelines. This is consistent with another study conducted by Wert et al. (92), where 47% to 72% of patients did not receive conventional therapies prior to initiating an isotretinoin treatment.

With the expiration of the patent held by the manufacturer of Accutane®, three generic forms of isotretinoin have entered the US market: Amnesteem® (November 2002), Sotret® (December 2002), and Claravis® (April 2003). These are expected to drive prices down, and further increase the use of

isotretinoin. As a result, it is likely that more individuals with mild-to-moderate acne or with other off-label indications will receive isotretinoin.

2.8.3 RATES OF ACNE RELAPSE

The effectiveness of isotretinoin at reducing acne lesions and preventing relapses has been documented in a number of observational studies. Seven of these studies were conducted in Europe (five in France and two in the United Kingdom [UK]) (99-105) , three in Asia (two in Singapore and one in the Philippines) (106-108), one in the Middle-East (Kuwait) (109), and only one in North America (US) (110). The relapse rates varied between studies, ranging from 5.6% to 65.4% (99-110). There are several possible explanations for this large discrepancy. First, these studies had small sample sizes, ranging between 52 and 299 patients (99-110). Second, some studies had short follow-up periods (105,106,108,109), and may have thus underestimated the relapse rate. Finally, relapse was not defined consistently across the different studies. A summary of these studies is presented in Table 4.

In 1986, Harms et al. (99) published a prospective cohort of 89 patients with severe acne recruited from a French dermatology clinic. Patients were followed for up to 47 months from the initiation of their isotretinoin treatment. A total of 13 (14.6%) patients relapsed during follow-up. Isotretinoin

cumulative dose was not found to be a predictor of acne relapse. Moreover, more males tended to relapse than females (16.6% versus 8.6%), while younger patients relapsed more frequently than older patients.

In another study, Chivot and Midoun (100) investigated 172 patients who underwent isotretinoin therapy in a French dermatology clinic. Patients were followed from a minimum of 12 to 41 months after the end of their isotretinoin treatment. A total of 37 (21%) patients experienced an acne relapse. The authors determined whether the following variables were predictors of acne relapse: patients' age, duration of acne prior to the treatment, total dose received, daily dosage, the duration of treatment, and acne severity. Only young age and severity of acne were predictive of acne relapse.

In 1993, Stainforth et al. (101) published the largest study to date. They investigated 299 patients who have been treated with isotretinoin in a dermatology clinic in the UK, and which were followed for up to five years after their treatment. Out of the 299 patients, 68 (22.7%) patients required at least a second course of the treatment during the follow-up period. Interestingly, 75% of those patients relapsed in the first 12 months and most only required an additional course of treatment. Patients who had received lower dose regimens (0.1 to 0.5 mg/kg), had severe acne, were females over the age of 25 at the time of the first treatment, and had a long history of acne

were more prone to repeat a course of isotretinoin. The authors did not perform any analyses to adjust for potential confounding factors.

Lehucher-Ceyrac and Weber-Buisset (102) conducted a prospective cohort study of 188 treated with isotretinoin at a dermatology clinic in France. Patients were followed for up to nine years from the initiation of the treatment. Patients were evaluated at regular intervals for signs of acne relapse. Patients underwent a new treatment course if the relapse resulted in an acne grade greater than two (considered the pre-nodular threshold). The authors categorized the outcome of the patients according to the following algorithm: 1) immediate, long-term remissions following one course of isotretinoin, 2) stable remissions after two to three courses of isotretinoin, and 3) partial remissions. A total of 111 (59%), 54 (29%), and 23 (12%) patients were categorized according to the algorithm above. There were statistical differences between the first and second groups with respect to age, sex, acne grade and duration of acne prior to the first isotretinoin treatment. The third group had a greater proportion of patients with microcystic acne and women with endocrinological problems than the other two groups.

In a smaller study, Layton et al. (103) studied 88 patients treated with isotretinoin to determine factors which might affect long-term outcomes.

Patients were recruited from a dermatology clinic in the UK and followed for up to 10 years after their isotretinoin treatment. To date, this is the study with the longest follow-up. A total of 21 (31%) patients experienced a relapse in their acne, and 96% of them did so with three years after the isotretinoin treatment. Twenty-three percent of all patients required a second isotretinoin treatment. The authors report that age, sex and duration of acne were not predictive of acne relapse. On the other hand, patients with truncal acne were at a greater risk of relapse than other patients. Cumulative dose was also a predictor of relapse, where those who received a cumulative dose of < 120 mg/kg were at a greater risk.

In a study conducted in a skin clinic in Singapore, Shahidullah et al. (106) investigated the case records of 250 patients with severe inflammatory and nodulocystic acne treated with isotretinoin. The authors collected data pertaining to the patients' demographics, response to isotretinoin, clinical follow-up, and relapse. Acne relapse occurred in 14 (5.6%) patients over a six-month follow-up period. Predictors of relapse were not reported by the authors.

In Kuwait, Al-Mutairi et al. (109) followed 160 patients with moderate-to-severe acne treated with isotretinoin. Patients were followed regularly for a period of 12 months after the end of the isotretinoin treatment. Relapse was

defined as having a reccurence of mild acne eight weeks after the end of the isotretinoin treatment. Patients were followed up regularly for a period of 12 months after stoppage of isotretinoin for any evidence of relapse. In the event of a recurrence greater than mild acne after eight weeks of stoppage of isotretinoin therapy, the patients were given another course of the drug. Patients were considered to be non-relapsing if they had no evidence of recurrence after 12 months of follow-up. Twenty seven patients were excluded from the study. Of the remaining 133 patients (51 male and 82 female) only 117 patients (36 male and 81 female) could follow up for at least 12 months after stopping therapy. Of the 133 patients, a total of 127 patients (95.5%) achieved complete or partial clearance. Forty two percent (total 49 patients: 20 male and 29 female) experienced relapse after stopping therapy. Of these, 21 (42.85%) were given a second course of the drug. None of the patients developed a rise in lipids levels significant enough to warrant stoppage of the drug.

Table 4. Acne relapse following an isotretinoin treatment

Authors	Year	Number of patients	Study design	Setting	Duration of follow-up	Relapse rate
Harms et al. (99)	1986	89	Prospective cohort	Dermatology clinic (France)	47 months	15%
Chivot and Midoun (100)	1990	172	Prospective cohort	Dermatology clinic (France)	41 months	21%
Stainforth et al. (101)	1993	299	Prospective cohort	Dermatology clinic (UK)	60 months	23%
Lehucher-Ceyrac and Weber-Buisset (102)	1993	188	Prospective cohort	Dermatology clinic (France)	108 months	42%
Layton et al. (103)	1993	88	Prospective cohort	Dermatology clinic (UK)	120 months	31%
Shahidullah et al. (106)	1994	250	Retrospective cohort	Dermatology clinic (Singapore)	6 months	6%
White et al. (110)	1998	179	Retrospective cohort	Kaiser Permanente data (US)	36 months	65%
Lehucher-Ceyrac et al. (104)	1999	237	Prospective cohort	Dermatology clinic (France)	60 months	48%
Ng and Goh (108)	1999	89	Retrospective cohort	Dermatology clinic (Singapore)	12 months	47%
Haryati and Jacinto (107)	2005	240	Retrospective cohort	Dermatology clinic (Philippines)	120 months	40%
Al-Mutairi et al. (109)	2005	160	Prospective cohort	Hospital (Kuwait)	12 months	42%
Quereux et al. (105)	2006	52	Prospective cohort	Hospital dermatology clinic (France)	12 months	52%

2.8.5 SIDE EFFECTS

Since isotretinoin is a vitamin A analogue, many of the side effects of this drug are similar to what is observed in hypervitaminosis A syndrome (3). Side effects of all sorts have been documented; mucocutaneous, ophthalmologic, neuromuscular, and elevations in plasma cholesterol and liver enzymes.

2.8.5.1 TERATOGENECITY OF ISOTRETINOIN

Before the launch of isotretinoin in the US market in 1982, its teratogenecity was well known based on animal studies (111). However, since isotretinoin was seen by many physicians as a cure for acne, it was a question of time until infants would be born after being exposed to isotretinoin in utero (112). The teratogenic effects of isotretinoin have been reported as early as 1983 by Rosa et al. (113), in which they described congenital abnormalities in four infants exposed early in gestation. Following that report, the FDA listed isotretinoin as a severe hazard during pregnancy (114). Despite the new FDA warnings, exposed pregnancies continued to occur (112,115,116).

2.8.5.1.1 WARNING SYMBOLS ON CAPSULES

In an effort to inform patients about the teratogenic risk of isotretinoin, the manufacturer of the drug used a warning symbol depicting the silhouette of a

pregnant woman covered by the symbol for "No". In 1989, isotretinoin packaging was changed from loose pills in a bottle to a blister pack, and the 'no pregnancy' symbol was placed behind every capsule (2). The goal of such a symbol was to inform non-pregnant women who were taking isotretinoin not to become pregnant while on treatment, or women who were pregnant not take the drug. Daniel et al. (117) were interested in determining patient interpretation of the symbol, and whether it had a place in a patient education program. They recruited 97 women from 10 different locations, and administered a questionnaire pertaining to the interpretation of the symbol. They found that only 21% of the women correctly identified the symbol. Twenty-seven percent responded the package contained birth control medication, and 24% said the package simply contained drugs. Moreover, seven percent said they did not know what the symbol meant. Alarmingly, 39% of respondents claimed there were circumstances in which the drug might be shared. This study illustrates that misinterpretation of warning symbols may potentially lead to serious consequences. The authors advocate that careful pretesting and modification of warning symbols should be done before they appear on drugs that have a teratogenic risk.

2.8.2.1.2 CONGENITAL MALFORMATIONS ASSOCIATED TO ISOTRETINOIN

There are several congenital malformations associated to isotretinoin exposure in utero. Since its marketing in 1982 in the US, and 1983 in

Canada, several reports have been published on its teratogenic effects. Table 5 below displays the main congenital malformations associated with isotretinoin-exposed pregnancies.

Table 5. Congenital malformations associated with isotretinoin exposure
Craniofacial malformations Frontal bossing (112) Microphthalamia (2,112,118) Cleft palate (112,118,119) Small mouth (112) Triangular microcephalic skull (118) Depressed midface (118) Depressed nasal bridge (119) Micrognathia (118,119) Confluent eyebrows (2) Unspecified craniofacial malformations (120-122)
Ear malformations Undifferentiated ears (112,118) Absent or imperforate auditory canal (118) Small ear canals (112) Anotia (123-125) Microtia (123,124) Unspecified ear malformations (2)
Cardiovascular malformations Congenital heart disease (112) Overriding aorta (118) Hypoplastic aortic arch (118) Septation defects of atria or ventricles (118,119) Abnormal subclavian arteries (118) Double-outlet right ventricle with dextrocardia (121) Unspecified cardiovascular malformations (118,120,124)
Central nervous system malformation Microcephaly (119,124,126) Hydrocephaly (112,124) Unspecified central nervous malformations (118,120,123)
Other malformations Limb reduction defect (118) Dandy-Walker malformation (112) Hypoplastic scrotum (2)

2.8.5.1.3 THE PREGNANCY PREVENTION PROGRAM

Since nearly 50% of all pregnancies in North America are unplanned (127), an inadvertent exposure to a teratogenic drug may lead to disastrous consequences. Therefore, to ensure a zero pregnancy tolerance while on isotretinoin, the manufacturer of the drug and the FDA jointly instituted the Pregnancy Prevention Program (PPP) in October 1988. The PPP instructs physicians that women of childbearing age should meet the following three conditions:

1. Signing of a consent form
2. Taking a pregnancy test seven days prior to initiation of the treatment
3. Using two forms of contraception simultaneously during and a month after the treatment, unless the patient claims she is not sexually active

Despite the implementation of the PPP, isotretinoin exposed pregnancies continued to occur (2,128). This is because there were no means of verifying that patients and physicians complied with the program. In 1992, Dai et al. (120) sought to determine the reasons for and outcomes of in utero isotretinoin exposure. They used spontaneous reports of isotretinoin-exposed pregnancies that were voluntarily submitted to the manufacturer of the drug (Hoffmann-La Roche Inc.) in the US from September 1982 to July 1989. The reports of 433 isotretinoin-exposed were obtained, but timing of conception in relation to isotretinoin exposure was known for only 396

women. Of these, 133 (33%) were already pregnant before isotretinoin therapy was initiated, and 65 (16%) patients became pregnant in the first three weeks of isotretinoin use. The authors also found that the rates of pregnancy while on treatment declined from 1982 to 1988. However, these were *reporting* rates and not absolute rates. The numerator was based on spontaneous reports, and thus did not reflect the true number of pregnancies that have occurred during the treatment. Furthermore, the denominator was calculated by projecting isotretinoin use among female patients between 12 and 44 years of age. Dai et al. (120) were able to obtain the pregnancy outcomes for 409 out of the 433 patients. Of these, 222 (54%) ended in elective termination, and 29 (7%) in spontaneous or missed abortion. There were 151 births; 72 (48%) were normal, 71 (47%) had congenital malformations, and eight (5%) had abnormalities other than malformations. There were 94 live births; 28% had congenital malformations.

In 1995, Mitchell et al. (2) from the Slone Epidemiology Unit were the first to assess the compliance of physicians and patients with the PPP. They enrolled women through their physician, by filling out a form in their medication package, or by calling a toll-free telephone number. As a means to increase participation, patients received $10 for taking part in the study. As such, this study was limited to those who accepted to participate, and therefore, these patients may have been inherently different from those who did not accept to participate. Furthermore, the physicians were asked to

encourage patients to participate in the study. This may have increased physician awareness of the study objectives, and thus it is possible that it had an impact on the implementation and compliance with the PPP. The same could be said about the patients who volunteered to participate in the study. Accepting to participate in the study may have also increased their awareness of the teratogenecity of isotretinoin. In addition, patients were contacted at the start of therapy as well as during the treatment. The authors acknowledged that these inquiries might have "*transformed the survey, which was intended to be observational, into a form of intervention*" (2).

Despite these limitations, this study remains a hallmark on the effectiveness of the PPP. Between 1989 and 1993, 177,216 eligible women were enrolled in the survey. For the 24,503 women interviewed within one month of enrollment, 99% revealed that they had been told to avoid pregnancy. Furthermore, 78% were told to wait for pregnancy test results and 63% to wait until the next menstrual period before starting isotretinoin, and 60% had a pregnancy test.

Mitchell et al. (2) found an overall pregnancy rate during isotretinoin of 3.4 per 1000 for a 20-week course of isotretinoin. Of the women who became pregnant during the treatment, they found that 72% had elective

terminations. Among the live births, the authors found that 38% had a congenital abnormality compatible with isotretinoin exposure.

In 2007, Bérard et al. (129) published a study on a cohort of 8609 women undergoing a first isotretinoin treatment between 1984 and 2003. The pregnancy rate during the treatment was 12.6 (95% CI 10.2, 15.4) per 1000 for a 20-week course of isotretinoin. This rate was nearly four times greater than the one reported by Mitchell et al. (2). A possible explanation for this large discrepancy between studies is the observational approach in the study conducted by Bérard et al., compared to the more interventional approach employed by Mitchell et al. (2). Interestingly, there were no reductions in the pregnancy rate after the implementation of the PPP in October 1988, indicating potential failures of the program at preventing pregnancies in this population. Finally, the rate of elective abortions was relatively high (84%), although the rate of congenital malformations was low (11%).

2.8.5.1.4 THE SMART PROGRAM

Because of the failure of the PPP to prevent isotretinoin-exposed pregnancies, the System to Manage Accutane Related Teratogenicity (SMART) program was implemented in April 2002 in the US. This program was aimed at improving the PPP by additionally requiring that two pregnancy tests be performed before initiation of treatment, while improving patient

education of the risks related to the treatment. In addition, the SMART program required yellow qualification stickers on all prescriptions. The qualification stickers were meant to be filled out by prescribers in order to ascertain that all female patients receiving isotretinoin are qualified (two negative pregnancy tests prior to treatment, and that they are using two forms of birth control). Pharmacists were instructed to fill only those prescriptions with qualification stickers (130).

Despite these new regulations, the performance of the SMART program was deemed suboptimal. In 2005, Brinker et al. (130) published a study in which 9% of women received a qualification sticker without taking a pregnancy test. Thirty-four percent of women failed to receive two pregnancy tests, and 54% did not use two birth control methods. Despite increasing patient awareness of the risks associated with an isotretinoin-exposed pregnancy, the SMART program did not significantly reduce the number of exposed pregnancies as compared to the PPP (130). Reasons cited for these failures include prescriber under-compliance with the program, lack of motivation from the patients, or the ability to use to two forms of contraception during the treatment (131).

2.8.5.1.5 THE IPLEDGE PROGRAM

The iPLEDGE program was implemented in March 2006 in the US. It is more stringent than its predecessor, the SMART program. iPLEDGE is a computer-based risk management program that was designed to further prevent isotretinoin-exposed pregnancies. Contrary to past programs, both male and female isotretinoin users must register online (www.ipledgeprogram.com) or by telephone. Furthermore, prescribers as well as wholesalers of isotretinoin must register in the database. Under the iPLEDGE program, prescribers must enter the results of two negative pregnancy tests, specify the two forms of contraception the patient agreed to use, perform monthly pregnancy tests, provide pregnancy prevention counseling, and identify at every month the patient's contraception choices. The patient on the other hand, must register in the database, sign a consent form, and identify their two forms of contraception on a monthly basis (which must match the prescriber's entries). Finally, pharmacists can only dispense isotretinoin when both prescriber and patient have met all system requirements. To date, the iPLEDGE program has not been formally evaluated.

2.8.5.2 MUCOCUTANEOUS SIDE EFFECTS

Many of the mucocutaneous side effects of isotretinoin are dose-dependent. It has been proposed that twice daily dosing regimens of the drug can decrease the appearance of side effects (132).

Cheilitis (inflammation and cracking of the skin of the lips) is one of the most common side effects of isotretinoin therapy, affecting close to 100% of patients (3). Interestingly, the absence of cheilitis during the treatment may be an indicator of non-compliance (132). Other mucocutaneous side effects have been reports of the thinning of the hair and increased brittleness of the nails. This occurs three to eight weeks into the treatment, but stops six to eight weeks after stopping the drug (133). In one study of 720 patients followed-up for a mean of 4.9 years, alopecia was reported in two (0.3%) patients only (134).

In a study evaluating 104 reports sent to Adverse Drug Reaction Reporting System between 1982 and 1985, 29/104 (28%) reports were related to mucocutaneous side effects (135). Because these were based on spontaneous reports, it was not possible to estimate the incidence of such complications. Between 1982 and 1987, McElwee et al. (136) prospectively followed 466 patients who were prescribed isotretinoin throughout a four- to

five-month course treatment. Nearly all patients (97%) were found to develop mucocutaneous side effects.

2.8.5.3 OPHTHALMOLOGIC SIDE EFFECTS

In addition to mucocutaneous side effects, isotretinoin can induce ophthalmologic conditions such as the drying of the ocular conjunctivae (134). It appears that isotretinoin decreases secretions from the meibomian gland just as it does with sebaceous glands (3). This results in the loss of the surface lipid layer over the corneal tear film and thus increases evaporation of basal tears and leads to dry eye syndrome. For this reason, the wear of contact lenses during the treatment is not recommended in order to avoid more serious complications (137). Dry eye syndrome may persist after isotretinoin discontinuation, although this occurs in only one percent of patients (134).

Fraunfelder et al. (138) investigated all types of ocular side effects that may be associated with isotretinoin exposure. They reviewed 1741 spontaneous reports that were sent to the manufacturer of the drug or found in literature and classified them according to the World Health Organization Causality Assessment Guide of Suspected Adverse Reactions. Symptoms or abnormalities were classified as either “certain”, “probable/likely”, “possible”, “unlikely”, or “conditional/unclassifiable”. Side effects that were classified as

"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. "Probable/likely" side effects included decreased color vision (reversible) and permanent loss of dark adaptation. Those that had a "possible" association included permanent keratoconjunctivitis sicca. Because these were derived from spontaneous reports, it is not possible to calculate the incidence of these ophthalmologic complications since there is no denominator. Egger et al. (139) prospectively followed 55 patients before, during and after an isotretinoin treatment. Staphylococcus aureus in the corneal sac was found in 7.3% of patients before initiation of treatment and increased to 61.8% during treatment. In addition, 40% developed blepharitis (inflammation of the eyelids), although all ocular side effects disappeared completely one month after stopping the treatment (139).

The studies above were limited by their designs and sample sizes. Since ocular side effects are rare events, large prospective studies would be needed to investigate the incidence of these complications.

2.8.5.4 NEUROMUSCULAR SIDE EFFECTS

Headache, fatigue and lethargy have been associated with isotretinoin therapy (3). It is recommended that isotretinoin therapy be discontinued if headaches become persistent, since they may be associated with papilledema (swelling around the optic nerve) and pseudotumor cerebri (intracranial hypertension). If that were the case, the use of concomitant drugs such as tetracyclines should be avoided (3). Some patients report more muscle pain while on isotretinoin. This is especially true for those who exercise regularly; gymnasts, competitive ice skaters, ballet students, and long distance runners (137). In a study of 466 patients who were followed throughout their isotretinoin treatment, 42% reported musculoskeletal side effects (136).

2.8.5.5 ELEVATION IN PLASMA LIPIDS AND LIVER SIDE EFFECTS

Elevations in plasma cholesterol and triglyceride levels are known to accelerate atherosclerotic disease, and induce eruptive xanthomas (irregular yellow nodules on the skin, usually the eyelids, neck and back) or acute pancreatitis (140). In the early 1980s, several studies found that isotretinoin may cause increases in plasma lipids and liver enzymes. In 1983, Zech et al. (141) studied 20 male patients treated with isotretinoin with an initial dose of two mg/kg/day. They measured plasma lipids and lipoprotein levels before and during the treatment. Isotretinoin induced elevations that were 67% greater for plasma triglyceride and 16% greater for cholesterol. Increases of

56% and 22% were found for very-low-density lipoprotein and low-density lipoprotein, respectively. Similarly, in a study of 60 patients, 17% had elevations in triglycerides, cholesterol, and low-density lipoprotein (142). This concurred with two other smaller studies; one of 18 patients (143) and the other of seven patients only (144). In another study of 30 patients, Georgala et al. (145) also found elevated levels of plasma lipids and liver enzymes in patients treated with isotretinoin. In addition, high-density lipoprotein levels were significantly reduced at the end of the treatment, prompting the authors to suggest that isotretinoin can be used as a lipoprotein reducing agent in the future (145). A major problem with the studies above is the small sample size. Furthermore, little is known about the long-term effects of isotretinoin on conditions compatible with elevated plasma cholesterol and triglyceride levels, although these studies found levels returned to baseline in the month following termination of treatment.

Because of the health risks elevations of plasma cholesterol and triglyceride levels may pose, isotretinoin guidelines have emphasized the importance of monitoring these levels throughout the treatment. However, the need for such routine tests has been a matter of debate. Barth et al. (146) conducted a retrospective analysis of 209 patients who had been treated with isotretinoin. They found significant elevations of triglycerides and plasma cholesterol at eight and 16 weeks, but pointed out that those with elevated plasma cholesterol had higher levels prior to initiation of treatment. As for

triglyceride levels, they reached their peak at eight weeks into the treatment, and did not increase thereafter. No significant change was observed for liver function. In another retrospective study of 1292 patients treated with isotretinoin, only 1.5% of patients were found to have abnormal triglyceride levels (147). Furthermore, no laboratory abnormalities necessitated discontinuation of the drug (147). Supporting these results, Altman et al. (148) found few statistically significant elevations in plasma lipids and liver enzymes in 141 patients treated with isotretinoin; only one patient had elevations that warranted discontinuation of the drug.

2.8.5.6 PSYCHIATRIC EFFECTS OF ISOTRETINOIN

The role of isotretinoin in the occurrence of depression, suicidal ideation, and suicide is a controversial issue that has received massive media attention. The debate has been fueled by case reports and case series linking isotretinoin to depression, and by signals detected in adverse reaction databases. The few controlled studies that have investigated the relationship found no association, but were dismissed because of methodological flaws. The present section will describe the current literature, and will end by describing the biological plausibility of such an association.

2.8.5.6.1 CASE REPORTS

A total of 11 case reports have been published from 1986 to 2005 (38,149-158), although one of them reported depressive mood changes in two-year old child treated with isotretinoin for nodulocystic acne (159). The first report was by Lindemayr (149). He describes the case of a subject who took 800 mg of isotretinoin and attempted suicide. However, it is unknown whether the subject attempted suicide because of isotretinoin intoxication, or whether isotretinoin intoxication was a means to attempt suicide. A similar case of isotretinoin intoxication was reported by Hepburn in 1990 (160).

In 1989, Villalobos et al. (151) reported a case in which isotretinoin induced hallucinations, paranoia, and incoherence. When isotretinoin therapy was discontinued, symptoms subsided. However, symptoms reappeared with readministration of isotretinoin. Other case reports have reported that discontinuation of isotretinoin therapy results to a return to normal functioning. These include a report by Cott and Wisner (161) in which a patient with a previous history of bipolar disorder experienced an exacerbation of her psychosis following administration of isotretinoin. She returned to her normal state after discontinuing the therapy. In a detailed report by Ng et al. (157), a 17-year old man is described having symptoms of acute depression two weeks after beginning an isotretinoin treatment. The depressive symptoms improved as the dose was reduced and the patient was treated with a selective serotonin reuptake inhibitor (SSRI). Interestingly,

the depressive symptoms worsened as the dose was increased. Despite an improvement in acne severity, the depressive symptoms led the patient to an unsuccessful suicide attempt.

Depression and suicidal ideation are not the only psychiatric effects reported in case reports. In 1999, Middelkoop (156) reported a patient with depression, but who also experienced withdrawn behavior and social impairment, decreased appetite, loss of interest, fatigue, as well as changes in personality and behavior. This patient committed suicide after four months on the treatment. It must be noted that the patient had no history of depression or family depression.

Based on case reports, depression may occur as early as one day (162) to four months (38) after the initiation of an isotretinoin treatment. Some may even experience symptoms of depression one month after completing the treatment regimen (153).

2.8.5.6.2 CASE SERIES

The first case series was published in 1983 (5), a year after isotretinoin was marketed in the US, and the same year it was introduced in Canada. Hazen et al. (5) reported depressive symptoms in six of 110 (5.5%) patients treated with isotretinoin one to two mg/kg per day. The average age of the cases was 28.5 years. The depressive symptoms were described as malaise, crying spells, and forgetfulness, all of which started two weeks after initiating the isotretinoin treatment. All except one patient completed the treatment.

In 1984, Bruno et al. (163) compared the toxicity of two isotretinoin dosage regimens in 94 patients with severe cystic acne. Patients in the low dosage group received isotretinoin dosages ranging from 0.1-0.22 mg/kg/day, whereas patients in the high dosage group received dosages ranging from 0.75-1.21 mg/kg/day. By the end of the 16-week treatment period, 11% of patients in low dosage group and 11% in the high dosage group reported depressive symptoms. The average onset of depressive symptoms in both groups was after one month of isotretinoin therapy. The authors did not observe a dose-related difference in the onset of depressive symptoms.

In 1988, Bigby and Stern (135) reviewed 104 suspected adverse reactions related to isotretinoin use that had been recorded in the Adverse Drug Reaction Reporting System between 1982 and 1985. Of the 104 reports, 23

(22%) were related to the central nervous system. These included reports of headache, depression, dizziness, personality disorder, and pseudotumor cerebri. Three cases were related to depression, where two appeared to have a temporal relationship with isotretinoin.

In 1990, Scheinman et al. (164) investigated 700 patients treated with isotretinoin who received the treatment for various conditions that included acne, basal cell carcinoma, and psoriasis. Seven patients (one percent) spontaneously reported having depressive symptoms. Symptoms included crying spells, fatigue, malaise, and forgetfulness. One patient (0.14%) reported suicidal ideation. When patients were dechallenged to the drug, the symptoms subsided within one week after termination and resumed after being rechallenged. Five of the seven patients were females, and two were males where their ages ranged from 22 to 47 years with a mean of 32 years. The average dose was 0.7 mg/kg/day. Five of the seven patients developed depression during a first course of isotretinoin therapy. Only two patients had a previous history of depression.

Duke and Guenther (165) published a case series on two adolescents who displayed depressive symptoms, irritability, disobedience, appetite and sleep disturbances. The first case is of a 15-year old girl who developed behavioral changes one month after initiating an isotretinoin treatment (40 mg/day).

Behavioral changes included cutting her hair off on one side of her head, personality changes, and left her home. She also developed sleep disturbances, irritability, and became withdrawn. She also threatened to cut her wrists and set her clothes on fire. Her behavior returned to normal after several months of being off isotretinoin. The girl had no history of depression prior to the initiation of treatment. The second case is of a 17-year old boy initially treated with 80 mg/day of isotretinoin, which was later reduced to 40 mg/day because of side effects. As with the first case, the boy developed behavioral changes one month after initiation of treatment. He displayed mood swings, depression, decreased appetite, weight loss and moved out of his parent's house. The physician terminated the treatment three months after initiation. The boy's symptoms returned to normal three days after the end of treatment. The boy had no history of depression prior to the initiation of treatment.

In 1998, Byrne et al. (166) reported about three patients, aged 18 to 28 years, who developed depression and related symptoms after initiating an isotretinoin treatment. The first is a female patient who exhibited depressed mood, irritability, aggression, agitation, decreased sleep, decreased appetite, reduced concentration, anhedonia, and early morning wakening. These symptoms eventually led to the breakdown of her marriage. She had no personal or family history of depression. Five weeks after isotretinoin was discontinued coupled with an antidepressant treatment, her symptoms

subsided. The second case pertains to a patient who attempted suicide while on isotretinoin. He had no personal or family history of depression. After discontinuation of isotretinoin and administration of an antidepressant there was an improvement in mood over four weeks. The third patient also developed depression and had suicidal tendencies during an isotretinoin treatment. Discontinuation of isotretinoin and treatment with antidepressants led to an improvement in symptoms.

A summary of the case reports and case series is presented in Table 6 below.

Table 6. Case reports and case series associating isotretinoin to depression

Type of publication	Year	Total number of cases	Number of depression cases	Number of suicide/ attempted suicide cases
Case reports				
Lindemayr (149)	1986	1	0	1
Burket and Storrs (167)	1987	1	1	0
Villalobos et al. (151)	1989	1	1	0
Hepburn (168)	1990	1	0	1
Gatti and Serri (153)	1991	1	0	1
Aubin et al. (169)	1995	1	0	1
Cotterill and Cunliffe (38)	1997	1	0	1
Cott and Wisner (170)	1999	1	1	0
Middelkoop (156)	1999	1	0	1
Ng et al. (157)	2001	1	0	1
La Placa (171)	2005	1	1	0
Case series				
Hazen et al. (5)	1983	6	6	0
Bruno et al. (172)	1984	22	22	0
Bigby and Stern (135)	1988	3	3	0
Scheinman et al. (164)	1990	8	7	1
Duke and Guenther (165)	1993	2	1	1
Byrne et al. (166)	1995	3	2	1

2.8.5.6.3 ADVERSE DRUG EVENT REPORTING SYSTEMS

Adverse drug event reporting systems (ADERS) represent another source of information regarding the association between isotretinoin and depression. ADERS are databases maintained by governments that receive drug-related adverse event reports. Because such reports are voluntary, these databases underestimate the true frequency of adverse events related to a particular drug. Furthermore, their value is diminished when the baseline rate of an outcome is high. Causality is often impossible to establish since both the adverse event and drug exposure are reported at the same time. In addition, spontaneous reports often lack consistency which limits their interpretability. Despite these limitations, adverse events recorded in ADERS may point to a potential signal that may warrant further investigation. The following section will review adverse events reported to the World Health Organization (WHO), the UK Medicines Control Agency (MCA), the Adverse Event Reporting System (AERS) of the FDA, and the Canadian ADERS.

In 1999, Middelkoop (156) investigated the relationship between six anti-acne medications and suicide, suicide attempt, and suicidal ideation using the WHO and the UK MCA ADERS. The six medications were isotretinoin, minocycline, doxycycline, tetracycline, ethinyl estradiol/cyproterone acetate, and oxytetracycline. From 1965 to 1998, there were 170 cases of suicide, suicide attempt, and suicide ideation related to isotretinoin reported to the WHO ADERS, compared to a total of eight reports for the other anti-acne

medications. There were 47 cases of suicide, 67 suicide attempts, and 56 suicidal ideations. The numbers were even more dramatic in the UK MCA ADERS, where virtually all reports of suicide, suicide attempt, and suicidal ideation were related to isotretinoin despite the smaller number of prescriptions (Table 7).

Table 7. Cases of suicide, suicide attempt, and suicidal ideation reported in UK MCA ADERS (156)*					
Medication	**Number of prescriptions**	**Total**	**Suicides**	**Suicide attempts**	**Suicidal ideation**
Isotretinoin	12,400	23	9	8	6
Tetracycline	147,237,000	0	0	0	0
Oxytetracycline	31,301,700	0	0	0	0
Minocycline	8,802,900	0	0	0	0
ethinyl estradiol/cyproterone acetate	1,214,000	0	0	0	0
*From February 1993 to July 1999.					

In 2001, Wysowski et al. (173) analyzed reports of depression, suicidal ideation, suicide attempt, and suicide in US isotretinoin users that were voluntarily submitted to the FDA's AERS database from the time of its marketing in 1982 to 2000. A total of 431 reports were found, that included both hospitalized and non-hospitalized cases.

One hundred one cases were hospitalized for depression, suicidal ideation, suicide attempt, and suicide. Of those, 85 were hospitalized while using isotretinoin and 25 after stopping the medication. The median time of onset of symptoms in those who were currently using isotretinoin was one month from the start of therapy. In those who stopped isotretinoin, the median time of onset of symptoms was three months. There were 284 non-hospitalized cases, where 128 (45%) reports were received after suicide and depression were added as warnings on the product labeling in 1998. The authors did not specify the median time of onset of symptoms in non-hospitalized cases. Thirty-seven cases were reported to have committed suicide, 24 while using isotretinoin and 13 after stopping the treatment. Using data mining techniques, only six reports of suicide were expected compared to the 37 reported (173).

In comparison to all medications in the AERS database, isotretinoin was ranked fourth and fifth in the number of reports of depression and serious

depression, respectively (173). It was also ranked tenth in the number of reports of suicide attempt. The authors noted that of all top ranked medications, isotretinoin was the only one not to have psychoactive properties and a psychiatric indication.

In Canada, Wooltorton (174) reported that there has been 222 adverse events reported to Health Canada from 1983, the year isotretinoin was marketed in Canada, up to 2002. Of those, 56 (25%) were psychiatric and included depression and suicidal ideation.

2.8.5.6.4 PACKAGE LABEL CHANGES AND OTHER WARNINGS

The case reports, case series, and signals detected in ADERS have prompted several governments to modify the isotretinoin package labeling to include psychiatric events as potential side effects. In March 1997, France was the first to modify their label which specifically mentioned depression and suicide (175). The US modified their packaging label in February 1998, followed by Canada in May 2000 (176). In March 2001, a Dear Health Care Professional Letter was sent to Canadian physicians (177). This letter advised physicians to closely monitor patients undergoing isotretinoin therapy for psychiatric symptoms during the course of the treatment (177).

2.8.5.6.5 OBSERVATIONAL STUDIES

Several observational studies have been conducted to determine whether there was an association between isotretinoin and depression. The majority of these studies were either uncontrolled, had small sample sizes, or suffered from other methodological problems. These observational studies are reviewed in the present section. A summary of these studies is also presented in Table 8.

In 1999, Kellet and Gawkrodger (31) conducted a prospective study on 34 patients with chronic acne undergoing isotretinoin therapy (one mg/kg/day). These patients were recruited by a consultant dermatologist in an outpatient clinic. Patients were followed for 16 weeks, and their emotional status was determined at four different points in time during the treatment (T1-T4). The authors used the Hospital Anxiety and Depression Scale (HAD) to measure anxiety and depression. Clinically significant depression is defined as having a HAD score greater than 10. At T4, only 15 patients responded to questionnaires. The authors found an improvement in depressive symptoms in patients treated with isotretinoin. Specifically, there were 6/34 (18%) patients with a HAD score greater than 10 at baseline compared to 0/15 (0%) at the end of treatment. Thus, the authors concluded that isotretinoin does not cause depressive symptoms, and in fact, it is associated with an improvement of such symptoms. However, this study does have several limitations. The first is the small sample size. The authors did not have the

necessary power to capture rare psychiatric events. Second, only 15 out of the initial 34 patients completed the study, which translates to a 56% drop out rate. The authors did not state any reason why patients dropped out of the study. The study may be biased if patients dropped out of the study because they experienced the outcome. Third, the authors only presented unadjusted analyses. No attempt was made to control for possible confounders that could have potentially biased the results. Finally, the isotretinoin cohort was not compared to another cohort treated with an agent known to have no psychiatric effects. Thus, rates of depression among patients receiving isotretinoin could not be compared with patients receiving an alternative treatment.

In 2000, Hull and Demkiw-Bartel (178) published a study where they prospectively followed 124 users of isotretinoin from 1991 to 1996 for any type of side effect. Patients were treated for 16 weeks at one mg/kg per day and a questionnaire was administered monthly to record any side effects that may appear during the treatment. The majority of patients had mucocutaneous or musculoskeletal side effects. Only four percent of patients reported depression, although symptoms were reported to remain consistent throughout the treatment. This study was limited by its small sample size. It was also limited in that it only recorded reports of depression, and did not enquire about suicide attempts or suicides during and after the treatment.

Finally, there was no comparator group to which rates of depression could be compared.

To date, Jick et al. (179) conducted the largest population-based study on the isotretinoin-depression association. Data were obtained from two databases, the Canadian Saskatchewan Database and the United Kingdom General Practice Research Database (GPRD), from 1983 to 1997. The Canadian Saskatchewan Database contains over one million people who benefit from health care coverage in the province of Saskatchewan. The GPRD on the other hand, has in its banks over four million people. General practitioners who have agreed to provide data for research purposes continuously enter patient data through a computerized system.

The authors determined the rates of depression, psychotic symptoms, suicide and suicide attempts using two cohorts, one from the Saskatchewan database and one from the GPRD. Two analyses were conducted on each cohort. In the first analysis, a cohort of patients treated with isotretinoin (7195 from the Saskatchewan database, and 340 from the GPRD) was compared to a cohort of patients treated with systemic antibiotics (13700 from Saskatchewan database, and 676 from the GPRD). The systemic antibiotics included tetracycline, erythromycin, clindamycin, minocycline, or doxycycline, received within 30 days following an acne diagnosis. Patients were

categorized as either being currently exposed, recently exposed, or non-exposed. Patients currently exposed were defined as those receiving isotretinoin or a systemic antibiotic from the first prescription through three months after receiving the last prescription. Recent users were defined as those who received their last prescription four to six months before. Non-exposed patients were those who received their last prescription more than six months before. Cases of depression, suicide or suicide attempts were defined using diagnostic codes (International Classification of Diseases, ninth revision (ICD-9): 296-301). The authors calculate relative risks (RR) by comparing cases of depression, suicide or suicide attempts in the currently exposed and recent users groups to the non-exposed group. In the second analysis, isotretinoin users were evaluated by comparing rates of neurotic and psychotic disorders in the six months after the first prescription to the six months before the prescription.

In the Saskatchewan database, RRs (95% confidence interval [CI]) of neurotic and psychotic disorders in current and recent isotretinoin users were 1.0 (0.7, 1.3) and 0.9 (0.6, 1.4), respectively. RRs (95% CI) of suicide and attempted suicide in current and recent isotretinoin users were 0.9 (0.3, 2.4) and 1.1 (0.2, 3.7), respectively. In the GPRD, RRs (95% CI) of neurotic and psychotic disorders in current and recent isotretinoin users were 1.8 (0.4, 5.2) and 1.8 (0.3, 6.1), respectively. There was only one suicide attempt in the GPRD, and that patient was unexposed. In the Saskatchewan database,

RRs (95% CI) comparing post- to pre-treatment rates of neurotic and psychotic disorders were 1.2 (0.9, 1.7) in current users and recent users 1.0 (0.6, 1.5). In the GPRD, the RRs (95% CI) were 1.3 (0.2, 5.7) in current users and 1.1 (0.2, 5.7) in recent users.

The authors of the study described above concluded that isotretinoin users were not a greater risk of depression or psychosis than systemic antibiotic users. Although this was a large population-based study, it does have several limitations. The first limitation was that cases were identified using diagnostic codes alone. Therefore, it is possible that some cases were misclassified as non-cases. The authors did not take into account the use of psychoactive medications, such as antidepressants. The result is a bias of the RRs towards the null, possibly explaining the lack of association observed in this study. Others have also criticized the study for not including ICD-9 codes 309 (adjustment reactions) and 311 (depressive disorder, not classified elsewhere) (180). Second, the authors adjusted for previous psychiatric history using data recorded six months up to five years before the first isotretinoin prescription. It is possible that they did not capture all psychiatric events that have occurred, especially in those with less than one year recorded medical history. Therefore it is likely that some residual confounding occurred, which would have once again biased the RRs towards the null. Third, the authors did not consider dosage or duration of the isotretinoin in their models. Thus, it is unknown whether there is a dose-

response relationship between isotretinoin and psychotic disorders, depression or suicide. Fourth, the authors did not attempt to adjust for acne severity, which is a potential confounder of the isotretinoin-depression association. Fifth, the point estimates of the RRs in the GPRD were higher than in the Saskatchewan database. In fact, the RRs in the GPRD were 1.8 in current and recent users of isotretinoin, indicating an 80% increase in risk. Aside from the methodological problems mentioned above, the lack of statistical significance of these estimates may also be due to a lack of power due the small sample size of the GPRD cohort (n=340). Finally, this study was criticized for being sponsored by the manufacturer of the drug (181).

In 2001, McLane et al. (182) published a study where they evaluated 14 adverse events in patients participating in two isotretinoin trials. The first trial consisted of 67 patients who received isotretinoin one mg/kg/day as a single dose with food for 16 to 20 weeks. Patients were asked to grade the severity of adverse events using a 10 cm visual analog scale (VAS). The second trial consisted of 300 patients who received isotretinoin one mg/kg/day in two equally divided doses and followed for 20 weeks. Patients used a VAS to rate the severity of adverse events. No patient in the first trial reported any psychiatric problems, while 0.3% reported experiencing psychiatric problems in the second trial. The authors provide no other information, and do not describe the type of psychiatric disorders experienced by their patients.

Furthermore, this study had small sample sizes and did not compare the isotretinoin cohorts to other groups.

From December 1998 to March 2000, Ng et al. (183) prospectively followed 215 patients who were prescribed isotretinoin or antibiotics/topical treatments. The isotretinoin group (n=174) received 40 mg/day, followed by a one mg/kg/day increase for one month according to patient tolerability. Patients in the antibiotic/topical treatment group (n=74) received 100-200 mg/day of minocycline combined with a topical treatment of either adapalene 0.1%, tretinoin 0.05% or isotretinoin 0.05% gel. Patients were evaluated for depressive symptoms using the 21-item Beck Depression Inventory (BDI), and quality of life using the World Health Organization Quality of Life 100-item questionnaire (WHOQOL-BREF). Assessments were performed at baseline, one month, three months and at end of treatment or six months. The mean change in BDI scores did not significantly differ between the isotretinoin and minocycline/topical treatments groups. There were also no changes in quality of life scores between the two treatment groups. The incidence of isotretinoin patients with moderate depressive symptoms remained relatively the same throughout the treatment, and there was no correlation between isotretinoin dose and depression score (183). Although this is a well-conducted study, the authors acknowledged that it is limited by its small sample size. Interestingly, five patients from the isotretinoin group were withdrawn from the study because of worsening of mood. This did not

occur in the minocycline/topical treatments group. The authors dismissed any association between these mood changes and administration of isotretinoin.

In 2003, Hersom et al. (184) published a study investigating the prescription order of isotretinoin and antidepressants among incident users of both drugs. They employed the sequence symmetry method which works by calculating the ratio (adjusted risk ratio) of the number of patients who filled an isotretinoin prescription first versus second to an antidepressant. Their data was collected from the Quintiles Informatics Database from 1999 to 2000, and included 2821 patients aged 12 to 49 years of age. Patients were categorized into two groups: the causal group and the non-causal group. The causal group was composed of patients who received an isotretinoin prescription first and an antidepressant second. Similarly, the non-causal group was composed of patients who received an antidepressant first and isotretinoin second. A risk ratio is calculated by dividing the number of patients in the causal group to the number of patients in the non-causal group. The authors also performed a prescription sequence analysis using minocycline, a systemic antibiotic used in the treatment of acne known to have no psychiatric effects. The authors found no asymmetries between the casual and non-causal group, indicating that there is no association between isotretinoin and depression. As expected, the same results were obtained for minocycline.

The prescription sequence symmetry analysis is a variant of the case-crossover analysis, where cases serve as their own controls thereby automatically adjusting for time-dependent confounders (185). However, an inherent assumption of this study design is that medications must have a clear indication. This is not the case in the study conducted by Hersom et al. (184). Antidepressants are increasingly being prescribed for conditions other than depression. They include premenstrual dysphoric disorder, obesity, and smoking cessation (186). Thus, it is possible for a person to be treated with an antidepressant for smoking cessation, then undergo an isotretinoin treatment for acne, develop depression and require a new antidepressant treatment. Such a patient would be excluded from the discordant pair analysis because an antidepressant prescription preceded and followed the isotretinoin prescription. The failure to include this patient in the causal group would dilute the risk ratio towards the null.

In 2004, Ferahbas et al. (187) published a study of 45 patients with severe acne recruited by a consultant dermatologist in an outpatient clinic. Patients were treated with 0.5 to one mg/kg/day of isotretinoin for up to 16 weeks. Anxiety was measured using the Clinical Anxiety Scale and depression with the Montgomery-Asberg Depression Rating Scale. Both questionnaires were administered before and after treatment. Only 23 (51%) of patients completed the final assessment. The authors found a statistically significant decrease in anxiety scores, whereas depression scores also decreased but

did not reach statistical significance. The authors also reported that no patients attempted nor committed suicide. This study has several important limitations. No real conclusions can be drawn based on the small sample size. Furthermore, only 23 patients completed the final assessment. It is possible that those who experienced psychiatric effects withdrew from the study, which would have overestimated the positive psychological impact of isotretinoin in the remaining sample. Finally, there was no comparison group to which the anxiety and depression scores could have been compared.

Kellet and Gawkrodger (188) recruited 33 patients who consulted a dermatologist during routine clinical practice. The patients had not responded to conventional acne therapy. They were administered the 21-item BDI and the 20-item Beck Hopelessness Scale (BHS) at baseline, eight weeks (half-way through the treatment), and at the end of the 16-week treatment. Twenty-two (67%) patients completed the final assessment. At eight weeks into the treatment, patients displayed improvements in depressive symptoms compared to baseline. These improvements were not observed during the second phase of the treatment.

From October 1998 through December 2001, Chia et al. (189) recruited 132 patients with moderate-to-severe acne aged 12 to 19 years from two outpatient clinics. All patients with a history of major depression were

excluded from the study. Patients were assigned to either an isotretinoin therapy (one mg/kg/day) or a topical antibiotic or topical retinoid and a systemic antibiotic. Patients were not randomized to the treatment options, but rather the allocation of treatment was based on the physician's assessment of the patient's clinical history of acne. Depressive symptoms were recorded at baseline, and three to four months after initiation of therapy. Depressive symptoms were assessed using the 20-item Center for Epidemiologic Studies Depression Scale (CES-D). A score greater than 17 is indicative of clinically significant depression. One hundred one patients completed the study. At baseline, 14.3% of the isotretinoin group and 19.2% of the standard therapy group had a CES-D score greater than 17. At follow-up, 8.2% of the isotretinoin group and 15.4% of the standard therapy group had a CES-D score greater than 17. This difference was not statistically significant. The results of this study appear to indicate that there is no association between isotretinoin and depression. Furthermore, it appears from these results that isotretinoin may have beneficial effects in reducing symptoms of depression in patients with moderate-to-severe acne. However, a careful look into the methods employed in this study reveal several methodological problems. First, the sample size appears to be too small to detect cases of clinically significant depression. Second, there was a 23% loss to follow-up, and it is unknown whether this might have been related to the outcome. That is, those who experienced a clinically significant depression may have stopped their treatment and withdrawn from the study.

Furthermore, the authors fail to indicate which treatment groups lost the most patients, and only provide percentages and no raw data in their results. Third, the authors conducted multiple logistic regressions controlling for baseline CES-D and sex. They did not consider acne severity in their models, despite it being a potential confounder.

In 2007, Cohen et al. (190) published a study of 200 patients at least 14 years of age recruited from a community dermatology practice who were treated with either isotretinoin or other anti-acne agents. One hundred patients were treated with isotretinoin, and the remaining 100 were treated with either topical or oral agents. Depression was measured using the Zung Depression Status Inventory and the CES-D at baseline, and after 2 months into the treatment. The authors found no association between isotretinoin and depression. However, this study had several important limitations. First, the authors did not provide any sample size calculations, and it thus unknown how they derived their sample size. Second, it is unclear that the analyses were adjusted for potential confounders, such as age, sex, socio-economic status. Finally, depression was measured at baseline and two months into the treatment. It is possible patients experienced depression at a subsequent time in their treatment.

Table 8. Summary of observational studies on the association between isotretinoin and depression

Observational studies	Year	Study design	Number of isotretinoin users	Comparison group	Observation period	Main findings
Kellet and Gawkrodger (30)	1999	Prospective cohort	34	None	16 weeks	No patient had clinical depression at 16 weeks
Hull and Demkiw-Bartel (178)	2000	Prospective cohort	124	None	16 weeks	4% reported depression, although that estimate remained constant throughout the treatment
Jick et al. (179)	2000	Retrospective cohort	7195 (Saskatchewan) 340 (GPRD)	13700 antibiotic users (Canada) 676 antibiotic users (GPRD)	12 months from initiation of isotretinoin treatment	No increased risk of psychosis, suicide or suicidal ideation in isotretinoin users compared to antibiotic users
McLane et al. (182) (Trial 1)	2001	Prospective cohort	67	None	16-20 weeks	No psychiatric effects reported
McLane et al. (182) (Trial 2)	2001	Prospective cohort	300	None	20 weeks	0.3% reported psychiatric effects
Ng et al. (183)	2002	Prospective cohort	215	Minocycline/topical treatment	End of treatment or 6 months	No change in depressive symptoms or quality of life during treatment
Hersom et al. (184)	2003	Retrospective cohort	2821	Self-matched analysis	12 months before and after isotretinoin prescription	Adjusted risk ratios were not statistically greater than 1.0

Table 8. Summary of observational studies on the association between isotretinoin and depression (continuation)

Observational studies	Year	Study design	Number of isotretinoin users	Comparison group	Observation period	Main findings
Ferhabas et al. (187)	2004	Prospective cohort	45	None	16 weeks	Decrease in anxiety scores, and trend toward lower depression scores
Kellet and Gawkrodger (188)	2005	Prospective cohort	33	None	16 weeks	Improvement in depressive scores half-way through the treatment. Effect was not observed during second part of the treatment
Chia et al. (189)	2005	Prospective cohort	59	Topical antibiotic, topical retinoid and systemic antibiotic	Up to 16 weeks	No association between isotretinoin and depression. Their data suggests that it may even be protective of depression.
Friedman et al. (191)	2006	Retrospective cohort	1149	Subjects with psoriasis	5 years	Subjects exposed to isotretinoin were greater users of mental health services than psoriasis sufferers
Cohen et al. (190)	2007	Prospective cohort	100	Topical or oral therapy	2 months after initiation of treatment	No association between isotretinoin and depression.

2.8.5.6.6 BIOLOGICAL PLAUSIBILITY

Since isotretinoin and Vitamin A share similar chemical structures, many side effects of isotretinoin are similar to Vitamin A when taken in large doses (192). Hypervitaminosis A has been shown to induce irritability and depressive symptoms (133,193,194). One study found that exposure to retinoic acid results in hippocampal cell loss in mice (195). In humans, hippocampal volume has been shown to be inversely related to depression (196), indirectly supporting the hypothesis that isotretinoin may cause cell loss in this region of the brain. Another study found that daily intake of one mg/kg of isotretinoin for six weeks in young male mice (similar doses used in humans) was associated with depression-like behavior (197). Recently, Bremner et al. (198) assessed brain function in patients with acne treated with isotretinoin and antibiotics. They found that isotretinoin decreased metabolism in the orbitofrontal cortex, a region of the brain known to be involved in depression. This effect was not observed in patients treated with antibiotics. More research is needed to elucidate the exact mechanisms through which isotretinoin may induce depression.

2.8.6 COSTS

Because acne can be treated with a number of therapeutic treatments, it is informative to compare the cost of isotretinoin to that of other treatments. Along with this line of thinking, we must look at the short- and long-term costs of such treatments. In one study of 180 patients with severe acne not treated with isotretinoin, the authors calculated the costs of all drugs, investigations, physician visits and loss productivity over a one-year period. They found that the average total cost of non-isotretinoin treatments was 69% of the theoretical cost with isotretinoin (199).

Although isotretinoin may be more costly in the short-term, one must also look at the costs in the long-term. Because isotretinoin is able to maintain long-term treatment free remissions and permanent remissions (103,110), it would be expected to save costs in the long-term. An Australian study estimated the theoretical costs of treating patients over 2.5 years either with isotretinoin or with systemic antibiotics combined with two topical agents (200). The costs investigated included drugs, investigations and physician visits. They found that antibiotic therapy would have cost 35% more than isotretinoin over a 2.5-year period. However, the authors assumed there were no further courses of isotretinoin therapy after an initial course of treatment. Therefore, the long-term costs associated with isotretinoin may be

have underestimated in this study since it has been shown that over 23% of isotretinoin users require at least two courses of the drug (101).

Cunliffe et al. (201) investigated the actual costs over a three-year period for 364 patients treated with isotretinoin. These costs were compared to the long-term theoretical costs associated with systemic antibiotic therapy over the same time period. The theoretical costs included the price of the therapy, hospital visits and investigations. The mean three-year costs of an isotretinoin treatment were £732 for patients with moderate acne, and £803 for patients with severe acne. These costs included patients who required repeat courses of isotretinoin during the study period. In contrast, the mean theoretical costs associated with systemic antibiotic use were £1520 for patients with moderate acne, and £1856 for patients with severe acne.

Cost analyses of isotretinoin have been criticized for failing to measure the cost of important factors associated with the drug (202). Since isotretinoin can have a teratogenic effect on the fetus, women on the drug are subjected to pregnancy tests prior and during the treatment, contraceptive counseling, diagnostic techniques (such as ultrasound), genetic counseling for women with exposed pregnancies, termination costs for women who elected to remove the fetus, diagnostic tests to determine the health of live births following an exposed pregnancy, and of course life-time health costs for

babies born with major malformations (202). However, it has also been argued that the costs of avoiding pregnancy while using isotretinoin are not likely to be important factors (203). This is because many female patients would be using a form of contraception anyway and many isotretinoin patients are males and thus would not need to go through pregnancy prevention measures (203).

CHAPTER 3: OBJECTIVES AND HYPOTHESES

3.1 OBJECTIVES STUDY 1

The objectives of Study 1 were to:

1. Describe the patterns and trends of isotretinoin utilization between 1984 and 2003.
2. Describe the characteristics of isotretinoin users within that same time period.
3. Identify and quantify predictors of isotretinoin use.
4. Describe the impact of guidelines on isotretinoin utilization between 1984 and 2003.

3.2 HYPOTHESES STUDY 1

Previous US studies that have investigated the use of isotretinoin found that most treatments were initiated without prior consideration of conventional treatments. We hypothesized a similar situation in Quebec, especially since our study population was insured for their medications by the RAMQ drug plan, and thus had a relatively easy access to isotretinoin. We hypothesized however, that the different guidelines and programs implemented over the years would have an impact on prescribing patterns.

3.3 OBJECTIVES STUDY 2

The objectives of Study 2 were to:

1. Determine the incidence of patients initially treated with isotretinoin experiencing an acne relapse as defined by requiring further treatment with an anti-acne medication (either a second isotretinoin treatment or another anti-acne medication).
2. Identify and quantify predictors of experiencing an acne relapse.
3. Identify and quantify predictors of receiving a second isotretinoin treatment.

3.4 HYPOTHESIS STUDY 2

Several studies have determined the rate of acne relapse in patients initially treated with isotretinoin. However, these studies had several limitations, all of which were described in Section 2.8.3. As a result, the acne relapse rates reported in these studies may not have been accurate, and in some cases underestimated. Given that we assembled the largest isotretinoin cohort to date, followed for up to 20 years, we hypothesized a relatively high acne relapse rate in patients initially treated with isotretinoin.

3.5 OBJECTIVE STUDY 3

The objective of Study 3 was to determine whether there is an association between isotretinoin use and depression in patients with acne vulgaris.

3.6 HYPOTHESIS STUDY 3

Case reports and adverse reaction databases have signaled a possible association between isotretinoin and depression. Observational studies conducted on the subject found null results, but had several methodological limitations. Based on reports of depression in patients with no personal or family history of the condition, and reports of positive dechallenge and rechallenge to isotretinoin, we hypothesized that there is an association between isotretinoin use and depression.

3.7 OBJECTIVE STUDY 4

The objective of Study 4 was to use the case-time-control design to determine whether an exposure time-trend confounded the association between isotretinoin and depression.

3.8 HYPOTHESIS STUDY 4

Using a case-crossover design, we found an association between isotretinoin and depression. However, an association derived from the case-crossover design may be biased if there is an underlying exposure time-trend. To account for this possibility, we performed a case-time-control study. In theory, this design should correct for any exposure time-trend that may have confounded the association in the case-crossover design. Since the point estimates obtained in the case-crossover design were relatively high, we hypothesized that an exposure time-trend could not account for all of the association.

CHAPTER 4: METHODS

4.1 DATA SOURCES

4.1.1 RAMQ DATABASES

In Quebec, the Régie de l'Assurance Maladie du Québec (RAMQ) is the government body that administers the province's health-related matters. All healthcare services (other than hospitalizations) are recorded in the RAMQ administrative databases, which are composed of a set of claims files. The medical claim file contains patient characteristics (including age, gender, and place of residence), prescriber information (including age, gender, medical specialty, year of graduation, and place of graduation), and data regarding outpatient medical visits (this includes services received in emergency rooms). It also includes information on the date and type of services received, and diagnoses are classified according to the International Classification of Diseases, Ninth revision (ICD-9) (204). The pharmaceutical claims file contains information on the date a medication is dispensed, formulation, dose, duration of prescription, as well as quantity dispensed. It also includes the subjects' insurance status, whether they are welfare recipients or adherents to the RAMQ drug plan. Medications prescribed during hospitalizations are not included in the database. Prior to January 1, 1997, the RAMQ covered those who were 65 years and older, and welfare recipients and their children for their medications. After January 1, 1997, the RAMQ drug plan was modified to also include workers and their spouses/children who did not have access to a private medication insurance

program (adherents). Approximately 50% of all Quebec residents are covered by the RAMQ drug plan (205). All RAMQ claims files can be linked via an encrypted patient identification number. Both the medical and pharmaceutical claims databases have been validated and shown to be accurate for certain diagnoses (206,207).

4.1.2 MED-ÉCHO DATABASES

Med-Écho (Maintenance et Exploitation des Données pour l'Etude de la Clientèle Hospitalière) is Quebec's hospital discharge database that has been in place since 1980. It contains hospitalization-specific data on all Quebec residents. The database includes patient demographic information (age and sex), admission diagnosis, up to 15 secondary diagnoses, duration of stay, dates of admission and discharge, type of hospital where the services were rendered, as well as all services received during the hospitalization (this excludes services received in emergency rooms and outpatient clinics). All diagnoses in Med-Écho are coded according to the ICD-9 classification system (204). Medical diagnoses recorded in Med-Écho have been shown to be valid and precise (208). The RAMQ and Med-Écho databases can be linked using the patient's encrypted identification number.

4.2 STUDY POPULATION

The study population for the four studies described in this thesis was composed of all Quebec residents insured by the RAMQ drug plan who received at least one isotretinoin prescription, in either the 10 mg or 40 mg formulation (drug identification numbers 582344 and 582352, respectively), between January 1, 1984 and December 31, 2003. A total of 30,496 Quebec residents insured by the RAMQ drug plan were exposed to isotretinoin at least one during the study period.

Approval was obtained from the CHU Sainte-Justine Ethics Committee (Appendix I) and the Commission d'accès à l'information du Québec (Appendix II).

4.3 METHODS FOR STUDY 1

4.3.1 STUDY COHORT

The cohort for Study 1 was selected from the study population described in section 4.2. To be included in Study 1, subjects had to be between 13 and 45 years on the first day of the first isotretinoin prescription. These ages were chosen because isotretinoin is primarily prescribed during this age range. Subjects were also required to be continuously insured by the RAMQ drug plan for at least 12 months before and at least six months after the first day of the first isotretinoin prescription. This was deemed an appropriate time window to assess the use of healthcare services and medications, which are important markers of comorbidity. Furthermore, an isotretinoin treatment typically lasts between four and five months (93), and thus six-month coverage after the first prescription would ensure that subjects would be covered for their medications during the isotretinoin treatment. Finally, all subjects who received an isotretinoin in the 12 months prior to index date were excluded. Therefore those included in this study were considered incident users of isotretinoin. In the event that a subject had more than one isotretinoin treatment fitting the criteria described above, the first isotretinoin treatment present in a subject's record was considered for analysis.

4.3.2 TREATMENT DURATION AND MEAN DAILY DOSAGE

It was of interest to determine the median treatment duration of an isotretinoin treatment. Isotretinoin is typically prescribed at 30-day intervals. Therefore, an isotretinoin treatment was defined as receiving consecutive prescriptions with less than 30 days between renewals. The total treatment duration was calculated by adding the durations of all dispensations. The mean daily dosage (milligrams/day) was calculated by dividing to the cumulative dosage of isotretinoin prescribed (milligrams) during a given treatment by the total duration of treatment (days).

4.3.3 PREVIOUS ANTI-ACNE MEDICATIONS

We documented the types and number of anti-acne medications patients had received in the 12 months immediately prior to the index date. Both topical and systemic agents were considered: tretinoin, tazarotene, benzoyl peroxide, clindamycin, doxycycline, tetracycline, minocycline, erythromycin, azithromycin, and acne-specific oral contraceptives (Diane-35™). Adapalene and benzoyl peroxide/erythromycin combination were not included since they are not reimbursed by the RAMQ drug prescription plan. The drug identification numbers used to identify the anti-acne medications above are presented in Appendix III. Since systemic antibiotics are used to treat several conditions, it was necessary to ensure that these were prescribed for acne. Therefore, an acne diagnosis (ICD-9 code: 706.1) must have been present in

the database within 30 days of the dispensing of the systemic antibiotic. In the event of a missing acne diagnosis, we used procedure codes related to a dermatology visit within 30 days of the dispensing of the medication. These procedure codes are presented in Appendix IV.

4.3.4 CHARACTERISTICS OF ISOTRETINOIN USERS AND PREDICTORS OF UTILIZATION

Descriptive statistics were used to summarize the characteristics of the study cohort. Because of the teratogenic risks associated with isotretinoin and thus the differential management of males and females, we determined whether there were demographic and treatment differences between genders. Student's t-tests and chi-square tests were used to compare continuous and categorical variables, respectively. When normality was not observed, the Mann-Whitney U test was used to compare median values between groups. We also conducted univariate and multiple unconditional logistic regressions to determine factors associated with treatment duration ≥ 20 weeks. Both patient and prescriber characteristics were considered in the models. In addition, since our cohort spanned a 20-year period, it was necessary to adjust the model for the different practices and guidelines issued throughout the years. We therefore considered four different time periods: 1) the pre-PPP years, 2) implementation of the PPP in 1988, 3) Canadian Acne Treatment Guidelines issued in 1995 (85) and 4) the new Canadian

Consensus Guidelines on Treatment of Acne and Prevention of Scaring issued in 2000 (86,209).

4.3.5. INTERRUPTED TIME-SERIES MODELING

The study cohort spanned a 20-year period (from 1984 to 2003), which presented a unique opportunity to evaluate whether the implementation of the PPP in October 1988, and the Dear Healthcare Professional Letter (DHPL) regarding isotretinoin's possible psychiatric risks issued in March 2001, had any impact on prescribing patterns.

Interrupted time-series modeling, first proposed by Box and Tiao (210), were used to determine whether the PPP and the DHPL had any impact on the number of new isotretinoin users in the months that followed their introduction. Linear regression would not have been an appropriate analysis since it assumes independence between consecutive observations. With regards to prescribing patterns, this assumption is not likely to be valid since they are highly influenced by current practices and guidelines.

In interrupted time-series models, dummy variables are created with 0 and 1 representing pre- and post-interventions, respectively. The impact of the implementation of PPP in October 1988 on prescribing patterns was based

on 57 pre-intervention and 15 post-intervention months (from January 1984 to December 1989), and the impact of the DHPL issued in March 2001 was based on 134 pre-intervention and 22 post-intervention months (from January 1990 to December 2002). The interventions were assumed to have a gradual, permanent impact and thus each model contained both abrupt (ω) and gradual (δ) effect parameters. Impact of the PPP was assessed in female patients, whereas impact of the DHPL was assessed in both genders.

Autoregressive integrated moving average (ARIMA) was used to model the time-series and predict post-intervention rates with 95% confidence intervals. To stabilize the variability within the series, Box-Cox transformations were employed. When trend was observed, we differenced rates between successive months. Seasonal troughs were observed at every mid-summer and were therefore removed by differencing rates using a seasonal period of 12 months. To identify models, we examined the estimated autocorrelation and partial correlation functions of the stationary series. Ljung-Box test and Akaike's information criterion were used as guides for choosing the best model. In all chosen models, normality and stability of the variance of the residuals was ascertained.

Incident isotretinoin users were expressed as the number of users per 100,000 persons insured by the RAMQ drug prescription plan per calendar

year. Given the fact that our cohort only included users of isotretinoin, and thus trends in time could reflect the increase in the number of people insured and not an increase in the number of users, we had to define a common denominator. To do this, the total number of patients eligible in the RAMQ drug prescription plan for each calendar year from 1984 to 2003 was obtained from the RAMQ's annual statistics (211). These statistics include the mean number of beneficiaries for each calendar year stratified by age and gender.

4.4 METHODS FOR STUDY 2

4.4.1 STUDY COHORT

The members of the study cohort from Study 1, composed of 17,351 first-time isotretinoin users, were followed from the end of their isotretinoin treatment until they experienced an acne relapse (defined as receiving an anti-acne medication, isotretinoin or other), they were no longer insured by the RAMQ drug plan, or the end of the study period (June 30, 2003), whichever came first. Detailed descriptions of the methods used to conduct Study 2 are described below.

4.4.2 STUDY DESIGN

A nested case-control design was used in Study 2 to determine predictors of experiencing an acne relapse (defined as receiving an anti-acne medication, isotretinoin or other) after being initially treated with isotretinoin. This design allowed the use of incidence density sampling, whereby a patient could serve as a control for more than one case. Moreover, cases could serve as controls before they become cases.

Two nested case-control analyses were conducted using a SAS incidence density program that was adapted for the purposes of the present study (212). The first nested case-control analysis determined predictors of

receiving an anti-acne medication (isotretinoin or other) after being initially treated with isotretinoin. The second nested case-control analysis determined predictors of receiving a second isotretinoin treatment. For both nested case-control analyses, five controls were randomly selected from the cases' risk set and matched to each case on the time accrued from the end of the first isotretinoin treatment to the acne relapse.

4.4.3 COHORT ENTRY AND EXIT

The date of entry in the cohort for the first nested case-control started the day after the end of the first isotretinoin treatment. This is because it was possible to receive an anti-acne medication at any time after the first isotretinoin treatment.

With regards to the second nested case-control study, the date of entry in the cohort for all patients started only 30 days after the end of their first isotretinoin treatment. This is because an isotretinoin treatment was defined as filling consecutive prescriptions with fewer than 30 days between renewals. Therefore by design, there were no isotretinoin prescriptions in the 30 days after the end of the first treatment. This was done to avoid immortal bias (213), where the person-time at which patients were not at risk of receiving an isotretinoin prescription was excluded. Patients in both nested case-control analyses were followed until they became cases, were no

longer covered by the RAMQ drug plan, or until June 30, 2003, whichever came first.

4.4.4 CASE AND CONTROL DEFINTION

4.4.4.1 DEFINITION FOR FIRST NESTED CASE-CONTROL STUDY

Cases for the first nested case-control analysis consisted of patients who experienced an acne relapse and required further treatment with an anti-acne medication (isotretinoin or other). For those cases, the index date was the calendar date of the dispensing of the anti-acne medication (isotretinoin or other). Eligible controls were patients who were still present in the cohort at the time of the cases' index date and had not received any anti-acne medications (isotretinoin or other) prior to that date.

An acne-relapse was defined as receiving any of the following anti-acne medications: isotretinoin, tretinoin, tazarotene, benzoyl peroxide, topical clindamycin, topical erythromycin, systemic doxycycline, systemic tetracycline, systemic minocycline, systemic erythromycin, systemic azithromycin, and acne-specific oral contraceptives (Diane-35™) (Appendix III). Adapalene and benzoyl peroxide/erythromycin combination were not considered since they are not reimbursed by the RAMQ drug plan. Systemic antibiotics are prescribed for a variety of conditions, it was thus necessary to ascertain that those considered as acne treatments were truly for acne.

Therefore, an acne diagnosis (ICD-9 code: 706.1) must have been present in the database within 30 days of the dispensing of the systemic antibiotic to be considered an anti-acne treatment. In the event of a missing acne diagnosis, we used dermatologic procedure codes recorded within 30 days of the dispensing of the medication (Appendix IV).

4.4.4.2 DEFINTION FOR SECOND NESTED CASE-CONTROL STUDY

Cases for the second nested case-control analysis consisted of patients who experienced an acne relapse severe enough to require a second isotretinoin treatment. As such, the index date was the calendar date of the dispensing of the second isotretinoin treatment. Eligible controls were patients who were still present in the cohort at the time of the cases' index date and had not received any isotretinoin prescriptions prior to that date.

4.4.5 POTENTIAL PREDICTORS

Potential predictors for both nested case-control analyses were assessed in four different time periods. The time periods were at the 1) index date, 2) between the end of the first isotretinoin treatment and index date (follow-up period), 3) during the first isotretinoin treatment, and 4) in the 12 months prior to the first isotretinoin treatment. The predictors considered in the four time periods related to patient socio-demographic information (age, gender, place of residence, adherent of the RAMQ drug plan/welfare recipient),

healthcare and medication utilization (visits to the physician, emergency department visits, all cause hospitalizations, and number of different types of medications) as well as prescriber information (specialty, gender of prescriber, and whether isotretinoin was prescribed by more than two physicians during the first treatment). Other predictors for requiring further treatment with an anti-acne medication (isotretinoin or other) included isotretinoin average daily dose during the first treatment stratified according to its 40 mg formulation, and median duration of the first isotretinoin treatment (≥121 days).

Since our cohort spanned a 20-year period, we also adjusted the models on the calendar time periods of the different Canadian programs and guidelines promulgated over the years. We considered the following three programs and guidelines. The first was the Pregnancy Prevention Program (PPP) implemented in October 1988, whose goal was to prevent isotretinoin-exposed pregnancies in females of childbearing age. The second were the Canadian Acne Treatment Guidelines published in 1995 (209).These guidelines recommended up to three courses of systemic antibiotics before considering isotretinoin. The third were the Canadian Consensus Guidelines on Treatment of Acne and Prevention of Scarring published in 2000 (86). These guidelines recommended that isotretinoin be prescribed primarily to patients with scarring acne, regardless of severity.

4.4.6 STATISTICAL ANALYSIS

Descriptive statistics were used to summarize the characteristics of the study population. Kaplan-Meier survival analyses were performed to determine the time until receipt of an anti-acne medication (isotretinoin other). Rate ratios (RR) along with 95% confidence intervals (95% CI) were estimated using conditional logistic regression. Crude and adjusted RRs were calculated for both nested case-control analyses. All analyses were conducted using SAS version 8.2 (SAS Institute Inc, Cary, North Carolina).

4.5 METHODS FOR STUDY 3

4.5.1 STUDY BASE

As with Studies 1 and 2, Study 3 was conducted among a population-based cohort of patients who had received at least one isotretinoin prescription from January 1, 1984 to December 31, 2003 within the RAMQ drug plan.

4.5.2 STUDY DESIGN

A case-crossover design was used to determine whether there is an association between isotretinoin and depression. This design was developed by Maclure (214) in 1991 to study the transient effect of brief exposures on rare acute events. The case-crossover design is similar to a matched case-control study where cases serve as their own controls by assessing exposure at different points in time. The time intervals in which exposure is assessed are the risk and control periods. The risk period is a time interval immediately prior to the event. The risk period must take into account the following parameters: induction time, effect period, and an exposure time window. The induction time can be defined as the time between the last component of a causal pathway (the trigger) and the onset of an event. Most case-crossover studies have assumed a minimum induction time of zero (185), although incubation periods have been accounted for in certain situations (215). The effect period is the time between the minimum and maximum induction times in the population. In situations where the minimum

induction time is zero, the effect period is equal to the maximum induction time. Finally, the risk period is equal to the minimum exposure time window necessary for the event to occur, plus the effect period. When the exposure is instantaneous, such as point exposures, the risk period equals the effect period. When the exposure is not instantaneous, such as prolonged drug exposures, the risk period is longer than the effect period.

The control period is a time interval of equal length prior, and not overlapping with the risk period, that provides an expected frequency of exposure for each study subject. Similar to matched case-control studies, case-crossover studies allow selecting one or several control periods for each risk period. In addition, since patients serve as their own controls, time-independent variables are automatically adjusted by design. However, variables that change with time must be adjusted for in analyses. The analysis of a case-crossover study is essentially the same as that of a matched case-control study, where the individual patient is the stratifying variable. In a matched case-control study, concordant and discordant pairs are formed between case and control subjects. In a case-crossover study, concordant and discordant pairs are formed between risk and control periods. In both designs, the odds ratio is calculated by the ratio of discordant pairs.

4.5.3 CASE DEFINITION

According to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) (216), clinical depression occurs when an individual experiences at least five of nine symptoms for a period of two weeks or more, for most of the time almost every day. Because of this stringent definition, the validity of using administrative databases to identify cases of depression can be put into question. Hence, using diagnostic codes alone is not sufficient. Furthermore, identification of cases using antidepressants alone can also be problematic, since depression is not the sole indication for these agents. Therefore, cases were defined according to the following algorithm. We identified all subjects with a first diagnosis or hospitalization for depression (ICD-9 codes: 296.2, major depressive disorder, single episode; 298.0, depressive type psychosis, 300.4, neurotic depression; 309.0, brief depressive reaction; 309.1 prolonged depressive reaction; 311, depressive disorder, not elsewhere classified) during the study period (1984-2003). In addition to having been diagnosed or hospitalized for depression, cases were required to have filled an antidepressant prescription (American Hospital Formulary System code: 28:16.04) within the 30 days following their diagnosis or hospitalization. The index date was defined as the calendar date of the diagnosis or hospitalization for depression.

Furthermore, cases had to be covered by the RAMQ drug plan for at least 12 months prior to the index date. This was deemed necessary to ensure that

drug exposure information was available during the time periods of interest. In addition, cases had to have at least one diagnosis of acne vulgaris (ICD-9 code: 706.1) at any time in the 12 months prior to the index date. This criterion ensured that cases had acne and thus had an exposure opportunity to receiving isotretinoin. Finally, cases were excluded if they had received an antidepressant prescription in the 12 months prior to the index date. Since by design, the index date was defined as the subject's first diagnosis or hospitalization for depression in their medical history, none had any diagnoses or hospitalizations for depression at any time prior to the index date. That time period ranged from a minimum of 12 months up to 20 years.

4.5.4 TIME WINDOWS

Determining the length of the risk and control periods necessitates knowledge of the duration of exposure necessary to alter the risk for an outcome, as well as the induction period in which the outcome is presumed to develop. In claims data, the induction period is further defined as the time it takes after exposure for the outcome to develop, become noticed by the healthcare professional, and then be recorded in the administrative database (217). In the case of isotretinoin, depression has been reported as early as one day, two weeks, one month, and up to four months after initiation of treatment (5,156,165,218). Furthermore, depression is an insidious outcome which results in a time lag between actual onset of symptoms and clinical

diagnosis. Thus, the length of the time window for the risk period should take into account these factors.

Assuming a minimum induction time of zero, the effect period should equal the maximum induction time. For isotretinoin, the maximum induction time was hypothesized to be four months based on data found in the literature (5,156,165,219). In addition to this induction time, a time lag of one month was hypothesized to exist between the actual onset of depression and its clinical diagnosis. Patients undergoing isotretinoin treatment are typically seen by their treating physicians at one-month intervals. As such, if depressive symptoms do appear, physicians would be expected to diagnose them at one of those follow-up visits. Therefore, the risk period was set to be a total of five months. A five-month control window was separated from the risk window by a two-month washout period. A two-month washout period was chosen because product guidelines suggest initiating a second course of isotretinoin in those who have not responded to the treatment only eight weeks after the completion of a first course (92). This is because improvements continue to occur during that time period despite having terminated the treatment.

4.5.5 POTENTIAL CONFOUNDERS

In a case-crossover design, each patient serves as his own control which eliminates time-independent confounders (such as age, sex, socioeconomic status). Thus such variables were not included in the models. Characteristics that change with time (i.e. time-dependent confounders) must be adjusted for and therefore included in the models. The following potential time-dependent confounders were recorded in each time window and adjusted for in the models: non-dermatologic visits, dermatologic visits, at least one all-cause hospitalization, at least one emergency department visit, and comorbidity. Dermatologic visits were defined as consulting a dermatologist and/or being diagnosed with acne vulgaris (ICD-9 code: 706.1). Comorbidity was assessed using the total number of different types of medications prescribed, other than isotretinoin. The number of different types of medications has been shown to be a good predictor of healthcare utilization, similar to other comorbidity measures (220).

4.5.6 STATISTICAL ANALYSIS

Descriptive statistics were used to describe the characteristics of the cases. Relative risks (RR) along with 95% confidence intervals (CI) were estimated using conditional logistic regression with the individual case as the stratifying variable. In a first analysis, exposure to isotretinoin was entered as a dichotomous variable in the models (exposed at least once during each

specific time window, yes or no). The length of an isotretinoin prescription is typically 30-days. In a second analysis, we determined whether there was a dose-response of isotretinoin on the incidence of depression. The cumulative dose in milligrams of isotretinoin dispensed was calculated in each time window and entered as quartiles in the models. Crude and adjusted models were calculated for all situations. Analyses were two-sided and $p \leq 0.05$ was considered significant. SAS version 8.2 (SAS Institute, Cary, NC) was used to conduct the analyses.

4.6 METHODS FOR STUDY 4

4.6.1 CASE-CROSSOVER AND CASE-TIME-CONTROL DESIGNS

Using a case-crossover design, a statistically significant association between isotretinoin use and depression was found in Study 3. An assumption of the case-crossover design is that there is no exposure time-trend during the time periods of interest. Often this is not the case. Aggressive marketing of a medication may lead to an increase in its prescribing. Conversely, there are instances that may lead to sudden decreases in prescribing, such as when there is a shift in treatment guidelines. In either situation, a bias is introduced in the model because of the exposure time-trend. Thus, time-trend alone could explain an association or lack of association between a medication and an outcome.

The case-time-control introduced by Suissa in 1995 (221), is an extension of the case-crossover design whose goal is to correct for any exposure time-trend. A control group is selected around the same calendar period as the cases, in which a control-crossover is performed. The control-crossover provides an estimate of the exposure time-trend. The odds ratio (OR) of the case-crossover is then divided by the OR of the control-crossover to produce an OR adjusted for exposure time-trend (case-time-control). The OR of the control-crossover is determined using the same time window scheme as in the case-crossover.

In the case-time-control design, we used the same cases that were used in the case-crossover design. As for controls, they were selected according to the following algorithm. We first identified all subjects who were non-cases. For each subject in the non-case pool, we generated a random index date between the first and last day of their coverage in the RAMQ drug plan. Subjects had to be covered at least 12 months prior to the index date, and have at least one acne diagnosis (ICD-9: 706.1) during that same time period. Subjects were excluded of they had received an antidepressant prescription in the 12 months prior to the index date, or a diagnosis or hospitalization for depression (ICD-9 codes: 296.2, 298.0, 300.4, 309.0, 309.1, 311) at any time prior to the index date. Up to 10 controls were matched to cases on age (± three years), sex, and calendar year (± one year).

Exposure to isotretinoin was assessed using the same time window scheme as in the case-crossover design. Similarly, we adjusted the model for non-dermatologic visits, dermatologic visits, all-cause hospitalizations, emergency department visits, and comorbidity measured in the risk and control periods independently.

4.6.3 STATISTICAL ANALYSIS

Descriptive statistics were used to describe the characteristics of cases and controls in the different study designs. For the case-crossover design, relative risks along with 95% confidence intervals (CI) were estimated using conditional logistic regression using the individual subject as the stratifying variable. For the case-time-control, a conditional logistic regression was fitted with time (risk versus control periods) as the dependent variable and the exposure and an interaction term (the product of the exposure and case group) as the independent variables. In the adjusted model, interaction terms were added for each of the corresponding confounders. SAS version 8.2 (SAS Institute, Cary, NC) was used to carryout the analyses.

CHAPTER 5: MANUSCRIPTS

The results of this thesis are presented in the following four manuscripts:

5.1 Patterns and utilization of isotretinoin for acne from 1984 to 2003: Is there need for concern? Laurent Azoulay MSc, Driss Oraichi PhD, Anick Bérard PhD. European Journal of Clinical Pharmacology. 2006 Aug;62(8):667-74.

5.2 Isotretinoin therapy and the incidence of acne relapse: a nested case-control study. Laurent Azoulay MSc, Driss Oraichi PhD, Anick Bérard PhD. British Journal of Dermatology (in press).

5.3 Isotretinoin and the risk of depression in patients with acne vulgaris: a case-crossover study. Laurent Azoulay MSc, Lucie Blais PhD, Gideon Koren MD, Jacques LeLorier MD PhD, Anick Bérard PhD. Journal of Clinical Psychiatry (in press).

5.4 Isotretinoin and the risk of depression: a comparison of self-matched designs. Laurent Azoulay MSc, Driss Oraichi PhD, Anick Bérard PhD. Submitted to the American Journal of Epidemiology (September 2007).

The principal author confirms his original contribution to the cohort assemblies, statistical analyses and interpretation of the results, as well as in the writing of the research articles.

5.1 PATTERNS AND UTILIZATION OF ISOTRETINOIN FOR ACNE FROM 1984 TO 2003: IS THERE NEED FOR CONCERN?

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5.1.1 ABSTRACT

Objectives: To 1) describe the patterns and trends of isotretinoin utilization between 1984 and 2003, 2) describe the characteristics of isotretinoin users within that same time period, 3) identify and quantify predictors of isotretinoin use, and 4) describe the impact of guidelines on isotretinoin utilization between 1984 and 2003.

Methods: Using the Régie de l'Assurance Maladie du Québec (healthcare utilization, medications) and Med-Écho (hospitalizations) administrative databases, we conducted a descriptive study on a population-based sample of first-time isotretinoin users from 1984 to 2003. We determined the characteristics of these users, predictors of an isotretinoin treatment ≥20 weeks, and impact of guidelines on the number of new isotretinoin users. Guidelines included the implementation of the Pregnancy Prevention Program (PPP - 1988) and the Dear Healthcare Professional Letter regarding possible psychiatric risks issued to Canadian physicians (DHPL - 2001).

Results: Mean (SD) age was 23.9 (7.6) years; 50% males, 52% welfare recipients, 77% urban dwellers, and 55% of prescriptions were written by dermatologists. Sixty-four percent of patients did not receive any anti-acne

medications in the 12 months prior to receiving isotretinoin. Thirty-five percent of patients had an isotretinoin treatment ≥20 weeks suggested by product guidelines. The odds ratio of having a treatment ≥20 weeks significantly increased after the implementation of the PPP and other guidelines. There was no statistically significant decrease in the number of new isotretinoin users following the implementation of the PPP and DHPL.

Conclusion: These data suggest inappropriate isotretinoin utilization, even more so after guidelines were promulgated.

5.1.2 INTRODUCTION

Since its introduction in the US in 1982 and Canada in 1983, isotretinoin has become a popular therapeutic agent for patients with severe recalcitrant nodular acne. One study conducted in the US found that isotretinoin was prescribed 5.8 million times out of 35 million physician visits for acne (17% of visits) [1]. A second study conducted in the US found that isotretinoin prescriptions have more than doubled between 1992 and 2000 [2]. Despite being the most efficacious drug in the treatment of severe nodular acne, isotretinoin also acts as a potent teratogen [3, 4, 5, 6, 7, 8]. Additionally, mucocutaneous, ophthalmologic, neuromuscular, and gastrointestinal side effects have been documented [9].

Given the extent of its use and its documented risks, it is imperative to understand who uses isotretinoin and under what circumstances it is being prescribed. A concern in the US has been its increased prescribing to patients with mild-to-moderate acne between 1992 and 2000 [2]. In addition, 47% to 72% of patients do not receive conventional therapies prior to commencing isotretinoin as suggested by product guidelines [10]. Furthermore, new off-label indications such as gram-negative folliculitis, recalcitrant rosacea, pyoderma faciale, generalized lichen planus, psoriasis, cutaneous lupus erythematosus and acne fulminans for the drug have become a concern [11].

Since its marketing in Canada in 1983, several guidelines have been issued. In 1988, a Pregnancy Prevention Program (PPP) was implemented to prevent isotretinoin-exposed pregnancies in females of childbearing age. In 1995, the Canadian Acne Treatment Guidelines were published [12]. These guidelines recommended up to three courses of systemic antibiotics, each lasting four to six months, before considering isotretinoin. The Canadian Consensus Guidelines on Treatment of Acne and Prevention of Scarring became available in 2000. Their focus was that prescriptions should be given primarily on the presence of scarring regardless of severity [13, 14]. In addition to its known teratogenic risk and various side effects, case reports have suggested a possible association between isotretinoin and depression [15, 16, 17, 18]. This led Health Canada along with the manufacturer of the drug to issue a Dear Healthcare Professional Letter (DHPL) to Canadian physicians warning them of possible psychiatric risks associated with isotretinoin in 2001 [19].

Although population-based studies on isotretinoin have been previously published [20, 21], none have specifically examined its utilization from the time of its introduction into the market. Furthermore, no study has investigated the impact of the guidelines mentioned above on prescribing patterns over a 20-year period. As such, population-based data spanning this time period would provide an accurate representation of isotretinoin utilization. We therefore sought to 1) describe the patterns and trends of

isotretinoin utilization between 1984 and 2003, 2) describe the characteristics of isotretinoin users within that same time period, 3) identify and quantify predictors of isotretinoin use, and 4) describe the impact of guidelines on isotretinoin utilization between 1984 and 2003.

5.1.3 METHODS

5.1.3.1 DATA SOURCES

We conducted a population-based study on a cohort of patients who had received at least one isotretinoin prescription from January 1, 1984 to June 30, 2003 in the province of Quebec. Data were obtained from both the Régie de l'Assurance Maladie du Québec (RAMQ) and the Quebec's hospital discharge (Med-Écho) administrative databases. The RAMQ insures all Quebec residents for medical services. The RAMQ drug prescription plan insures approximately 50% of Quebec residents [22], which includes persons 65 years and older, welfare recipients and their children, and all workers and their spouse/children who do not have access to a private insurance program.

The medical and pharmaceutical databases of the RAMQ were linked by a unique patient identification number. The medical claims database includes information on the date and type of services received, and diagnoses are classified according to the International Classification of Diseases, Ninth

revision (ICD-9) [23]. The pharmaceutical claims database contains information on the date medications were dispensed, formulations, doses, duration of prescriptions, and quantities dispensed. Medications prescribed during hospitalizations are not included in the database. Both the medical and pharmaceutical claims databases have been validated and shown to be accurate [24, 25].

The unique patient identification number was also used to link the RAMQ to the Med-Écho administrative databases. Med-Écho contains hospitalization data on all Quebec residents. This data includes patient demographic information, physician characteristics, admission diagnostic, length of stay, as well as all services received during the hospitalization. Medical diagnoses recorded in Med-Écho have been shown to be valid and precise [26]. The study protocol was approved by the Sainte-Justine Hospital Ethics Committee and the Commission d'accès à l'information du Québec.

5.1.3.2 STUDY COHORT

All Quebec residents who received at least one isotretinoin prescription (Drug identification numbers: 582344 (10 mg) and 582352 (40 mg)) between January 1, 1984 and June 30, 2003 within the RAMQ drug prescription plan and who met the following inclusion criteria were included in the present study: a patient must have been between 13 and 45 years of age and

continuously insured by the RAMQ drug prescription plan for at least 12 months before and at least six months after the first day of the first isotretinoin prescription within the study period (index date). A patient was excluded if he/she had received a prescription for isotretinoin in the 12 months prior to index date.

5.1.3.3 INDICATION FOR ISOTRETINOIN

According to the product labeling, isotretinoin is indicated for patients with severe recalcitrant nodular acne who have not responded to conventional therapy [27]. Since the ICD-9 classification system does not distinguish between the different acne severities, it was not possible to determine whether isotretinoin was being prescribed for severe recalcitrant nodular acne. However, all diagnostic codes entered within 30 days of the index date were considered. Any ICD-9 code other than 706.1 (acne vulgaris) was considered an off-label indication.

5.1.3.4 TREATMENT DURATION AND MEAN DAILY DOSAGE

The duration of an isotretinoin treatment was defined as filling consecutive prescriptions with fewer than 30 days between renewals. The RAMQ pharmaceutical claims database contains information on the duration associated with a given drug prescription. Therefore, the cumulative treatment duration was calculated by adding the durations of all

dispensations of isotretinoin as prescribed by the physician. The recommended duration of an isotretinoin treatment is between 15 to 20 weeks (105 to 140 days) [28]. The mean daily dosage in milligrams/day was calculated for all patients.

5.1.3.5 PREVIOUS ANTI-ACNE MEDICATIONS

We documented the types and number of anti-acne medications patients had received in the 12 months immediately prior to the index date. Both topical and systemic agents were considered: tretinoin, tazarotene, benzoyl peroxide, clindamycin, doxycycline, tetracycline, minocycline, erythromycin, azithromycin, and acne-specific oral contraceptives (Diane-35™). Adapalene and benzoyl peroxide/erythromycin combination were not included since they are not reimbursed by the RAMQ drug prescription plan. Since systemic antibiotics are used to treat several conditions, it was necessary to ensure that these were prescribed for acne. Therefore, an acne diagnosis (ICD-9 code: 706.1) must have been present in the database within 30 days of the dispensing of the systemic antibiotic. In the event of a missing acne diagnosis, we used procedure codes related to a dermatology visit within 30 days of the dispensing of the medication.

5.1.3.6 STATISTICAL ANALYSIS

5.1.3.6.1 CHARACTERISTICS OF ISOTRETINOIN USERS AND PREDICTORS OF UTILIZATION

Descriptive statistics were used to summarize the characteristics of the study cohort. Because of the teratogenic risks associated with isotretinoin and thus the differential management of males and females, we determined whether there were demographic and treatment differences between genders. Student's t-tests and chi-square tests were used to compare continuous and categorical variables, respectively. When normality was not observed, the Mann-Whitney U test was used to compare median values between groups. We also conducted univariate and multiple unconditional logistic regressions to determine factors associated with treatment duration ≥ 20 weeks. Both patient (socio-demographic data, healthcare utilization, and markers of comorbidity such as the number of different medications dispensed) and prescriber characteristics (age, gender, and specialty) were considered in the models. In addition, since our cohort spanned a 20-year period, it was necessary to adjust the model for the different practices and guidelines issued throughout the years. We therefore considered four different time periods: 1) the pre-PPP years, 2) implementation of the PPP in 1988, 3) Canadian Acne Treatment Guidelines issued in 1995 [12] and 4) the new Canadian Consensus Guidelines on Treatment of Acne and Prevention of Scaring issued in 2000 [13, 14]. All analyses were conducted using SAS version 8.2 (SAS Institute Inc., Cary, North Carolina).

5.1.3.6.2 ISOTRETINOIN UTILIZATION AND IMPACT OF GUIDELINES

Incident isotretinoin users were expressed as the number of users per 100,000 persons insured by the RAMQ drug prescription plan per calendar year. Given the fact that our cohort only included users of isotretinoin, and thus trends in time could reflect the increase in the number of people insured and not an increase in the number of users, we had to define a common denominator. To do this, the total number of patients eligible in the RAMQ drug prescription plan for each calendar year from 1984 to 2003 was obtained from the RAMQ's annual statistics [29]. These statistics include the mean number of beneficiaries for each calendar year stratified by age and gender.

An impact in prescribing patterns was defined as an increase or decrease in the number of isotretinoin users following an intervention. The interventions considered were 1) the introduction of the PPP in October 1988, and 2) the DHPL about possible psychiatric risks issued in March 2001. Interrupted time-series analyses, first proposed by Box and Tiao [30], were used to determine whether these interventions had any impact on the prescribing patterns in the months that followed their introduction. In interrupted time-series models, dummy variables are created with 0 and 1 representing pre- and post-interventions, respectively. Intervention 1) was based on 57 pre-intervention and 15 post-intervention months (from January 1984 to

December 1989), and intervention 2) was based on 134 pre-intervention and 22 post-intervention months (from January 1990 to December 2002). The interventions were assumed to have a gradual, permanent impact and thus each model contained both abrupt (ω) and gradual (δ) effect parameters. Impact of the PPP was assessed in female patients, whereas impact of the DHPL was assessed in both genders.

Autoregressive integrated moving average (ARIMA) was used to model the time-series and predict post-intervention rates with 95% confidence intervals. To stabilize the variability within the series, Box-Cox transformations were employed. When trend was observed, we differenced rates between successive months. Seasonal troughs were observed at every mid-summer and were therefore removed by differencing rates using a seasonal period of 12 months. To identify models, we examined the estimated autocorrelation and partial correlation functions of the stationary series. Ljung-Box test and Akaike's information criterion were used as guides for choosing the best model. In all chosen models, normality and stability of the variance of the residuals was ascertained.

5.1.4 RESULTS

Of the 30,496 Quebec residents that had received at least one isotretinoin prescription between January 1, 1984 and June 30, 2003 within the RAMQ

drug prescription plan, a total of 17,351 patients met inclusion criteria, and were thus included in this analysis - these patients were considered new isotretinoin users. Specifically, 12,908 (74.4%) had one isotretinoin treatment, 2997 (17.3%) had two, and 1446 (8.3%) had three or more during the 20-year study period. Only the first isotretinoin treatment was considered in the following analyses.

5.1.4.1 INDICATION FOR ISOTRETINOIN

Seventy-nine percent of patients had a diagnosis for acne in the 30 days prior to the index date, while the remaining had either dermatologic diagnoses other than acne (9.8%), or other diagnoses (11.2%).

5.1.4.2 PATIENT AND PRESCRIBER CHARACTERISTICS

Table 1 presents unadjusted patient and prescriber characteristics. From 1984 to 2003, isotretinoin was similarly prescribed to males and females (8715 (50.2%) vs. 8636 (49.8%), respectively). Females were 4.5 years older than males at the index date, were more often living in urban settings as compared to males, and consulted physicians more often than males in the 12 months prior to the index date as well as were taking less anti-acne medications other than isotretinoin than males ($p < 0.05$). Emergency department (ED) visits were more common among males than females in the 12 months prior to the index date ($p = 0.0006$). With regards to

hospitalizations, they were more common among females than in males in the 12 months prior to the index date ($p < 0.0001$). The majority of prescriptions for isotretinoin at index date were written by male physicians (76.8%), and dermatologists (54.7%).

5.1.4.3 PREVIOUS ANTI-ACNE TREATMENTS

Some 36.9% of males and 34.4% of females had received at least one anti-acne medication in the 12 months prior to the index date before actually receiving their first isotretinoin prescription (Table 2). The most common type of anti-acne medication prescribed was systemic antibiotics (74.7%), in both males (74.5%) and females (74.8%).

5.1.4.4 TREATMENT CHARACTERISTICS

Table 3 presents treatment characteristics. The median treatment duration was 121 days for both males and females. There were 6099 (35.2%) patients who had treatment duration equal to or greater than the 20 weeks (140 days) suggested by product guidelines. Mean daily dosage was greater in males than females (49.4 mg versus 42.7 mg, $p < 0.0001$).

5.1.4.5 PREDICTORS OF INAPPROPRIATE ISOTRETINOIN USE

Table 4 displays predictors of having a treatment duration ≥ 20 weeks, which is considered inappropriate. In multivariable analyses, the following decreased the likelihood of having an isotretinoin treatment duration ≥ 20 weeks: older age, male gender, urban dwellers, welfare recipients, having ≥ two ED visits in the 12 months prior to the index date, and being treated by older male physicians. In contrast, the following increased the likelihood of having an isotretinoin treatment duration ≥ 20 weeks in multivariable analyses: receiving anti-acne medications concomitantly during the isotretinoin treatment, receiving anti-acne medications or other types of medications in the 12 months prior to the index date, having the first isotretinoin prescription written by a dermatologist, and being prescribed isotretinoin by ≥ two physicians during the isotretinoin treatment. Moreover, the estimated odds ratios for treatment durations ≥ 20 weeks significantly increased following the implementation of the PPP (after 1988).

5.1.4.6 IMPACT OF GUIDELINES

No significant impact of guidelines on the number of new isotretinoin users was noted in this study. The estimated interrupted time-series parameters for the implementation of the PPP in October 1988 in females users were $\omega = -2.09$ ($p = 0.008$) and $\delta = -0.21$ ($p = 0.642$). Since δ was not statistically significant while ω was, only an abrupt, permanent impact remains plausible.

With regard to the DHPL issued in March 2001, neither $\omega = -0.15$ ($p = 0.610$) nor $\delta = -0.10$ ($p = 0.996$) were statistically significant in female users, indicating no impact. The same was true for male users; $\omega = -0.46$ ($p = 0.475$) and $\delta = -0.06$ ($p = 0.967$).

5.1.5 DISCUSSION

To our knowledge, this is the first population-based study to specifically investigate isotretinoin utilization over a 20-year period (1984 to 2003). Our data indicate inappropriate isotretinoin utilization, even more so after the implementation of the PPP and introduction of other guidelines. Specifically, over 35% of patients had undergone an isotretinoin treatment longer than the 20 weeks suggested by the product guidelines. In addition, 64% of patients had not received any anti-acne medication in the 12 months prior to the index date. In the province of Quebec, the implementation of the PPP in 1988 and the DHPL issued in 2001 do not appear to have had any impact on prescribing patterns.

Isotretinoin is intended for severe recalcitrant nodular acne, and as such, it would be expected that all patients receiving the drug are acne patients. Stern [31] found that 97% of prescriptions for isotretinoin were indicated for acne. However, in the present study, we found that 79% of patients received an acne diagnosis in the 30 days prior to the index date. Although

isotretinoin is prescribed for other dermatologic and non-dermatologic conditions [9, 11], we believe our prevalence to be an underestimate given that diagnoses are often missing in administrative databases.

Dermatologists prescribed 55% of the isotretinoin prescriptions, a figure that is well below what has been reported in the literature [1, 31], although Chen et al. [32] found that 52% of prescriptions were written by dermatologists in a southern California HMO. In the present study, the low frequency of prescriptions written by dermatologists could be due to the universal healthcare system that is in place in the province of Quebec. Because of the high demand for such professionals, the waiting time to consult a dermatologist could be several weeks. As such, non-dermatologists, especially general practitioners become the best alternative. Unfortunately, a Canadian report suggested that non-dermatologists were not familiar with the components of the PPP, raising the concern of unintended isotretinoin-exposed pregnancies in females of childbearing age [33]. In addition, non-dermatologists may not be familiar with the numerous side effects associated with isotretinoin treatment, and thus may not have the proper training to counsel patients when symptoms appear.

We found that 35% of patients had treatment duration longer than the 20 weeks suggested by the product guidelines. This in itself is a troubling

finding since it unnecessarily prolongs exposure to a potent agent. Interestingly, receiving at least one anti-acne medication in the 12 months prior to isotretinoin was a predictor of having treatment duration longer than 20 weeks. One possibility is that those who received such medications have severe forms of acne that are resistant to conventional therapy, and thus would require longer isotretinoin treatment durations. In addition, the odds ratio of having treatment duration ≥ 20 weeks increased after the implementation of the PPP and other guidelines. This indicates that the implementation of the PPP and other guidelines were associated with longer treatment durations, contrary to what might have been expected. Furthermore, receiving isotretinoin from 2 or more physicians during the isotretinoin treatment more than doubled the odds of having treatment duration ≥ 20 weeks, indicating that unity of care is a marker for appropriate prescribing and utilization.

It is expected that patients with severe recalcitrant nodular acne obtain therapeutic treatments prior to commencing an isotretinoin treatment. In fact, Canadian consensus guidelines have suggested that isotretinoin should only be prescribed to those patients who did not respond to conventional therapy, including systemic antibiotics [12]. In 2000, new Canadian Consensus Guidelines on Treatment of Acne and Prevention of Scaring have suggested a more aggressive approach, primarily focusing on the presence of scarring regardless of severity [13, 14]. Our data indicate a sub-optimal rate of

physician adherence to guidelines. Over 64% of all patients had not received any anti-acne medication in the 12 months prior to the index date. In contrast, Chen et al. [32] found that 39% of patients had not received any anti-acne medication in the 6 months prior to the first isotretinoin prescription. Our lower prevalence of anti-acne medication utilization may indicate one of two things. First, isotretinoin is being utilized as a first line agent instead of being prescribed after having exhausted all other conventional therapies. Second, the absence of anti-acne medications in the 12 months prior to the index date may potentially be a proxy for acne severity, indicating that isotretinoin is being prescribed to patients with mild or moderate acne. We were not able to document the use of over-the-counter (OTC) anti-acne agents since they are not reimbursed by the RAMQ drug prescription plan. However, we believe that adequate treatment of severe nodular acne requires systemic agents, which for the most part are covered by the RAMQ drug prescription plan. Furthermore, given the fact that members of our cohort were all insured by the RAMQ drug prescription plan for their medications and thus had no incentive to buy medications OTC, the likelihood of OTC anti-acne medication use is minimal.

5.1.5.1 IMPACT OF GUIDELINES

Our results indicate that implementation of the PPP (1988) did not have a gradual, permanent effect on the number of new isotretinoin users. The PPP requires a strict follow-up of female patients throughout the treatment, and

thus would normally deter both physicians and patients from using isotretinoin. Likewise, the DHPL (2001) on possible psychiatric risks associated with isotretinoin utilization did not have a gradual, permanent effect on the number of new isotretinoin users. Our data suggest that both these interventions did not appear to have any effect in clinical practice. Several factors may explain this lack of effect. It is possible physicians were not fully familiar with the new guidelines when they were implemented, that they disagreed with them altogether, or that they lacked motivation in implementing them (inertia of previous practice) [34]. Future research should focus on the barriers to physician adherence to practice guidelines in relation to isotretinoin.

Despite its various side effects, isotretinoin remains the most effective drug in the treatment of severe acne. However, our study suggests inappropriate utilization since its introduction into the market more than 20 years ago. This problem may be exacerbated by the introduction of cheaper generic compounds which are likely to increase its availability. As such, more effective strategies should be put in place to improve its current utilization.

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Table 1. Characteristics of patients and prescribers

Patient characteristics	Total (n=17,351)	Males (n=8715)	Females (n=8636)	P-value‖
At index date:				
Age (years) (mean, SD)	23.9 (7.6)	21.6 (6.8)	26.1 (7.6)	<0 .0001
Urban dwellers (n, %)†	12,363 (77.0%)	6053 (75.4%)	6310 (78.6%)	0 .0208
Welfare recipients (n, %)	9023 (52.0%)	4499 (51.6%)	4524 (52.4%)	0 .7924
In the 12 months prior to index date:				
Anti-acne medications (n, %)‡	6195 (35.7%)	3220 (36.9%)	2975 (34.4%)	0.0006
Other medications (n, %)‡§	13,857 (79.9%)	6375 (73.1%)	7485 (86.7%)	< 0.0001
Visits to the MD (n, %)‡				
None	975 (5.6%)	701 (8.0%)	274 (3.2%)	< 0.0001
1	1821 (10.5%)	1222 (14.0%)	599 (6.9%)	
≥ 2	14,555 (83.9%)	6792 (77.9%)	7763 (89.9%)	
Visits to the ED (n, %)‡				
None	12,640 (72.8%)	6252 (71.7%)	6388 (74.0%)	0.0006
1	2664 (15.4%)	1426 (16.4%)	1238 (14.3%)	
≥ 2	2047 (11.8%)	1037 (11.9%)	1010 (11.7%)	
Hospitalizations (n, %)‡				
None	15,472 (89.2%)	8097 (92.9%)	7375 (85.4%)	< 0.0001
1	1468 (8.5%)	483 (5.5%)	985 (11.3%)	
≥ 2	411 (2.4%)	135 (1.6%)	276 (3.2%)	
Prescriber characteristics at index date				
Age (years) (mean, SD)††	53.3 (10.7)	54.9 (10.6)	47.9 (9.1)	< 0.0001
Males (n, %)	13,317 (76.8%)	6813 (78.2%)	6504 (75.3%)	< 0.0001
Number of patients treated by:				
Dermatologists (n, %)¶	9465 (54.7%)	4490 (51.7%)	4975 (57.8)	< 0.0001
General practitioners (n, %)¶	7529 (43.5%)	4042 (46.5%)	3487 (40.5%)	
Others (n, %)¶	308 (1.8%)	160 (1.8%)	148 (1.7%)	

Abbreviations: SD, standard deviation; MD, medical doctor; ED, emergency department.
‖Comparing males and females.
†Percentage based on 16,058 patients with available data; 8028 males and 8030 females.
‡Calculated in the 12 months immediately preceding the first isotretinoin prescription.
††Based on 17,240 patients with available data; 8663 males and 8577 females.
¶Percentage based on 17,302 patients with available data; 8692 males and 8610 females.
Note: Percentages may not add up to 100% due to rounding.

Table 2. Anti-acne medications dispensed in the 12 months immediately preceding the index date

Anti-acne medications	Total (n=6195)	Males (n=3220)	Females (n=2975)	P-value‖
Systemic antibiotics†	4625 (74.7%)	2399 (74.5%)	2226 (74.8%)	0.7721
Miscellaneous agents†	1478 (23.9%)	866 (26.9%)	612 (20.6%)	< 0.0001
Topical retinoids†	1017 (16.4%)	472 (14.7%)	545 (18.3%)	0.0001
Topical antibiotics†	805 (13.0%)	400 (12.4%)	405 (13.6%)	0.1636
At least any one of the agents above§	**35.7% (35.0, 36.4)**	**36.9% (36.2, 37.7)**	**34.4% (33.7, 35.2)**	**0.0006**

The categories above are not mutually exclusive since a patient may have received more than one type of medication.

‖Comparing males and females.

†Percentages were calculated by dividing the number of patients in each category by the total number of patients received at least one acne medication (n=6195).

§Defined as the percentage of patients who had received at least one these medications along with 95% confidence intervals.

Table 3. Characteristics related to the isotretinoin treatment

	Total (n=17,351)	Males (n=8715)	Females (n=8636)	P-value‖
Treatment duration, days (median, Q1-Q3)§	121 (66-155)	121 (66-156)	121 (66-154)	0.3666
Treatment duration (n, %)				
≥ 140 days	6099 (35.2%)	3096 (35.5%)	3003 (34.8%)	0.2996
≥ 150 days	4866 (28.0%)	2480 (28.5%)	2386 (27.6%)	0.2247
≥ 180 days	2362 (13.6%)	1231 (14.1%)	1131 (13.1%)	0.0482
Mean daily dosage (mg/day) (mean, SD)	46.1 (22.2)	49.4 (24.5)	42.7 (19.0)	< 0.0001
Isotretinoin Rxs in a treatment (mean, SD)	4.1 (2.5)	4.2 (2.6)	4.1 (2.4)	0.0008

Abbreviations: Q1-Q3, 25th percentile-75th percentile; SD, standard deviation; Rx, prescription.
‖Comparing males and females.
§Mann-Whitney U test was used to compare median values between males and females.
†Patients with at least one anti-acne medication other than isotretinoin during their treatment.

Table 4. Predictors of an isotretinoin treatment duration ≥ 20 weeks

	Crude OR (95% CI)	Adjusted OR (95% CI)[†]
Age of patients, years	0.97 (0.97, 0.98)	0.98 (0.97, 0.98)
Male patients	1.03 (0.97, 1.10)	0.92 (0.85, 0.99)
Urban dwellers	0.79 (0.73, 0.85)	0.87 (0.81, 0.95)
Welfare recipients	0.53 (0.49, 0.56)	0.75 (0.69, 0.81)
In the 12 months immediately prior to the first isotretinoin prescription:		
At least one anti-acne medication	1.48 (1.39, 1.58)	1.22 (1.14, 1.32)
At least one non anti-acne medication	1.02 (0.94, 1.10)	1.12 (1.03, 1.23)
Number of visits to the physician		
None	1.00 (Reference)	1.00 (Reference)
1	1.20 (1.01, 1.41)	1.13 (0.94, 1.35)
≥ 2	1.16 (1.01, 1.33)	1.04 (0.89, 1.23)
Number of emergency department visits		
None	1.00 (Reference)	1.00 (Reference)
1	0.98 (0.90, 1.07)	0.94 (0.86, 1.04)
≥ 2	0.85 (0.77, 0.93)	0.81 (0.73, 0.90)
Number of hospitalizations		
None	1.00 (Reference)	1.00 (Reference)
1	0.89 (0.80, 1.00)	1.04 (0.92, 1.18)
≥ 2	0.58 (0.46, 0.73)	0.78 (0.60, 1.02)
Time periods		
January 1, 1984 – September 30, 1988	1.00 (Reference)	1.00 (Reference)
October 1, 1988 – December 31, 1994	1.30 (1.14, 1.49)	1.24 (1.05, 1.47)
January 1, 1995 – December 31, 1999	2.38 (2.14, 2.65)	1.66 (1.42, 1.94)
January 1, 2000 – June 30, 2003	2.79 (2.51, 3.11)	1.70 (1.45, 2.01)
Age of physician, years	0.96 (0.96, 0.97)	0.97 (0.97, 0.98)
Treated by male physicians	0.68 (0.63, 0.73)	0.92 (0.85, 0.99)
Treated by dermatologists	0.96 (0.90, 1.02)	1.17 (1.09, 1.26)
Isotretinoin prescribed by ≥ 2 physicians	2.36 (2.10, 2.66)	2.42 (2.13, 2.77)
Concomitant anti-acne medications	1.44 (1.29, 1.62)	1.41 (1.25, 1.60)
Mean daily dosage (mg/day)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)

Abbreviations: OR, odds ratio; CI, confidence interval; SD, standard deviation.
[†]Adjusted for the covariates in the table.

5.2 ISOTRETINOIN THERAPY AND THE INCIDENCE OF ACNE RELAPSE: A NESTED CASE-CONTROL STUDY

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5.2.1 SUMMARY

Background: Previous studies on predictors of acne relapse in patients treated with isotretinoin had either small sample sizes, short follow-up periods, or lacked population-based data.

Objectives: To identify and quantify (1) predictors of acne relapse, and (2) predictors of receiving a second isotretinoin treatment.

Methods: Using the RAMQ and Med-Écho administrative databases, a population-based cohort of 17,351 first-time isotretinoin users was assembled between 1984 and 2003. A nested case-control analysis was performed to determine predictors of acne relapse (as defined by receiving an anti-acne medication). A second nested case-control analysis was performed to determine predictors of receiving a second isotretinoin treatment. The index date of cases was the calendar date of dispensing of an anti-acne medication (isotretinoin or other). Five controls were matched to each case on follow-up time. Rate ratios were estimated using conditional logistic regression.

Results: 7100 (40.9%) subjects experienced an acne relapse. These were matched to 35,500 controls. Being male, <16 years of age, living in urban

area, isotretinoin cumulative doses greater than 2450 mg and an isotretinoin treatment longer than 121 days were statistically associated ($p<0.05$) with acne relapse. The publishing of the different Canadian acne guidelines had no impact on the incidence of acne relapse ($p>0.05$). 4443 (25.6%) subjects required a second isotretinoin treatment. These were matched to 22,215 controls. There was a greater probability of receiving a second isotretinoin treatment after the publishing of the Canadian acne guidelines ($p<0.05$).

Conclusion: A relatively high rate of subjects experienced an acne relapse after an isotretinoin treatment.

5.2.2 INTRODUCTION

Since its introduction in the market more than 20 years ago, isotretinoin has revolutionized the treatment of severe nodular acne. However despite its remarkable effectiveness, isotretinoin has important side effects. It is a teratogen if taken during the first trimester of pregnancy.[1] In Canada, a pregnancy prevention program was implemented in 1988, but failed to prevent isotretinoin-exposed pregnancies.[2] Other side effects may be mucocutaneous, ophthalmologic, neuromuscular, and gastrointestinal problems.[3] In addition, an association between isotretinoin and depression has recently been found (Azoulay et al., submitted for publication).

Given isotretinoin's safety profile, it is important to determine which patients will benefit most from this treatment versus those who will not. As such, determining predictors of experiencing an acne relapse may be of great prognostic value to physicians who treat patients with acne. This is particularly important in countries such as Canada that have no restrictions as to which physicians may prescribe isotretinoin. Since its introduction in the US in 1982 and Canada the following year, several observational studies have examined predictors of experiencing an acne relapse after being initially treated with isotretinoin. The relapse rates varied between studies, ranging from 5.6% to 65.4%.[4-15] There are several possible explanations for this large discrepancy. First, these studies had small sample sizes, ranging

between 52 and 299 patients.[4-15] Second, some studies had short follow-up periods, and may have thus underestimated the relapse rate. Finally, relapse was not defined consistently across the different studies.

Given the limitations described above and lack of population-based data on the subject, we sought to (1) determine the characteristics of subjects initially treated with isotretinoin experiencing an acne relapse as defined by requiring further treatment with an anti-acne medication (either a second isotretinoin treatment or another anti-acne medication), (2) identify and quantify predictors of experiencing an acne relapse, and (3) identify and quantify predictors of receiving a second isotretinoin treatment.

5.2.3 METHODS

5.2.3.1 DATA SOURCES

Data were obtained from the Régie de l'Assurance Maladie du Québec (RAMQ) and Quebec's hospital discharge (Med-Écho) administrative databases. All Quebec residents are covered by the RAMQ for medical services. Prior to January 1, 1997, the RAMQ drug plan covered those who were 65 years and older, and welfare recipients and their children. After January 1, 1997, the RAMQ drug plan was changed to also include workers and their spouses/children who do not have access to a private medication insurance program. The RAMQ drug plan covers approximately 50% of Quebec residents.[16]

The medical and pharmaceutical databases of the RAMQ were linked by a unique patient identification number. The medical claims database includes information on the date and type of services received, and diagnoses are classified according to the International Classification of Diseases, Ninth revision (ICD-9).[17] The pharmaceutical claims database contains information on the date medications were dispensed, formulations, doses, duration of prescriptions, and quantities dispensed. Medications prescribed during hospitalizations are not included in the database. Both the medical and pharmaceutical claims databases have been validated and shown to be accurate for certain diagnoses.[18,19]

The unique patient identification number was also used to link the RAMQ to the Med-Écho administrative databases. Med-Écho contains hospitalization data on all Quebec residents. This data includes patient demographic information, physician characteristics, admission diagnostic, length of stay, as well as all services received during the hospitalization. Medical diagnoses recorded in Med-Écho have been shown to be valid and precise.[20]

The study protocol was approved by the CHU Sainte-Justine Ethics Committee and the Commission d'accès à l'information du Québec.

5.2.3.2 STUDY COHORT

We identified all Quebec residents who received a first isotretinoin treatment between January 1, 1984 and June 30, 2003 within the RAMQ drug plan. An isotretinoin treatment was defined as filling consecutive prescriptions with fewer than 30 days between renewals. These subjects were between 13 and 45 years of age on the first day of the first isotretinoin prescription within the study period. They were required to be continuously insured by the RAMQ drug plan for at least 12 months before and at least six months after the first day of the first isotretinoin prescription. Based on the criteria above, we identified 17,351 first-time isotretinoin users. A detailed description of the cohort has been described previously.[21]

5.2.3.3 STUDY DESIGN

Two nested case-control analyses were conducted using a SAS incidence density program[22] that was adapted for the purposes of the present study. The first nested case-control analysis determined predictors of receiving an anti-acne medication (isotretinoin or other) after being initially treated with isotretinoin. The second nested case-control analysis determined predictors of receiving a second isotretinoin treatment. With incidence density sampling, a subject could serve as a control for more than one case. Moreover, cases could serve as controls before they become cases. For both nested case-control analyses, controls were matched to cases on the

time since the end of their first isotretinoin treatment. Five controls were randomly matched to each case.

5.2.3.4 FOLLOW-UP

The date of entry in the cohort for the first nested case-control started the day after the end of the first isotretinoin treatment. This is because it was possible to receive an anti-acne medication at any time after the first isotretinoin treatment. As for the second nested case-control study, the date of entry in the cohort for all subjects started only 30 days after the end of their first isotretinoin treatment. This is because an isotretinoin treatment was defined as filling consecutive prescriptions with fewer than 30 days between renewals. Therefore by design, there were no isotretinoin prescriptions in the 30 days after the end of the first treatment. This was done to avoid immortal bias,[23,24] where the person-time at which subjects were not at risk of receiving an isotretinoin prescription was excluded. Subjects in both nested case-control analyses were followed until they became cases, were no longer covered by the RAMQ drug plan, or until June 30, 2003, whichever came first.

5.2.3.5 CASES AND CONTROLS

Cases for the first nested case-control analysis consisted of subjects who experienced an acne relapse and required further treatment with an anti-

acne medication (isotretinoin or other). For those cases, the index date was the calendar date of the dispensing of the anti-acne medication (isotretinoin or other). Eligible controls were subjects who were still present in the cohort at the time of the cases' index date and had not received any anti-acne medications (isotretinoin or other) prior to that date. The anti-acne medications considered were isotretinoin, tretinoin, tazarotene, benzoyl peroxide, topical clindamycin, topical erythromycin, systemic doxycycline, systemic tetracycline, systemic minocycline, systemic erythromycin, systemic azithromycin, and acne-specific oral contraceptives (Diane-35™). Adapalene and benzoyl peroxide/erythromycin combination were not considered since they are not reimbursed by the RAMQ drug plan. Given that systemic antibiotics are prescribed for a variety of conditions, it was necessary to ascertain that those considered as acne treatments were truly for acne. Therefore, an acne diagnosis (ICD-9 code: 706.1) must have been present in the database within 30 days of the dispensing of the systemic antibiotic to be considered an anti-acne treatment. In the event of a missing acne diagnosis, we used dermatologic procedure codes recorded within 30 days of the dispensing of the medication.

Cases for the second nested case-control analysis consisted of subjects who experienced an acne relapse severe enough to require a second isotretinoin treatment. As such, their index date was the calendar date of the dispensing of the second isotretinoin treatment. Eligible controls were subjects who

were still present in the cohort at the time of the cases' index date and had not received any isotretinoin prescriptions prior to that date.

5.2.3.6 POTENTIAL PREDICTORS

Potential predictors for both nested case-control analyses were assessed in four different time periods. The time periods were at the 1) index date, 2) between the end of the first isotretinoin treatment and index date (follow-up period), 3) during the first isotretinoin treatment, and 4) in the 12 months prior to the first isotretinoin treatment. The predictors considered in the four time periods related to subject socio-demographic information (age, gender, place of residence, adherent of the RAMQ drug plan/welfare recipient), healthcare and medication utilization (visits to the physician, emergency department visits, all cause hospitalizations, and number of different types of medications) as well as prescriber information (specialty, gender of prescriber, and whether isotretinoin was prescribed by more than two physicians during the first treatment). Other predictors for requiring further treatment with an anti-acne medication (isotretinoin or other) included median duration of the first isotretinoin treatment (≥121 days) and isotretinoin cumulative dose. The latter was entered as quartiles in the models. A cumulative dose of 2450 mg was considered equivalent to close to a two month's supply of isotretinoin, assuming an average dosage of 46 mg/day.[21]

Since our cohort spanned a 20-year period, we also adjusted the models on the calendar time periods of the different Canadian programs and guidelines promulgated over the years. We considered the following three programs and guidelines. The first was the Pregnancy Prevention Program (PPP) implemented in October 1988, whose goal was to prevent isotretinoin-exposed pregnancies in females of childbearing age. The second were the Canadian Acne Treatment Guidelines published in 1995.[25] These guidelines recommended up to three courses of systemic antibiotics before considering isotretinoin. The third were the Canadian Consensus Guidelines on Treatment of Acne and Prevention of Scarring published in 2000. These guidelines recommended that isotretinoin be prescribed primarily to patients with scarring acne, regardless of severity.[26,27]

5.2.3.7 STATISTICAL ANALYSIS

Descriptive statistics were used to summarize the characteristics of the study population. Kaplan-Meier survival curves were constructed to model the time from the end on the first isotretinoin treatment until receipt of an anti-acne medication (isotretinoin or other). Rate ratios (RR) along with 95% confidence intervals (95% CI) were estimated using conditional logistic regression. Crude and adjusted RRs were calculated for both nested case-control analyses. All analyses were conducted using SAS version 8.2 (SAS Institute Inc, Cary, North Carolina).

5.2.4 RESULTS

5.2.4.1 PREDICTORS OF RECEIVING AN ANTI-ACNE MEDICATION

Of the 17,351 first-time isotretinoin users in the cohort, a total of 7100 (40.9%, 95% CI: 40.4%, 41.4%) subjects (cases) required further treatment with an anti-acne medication (isotretinoin or other). There was a total of 36,911 person-years of follow-up, where the rate of receiving an anti-acne medication was 192/1000 persons per year. Half of the cohort received an anti-acne medication within 58.8 months (4.9 years) after the end of their isotretinoin treatment (Figure 1).

A total of 35,500 controls were matched to the 7100 cases. The characteristics of the cases and controls were similar (Table 1). Isotretinoin was dispensed to 4011 (56.5%) subjects, whereas 3089 (43.5%) required other anti-acne medications (Table 2). Out of the latter group, 432 (14.0%) received isotretinoin during the remainder of their follow-up.

Table 3 displays crude and adjusted RRs of receiving an anti-acne medication (isotretinoin or other) after being initially treated with isotretinoin. Male subjects and those under 16 years of age were more likely to receive an anti-acne medication. Subjects living in urban areas were also more likely to receive an anti-acne medication. The implementation of the PPP and publishing of other guidelines were not statistically associated with receiving

an anti-acne medication. Subjects who had received isotretinoin cumulative doses greater than 2450 mg compared to those who received cumulative doses less than 2450 mg during their first treatment were less likely to receive another anti-acne medication. Those whose first isotretinoin treatment was ≥121 days were also less likely to receive another anti-acne medication.

5.2.4.2 PREDICTORS OF RECEIVING A SECOND ISOTRETINOIN TREATMENT

Of the 17,351 first-time isotretinoin users in the cohort, 12,908 (74.4%) had one treatment, 2997 (17.3%) had two treatments, and 1446 (8.3%) had three or more isotretinoin treatments during the follow-up period. Thus a total of 4443 (25.6%, 95% CI: 25.1%, 26.0%) had two or more isotretinoin treatments during the study period. There was a total of 48,802 person-years of follow-up, where the rate of receiving a second isotretinoin treatment was 91/1000 persons per year. Nearly all subjects who received a second isotretinoin treatment did so within 25.4 months after the end of their first treatment (Figure 2).

There were 4443 cases and 22,215 controls in the nested case-control analysis. The characteristics of cases and controls were similar (Table 4). Table 5 presents crude and adjusted RRs of predictors of receiving a second

isotretinoin treatment. In adjusted analyses, subjects under 16 years of age, as well as males were more likely to receive a second isotretinoin treatment. The chances of receiving a second isotretinoin treatment increased after the implementation of the PPP and the publishing of the different guidelines. Subjects who had received isotretinoin cumulative doses greater than 2450 mg compared to those who received cumulative doses less than 2450 mg during their first treatment were less likely to receive a second isotretinoin treatment. Likewise, subjects who had an isotretinoin treatment ≥121 days were less likely to receive a second isotretinoin treatment.

5.2.5 DISCUSSION

In a cohort of first-time isotretinoin users, 41% of subjects experienced an acne relapse necessitating further treatment with an anti-acne medication (isotretinoin or other). Twenty-six percent of subjects experienced a relapse severe enough to receive a second isotretinoin treatment at some point during their follow-up. Younger age, male gender, living in an urban area, and several healthcare utilization variables were associated with receiving an anti-acne medication (isotretinoin or other). Guidelines published over the years had no impact on the incidence of acne relapse. However, subjects were more likely to receive isotretinoin after the publishing of these guidelines.

Forty-one percent of the cohort experienced an acne relapse necessitating further treatment with an anti-acne medication. This figure is similar to what has been published previously.[12-14] Male subjects and those under the age of 16 were more likely to require further treatment with an anti-acne medication. Compared to subjects living in rural areas, those living in urban areas were more likely to require further treatment. A possible explanation for this finding is that subjects living in urban areas had a greater accessibility to physicians than those living in rural areas, and were thus more likely to consult a physician and receive an anti-acne medication. Subjects who visited an emergency department or who were hospitalized after the end of their isotretinoin treatment were less likely to experience an acne relapse. It is possible that these subjects had other serious medical conditions that may have prevented them from receiving an anti-acne medication. Furthermore, subjects who had isotretinoin treatment durations longer than the median (121 days) were less likely to experience an acne relapse, as well as those who had cumulative doses greater than 2450 mg. This is consistent with other studies that have investigated cumulative dose on the incidence of acne relapse.[6,10]

Interestingly, the acne guidelines published over the years had no impact on the incidence of acne relapse. This suggests one of two possibilities. The first is that these guidelines may not have been adequate in preventing relapses in subjects initially treated with isotretinoin. As such, future research

should determine the effectiveness of such guidelines on patient outcomes. The second is that physicians did not fully adhere to these guidelines. If true, it may be due to lack of awareness, lack of familiarity with new guidelines, disagreement, or inertia of previous practice.[28]

Twenty-six percent of the cohort required a second isotretinoin treatment at some point during the follow-up. This estimate is similar to what has been published previously.[8,10] Most were dispensed isotretinoin within the first two years after the end of their first treatment. In contrast to the first analysis, subjects were more likely to receive a second isotretinoin treatment in the years after the implementation of the PPP and other guidelines. The PPP and the other guidelines were meant to increase physician awareness of isotretinoin's potential side effects so as to restrict its use to patients who most need it. It appears that such guidelines had no impact on prescribing patterns. This could be due to the increasing prescribing of isotretinoin to subjects with mild or moderate acne,[29] or the fact that it is increasingly being used as a first line agent.[21,30,31]

There are a number of differences between the present study and the ones published previously. First, the present study is the largest to date with a sample size exceeding seventeen thousand first-time isotretinoin users. Previous studies had smaller sample sizes.[4-15] Second, the majority of

previous studies recruited patients from specialized settings such as dermatology clinics and hospitals.[4,5,7-9,12,13,15] Although the motivation for using patients from these settings was to facilitate recruitment, it does limit the generalizability of their results. Although the subjects included in the present study came from restricted socio-economic backgrounds, they were treated by physicians who also treat patients from higher socio-economic backgrounds. Thus all residents of the province of Quebec have access to the same medical care regardless of their socio-economic status. As a result, it is unlikely that subjects from lower socio-economic backgrounds would be treated differently than subjects from higher socio-economic backgrounds given the fact that both groups were reimbursed for their medications. Thus, we believe our cohort is representative of the acne population. Third, we were able to follow subjects for up to 20 years since the end of their first isotretinoin treatment. This long-term follow-up is essential for an accurate detection of relapses. Fourth, administrative databases contain complete information on healthcare services received and medications dispensed. Thus, we were able to control for important variables that are seldom collected in field studies. In addition, we considered predictors of receiving an anti-acne medication in four different time periods, from 12 months prior to the first isotretinoin treatment to the index date.

Despite the strengths mentioned above, the present study does have some limitations inherent in the use of administrative databases. Administrative

databases provide information only on those subjects who filled their prescriptions. Therefore, the number of subjects who experienced a relapse and did not consult a physician is unknown. It is also unknown the number of subjects who were prescribed an anti-acne medication but did not fill them at the pharmacy, or the number of subjects who used over-the-counter (OTC) products to treat their acne. Although these are possibilities, they are unlikely for the following two reasons. First, it is reasonable to assume that subjects who were previously treated for their acne would seek further treatment had they experienced an acne relapse. Not consulting a physician for an acne relapse may be indicative that the relapse was not severe enough to warrant further intervention. Second, all subjects included in this study were covered for their medications by the RAMQ drug plan. Thus, the cost of the medications is not likely to have been a major factor for not getting anti-acne medications, had they been prescribed. The use of OTC products is also likely to have been minimal. Because of their insurance status, subjects were more likely to get a prescription for products also found OTC (such as benzoyl peroxide).

Another limitation was that acne relapse was defined as receiving either a topical or systemic anti-acne medication. The inclusion of topical agents in this definition could have included subjects with mild acne who would not have been defined as relapsers in a clinical study. However, topical agents accounted for less than 20% of all anti-acne medications prescribed.

Furthermore, the majority of these agents are also prescribed for moderate acne (e.g. tretinoin, benzoyl peroxide). With regards to anti-acne medications not reimbursed by the RAMQ drug plan (e.g. adapalene), the exclusion of these agents is not likely to have had an impact on the acne relapse rate. Although such agents may be covered by some private insurance programs, physicians will typically prescribe medications they know are covered by their patient's insurance program. Thus, it is likely that physicians would replace an anti-acne medication not covered by a given insurance program by one that is. Other limitations of this study were that we were not able to directly adjust for acne severity, or the site of acne. This is because the ICD-9 classification does not specify the severity or the location of the acne. However, we did use anti-acne medication dispensing information in time periods before the index date, cumulative dose and length of the first isotretinoin treatment as proxies for acne severity.

Isotretinoin is an effective medication associated with long-term remissions in patients with acne. However, it remains that 41% of patients may experience an acne relapse necessitating further treatment with anti-acne medications. Several patient characteristics have been found to be associated with acne relapses. These data could be of prognostic value to clinicians who treat patients with acne.

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Table 1. Characteristics of cases and controls for the anti-acne medication analysis

Characteristics	Cases (n=7,100)	Controls (n=35,500)
Age (mean, SD)	25.2 (8.1)	25.5 (7.9)
Males (n, %)	3770 (53.1%)	17,833 (50.2%)
Welfare recipients (n, %)	3993 (56.2%)	16,982 (52.2%)
Urban dwellers (n, %)	5732 (80.7%)	26,678 (78.2%)

Table 2. Type of anti-acne medications dispensed (n=7100)	
	n (%)
Systemic retinoids	
Isotretinoin	4011 (56.5%)
Systemic antibiotics	
Minocycline	678 (9.6%)
Tetracycline	264 (3.7%)
Doxycycline	185 (2.6%)
Erythromycin	136 (1.9%)
Clindamycin	94 (1.3%)
Azithromycin	90 (1.3%)
Anti-microbial and hormonal agents	
Benzoyl peroxide	406 (5.7%)
Acne-specific oral contraceptives	176 (2.5%)
Topical retinoids	
Tretinoin	468 (6.6%)
Tazarotene	0 (0.0%)
Topical antibiotics	
Erythromycin	366 (5.2%)
Clindamycin	1 (0.01%)
Treatment combinations	
Systemic antibiotic plus topical antibiotic	90 (1.3%)
Systemic antibiotic plus topical retinoid or benzoyl peroxide	78 (1.1%)
Two topical agents	46 (0.6%)
Two systemic antibiotics	6 (0.1%)
Acne-specific oral contraceptives plus systemic antibiotic	5 (0.1%)

Table 3. Predictors of receiving an anti-acne treatment after being initially treated with isotretinoin

	Crude Rate Ratio (95% CI)	Adjusted Rate Ratio† (95% CI)
At index date		
< 16 years of age	1.31 (1.19, 1.44)	1.40 (1.26, 1.54)
Male gender	0.89 (0.85, 0.94)	1.14 (1.07, 1.20)
Urban dweller	1.16 (1.09, 1.24)	1.09 (1.01, 1.16)
Welfare recipient	1.15 (1.09, 1.21)	1.01 (0.94, 1.09)
Time periods		
January 1, 1984 – September 30, 1988	1.00 (Reference)	1.00 (Reference)
October 1, 1988 – December 31, 1994	1.44 (1.30, 1.58)	1.07 (0.97, 1.19)
January 1, 1995 – December 31, 1999	1.22 (1.11, 1.33)	1.02 (0.92, 1.13)
January 1, 2000 – June 30, 2003	1.14 (1.05, 1.24)	1.04 (0.94, 1.16)
Between the end of the first treatment and index date		
Number of different types of medications	1.09 (1.09, 1.10)	1.08 (1.07, 1.09)
Visits to the physician		
None	1.00 (Reference)	1.00 (Reference)
≥1	4.00 (3.71, 4.32)	3.83 (3.53, 4.15)
Visits to the emergency department		
None	1.00 (Reference)	1.00 (Reference)
≥1	1.13 (1.06, 1.22)	0.80 (0.74, 0.87)
Hospitalizations		
None	1.00 (Reference)	1.00 (Reference)
≥1	1.46 (1.33, 1.61)	0.86 (0.76, 0.96)
During the first isotretinoin treatment		
Number of different types of medications	1.04 (1.02, 1.05)	0.98 (0.96, 0.99)
At least one anti-acne medication	1.82 (1.66, 1.99)	1.71 (1.55, 1.89)
Visits to the physician		
None	1.00 (Reference)	1.00 (Reference)
≥1	0.93 (0.86, 1.01)	0.89 (0.82, 0.97)
Visits to the emergency department		
None	1.00 (Reference)	1.00 (Reference)
≥1	0.96 (0.89, 1.05)	1.00 (0.92, 1.10)
Hospitalizations		
None	1.00 (Reference)	1.00 (Reference)
≥1	1.09 (0.93, 1.26)	0.91 (0.77, 1.07)
Age of treating physician, years	1.00 (1.00, 1.01)	0.99 (0.99, 1.00)
Treated by male physician	1.03 (0.97, 1.10)	1.03 (0.96, 1.10)
Treated by dermatologist	1.03 (0.98, 1.08)	1.09 (1.03, 1.16)
≥ 2 isotretinoin prescribers	1.00 (0.90, 1.10)	1.09 (0.98, 1.22)
Cumulative dose		
<2450 mg	1.00 (Reference)	1.00 (Reference)
2450 – 4840 mg	0.76 (0.71, 0.81)	0.82 (0.76, 0.88)
4840 – 7584 mg	0.62 (0.58, 0.67)	0.75 (0.68, 0.83)
≥ 7584 mg	0.52 (0.49, 0.56)	0.63 (0.57, 0.70)
Treatment duration ≥ 121 days	0.65 (0.61, 0.68)	0.83 (0.76, 0.89)

Table 3. Predictors of receiving an anti-acne treatment after being initially treated with isotretinoin (continuation)		
12 months prior to the first isotretinoin treatment		
Number of different types of medications	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
At least one anti-acne medication	1.34 (1.27, 1.41)	1.36 (1.29, 1.44)
Visits to the physician		
None	1.00 (Reference)	1.00 (Reference)
≥1	1.27 (1.13, 1.44)	0.86 (0.76, 0.99)
Visits to the emergency department		
None	1.00 (Reference)	1.00 (Reference)
≥1	1.05 (0.99, 1.11)	0.98 (0.92, 1.05)
Hospitalizations		
None	1.00 (Reference)	1.00 (Reference)
≥1	1.11 (1.03, 1.20)	0.94 (0.86, 1.02)

Abbreviation: SD, standard deviation.
[†]Adjusted for the covariates in the table.

Table 4. Characteristics of cases and controls for the isotretinoin analysis		
Characteristics	**Cases (n=4443)**	**Controls (n=22,215)**
Age, years (mean, SD)	24.8 (7.9)	25.3 (7.9)
Males (n, %)	2235 (50.3%)	10,792 (48.6%)
Adherents (n, %)	2518 (56.7%)	12,287 (55.3%)
Urban dwellers (n, %)	3534 (79.5%)	17,383 (78.9%)

Table 5. Predictors of receiving a second isotretinoin treatment

	Crude Rate Ratio (95% CI)	Adjusted Rate Ratio† (95% CI)
At index date		
< 16 years of age	1.30 (1.16, 1.46)	1.26 (1.12, 1.43)
Male gender	1.07 (1.01, 1.14)	1.32 (1.22, 1.41)
Urban dweller	1.04 (0.96, 1.12)	0.94 (0.86, 1.02)
Welfare recipient	1.14 (1.06, 1.21)	1.08 (0.99, 1.17)
Time periods		
January 1, 1984 – September 30, 1988	1.00 (Reference)	1.00 (Reference)
October 1, 1988 – December 31, 1994	1.16 (1.03, 1.31)	1.10 (0.97, 1.24)
January 1, 1995 – December 31, 1999	1.10 (0.99, 1.22)	1.22 (1.09, 1.37)
January 1, 2000 – June 30, 2003	1.06 (0.96, 1.17)	1.29 (1.15, 1.46)
Between the end of the first treatment and index date		
Number of different types of medications	1.09 (1.08, 1.09)	1.11 (1.10, 1.12)
At least one anti-acne medication	2.06 (1.87, 2.27)	1.51 (1.36, 1.68)
Visits to the physician		
None	1.00 (Reference)	1.00 (Reference)
≥1	2.75 (2.52, 3.01)	2.71 (2.46, 2.98)
Visits to the emergency department		
None	1.00 (Reference)	1.00 (Reference)
≥1	1.05 (0.96, 1.15)	0.78 (0.70, 0.86)
Hospitalizations		
None	1.00 (Reference)	1.00 (Reference)
≥1	1.13 (1.00, 1.29)	0.76 (0.65, 0.88)
During the first isotretinoin treatment		
Number of different types of medications	1.00 (0.98, 1.01)	0.95 (0.93, 0.98)
At least one anti-acne medication	1.08 (0.95, 1.22)	0.94 (0.82, 1.08)
Visits to the physician		
None	1.00 (Reference)	1.00 (Reference)
≥1	0.74 (0.67, 0.81)	0.81 (0.73, 0.89)
Visits to the emergency department		
None	1.00 (Reference)	1.00 (Reference)
≥1	0.92 (0.83, 1.02)	1.03 (0.91, 1.15)
Hospitalizations		
None	1.00 (Reference)	1.00 (Reference)
≥1	0.99 (0.82, 1.21)	1.04 (0.84, 1.29)
Age of treating physician, years	1.01 (1.00, 1.01)	1.00 (1.00, 1.00)
Treated by male physician	1.15 (1.06, 1.24)	1.20 (1.10, 1.31)
Treated by dermatologist	1.00 (0.93, 1.06)	1.08 (1.00, 1.16)
≥ 2 isotretinoin prescribers	0.88 (0.77, 1.00)	1.09 (0.94, 1.26)
Cumulative dose		
<2450 mg	1.00 (Reference)	1.00 (Reference)
2450 – 4840 mg	0.71 (0.65, 0.77)	0.85 (0.77, 0.93)
4840 – 7584 mg	0.54 (0.50, 0.59)	0.80 (0.71, 0.90)
≥ 7584 mg	0.41 (0.37, 0.45)	0.62 (0.54, 0.71)
Treatment duration ≥ 121 days	0.52 (0.48, 0.55)	0.69 (0.62, 0.76)

Table 5. Predictors of receiving a second isotretinoin treatment (continuation)		
months prior to the first isotretinoin treatment		
Number of different types of medications	1.00 (1.00, 1.00)	0.99 (0.99, 0.99)
At least one anti-acne medication	1.13 (1.06, 1.21)	1.15 (1.07, 1.24)
Visits to the physician		
None	1.00 (Reference)	1.00 (Reference)
≥1	1.14 (0.99, 1.32)	0.90 (0.77, 1.06)
Visits to the emergency department		
None	1.00 (Reference)	1.00 (Reference)
≥1	1.05 (0.98, 1.13)	0.98 (0.90, 1.06)
Hospitalizations		
None	1.00 (Reference)	1.00 (Reference)
≥1	1.02 (0.92, 1.12)	0.95 (0.85, 1.06)

Abbreviation: SD, standard deviation.
[†]Adjusted for the covariates in the table.

Figure 1. Kaplan-Meier curve of first-time isotretinoin users requiring further treatment with an anti-acne medication (isotretinoin or other).

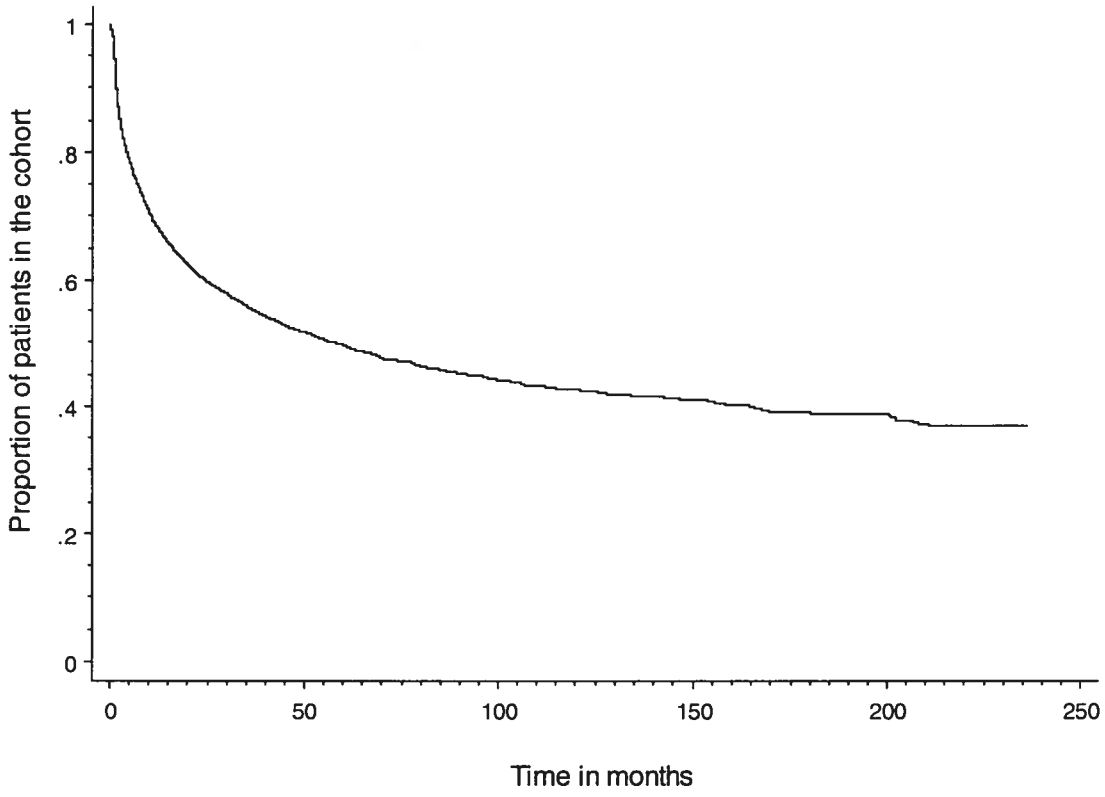
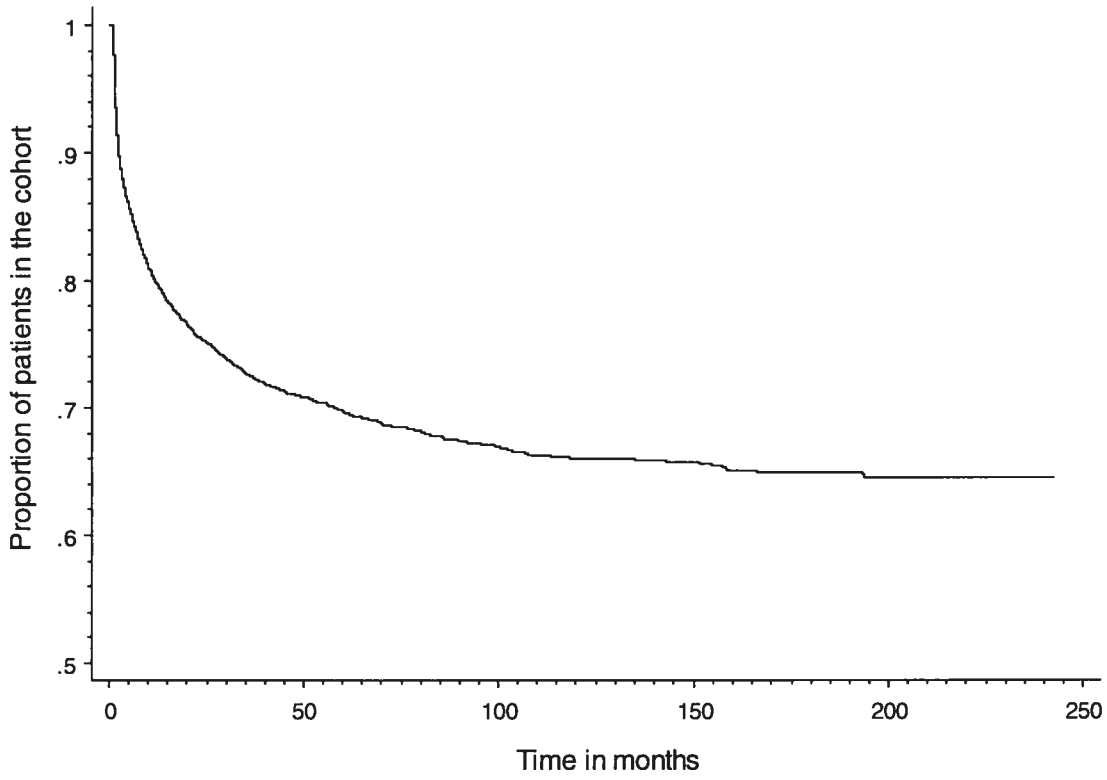


Figure 2. Kaplan-Meier curve of first-time isotretinoin users requiring a second isotretinoin treatment.



5.3 ISOTRETINOIN AND THE RISK OF DEPRESSION IN PATIENTS WITH ACNE VULGARIS: A CASE-CROSSOVER STUDY

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5.3.1 ABSTRACT

Objective: To determine whether isotretinoin increases the risk of depression in patients with acne vulgaris.

Methods: A case-crossover study was performed among subjects who received ≥1 isotretinoin prescription between 1984 and 2003. Data were obtained from the Régie de l'Assurance Maladie du Québec (RAMQ) and Quebec's hospital discharge (Med-Écho) administrative databases. Cases were defined as those with a first diagnosis or hospitalization for depression (ICD-9 codes: 296.2, 298.0, 300.4, 309.0, 309.1, and 311.0) during the study period (1984-2003), and who filled a prescription for an antidepressant in the 30 days following their diagnosis or hospitalization. The index date was the calendar date of the diagnosis or hospitalization for depression. Cases were covered by the RAMQ drug plan and had ≥1 acne diagnosis in the 12 months prior to the index date. Those who received an antidepressant in 12 months prior to the index date were excluded. Exposure to isotretinoin in a 5-month risk period immediately prior to the index date was compared to a 5-month control period. Relative risks (RR) along with 95% confidence intervals (CI) were estimated using conditional logistic regression.

Results: Of the 30,496 subjects in the initial cohort, 126 (0.4%) cases met inclusion criteria. The crude RR was 2.00 (95% CI: 1.03, 3.89). After

adjusting for potential time-dependent confounders, the RR was 2.68 (95%CI: 1.10, 6.48).

Conclusion: This is the first controlled study to find a statistically significant association between isotretinoin and depression. Because depression could have serious consequences, close monitoring of isotretinoin users is indicated.

5.3.2 INTRODUCTION

Isotretinoin is an effective medication in the treatment of severe recalcitrant nodular acne. Therefore, the expected result of a successful treatment would be improvements in quality of life, and decreases in rates of anxiety and depression.[1-5] However over the past two decades, case reports have suggested a controversial association between isotretinoin and depression.[6-10]

Observational studies investigating this association have produced contradictory results. Whereas in some studies no association was found between isotretinoin and depression,[11,12] one study found that it increases the use of mental health services.[13] Against this backdrop, the US Food and Drug Administration has received reports of 394 cases of depression, and 37 suicides in patients exposed to isotretinoin between 1982 and 2000.[14,15] In the US Adverse Event Reporting System (AERS), isotretinoin is the fifth most common medication linked to depression, and the tenth most common linked to suicide reports.[14] Using data mining techniques, Wysowski et al.[14] estimated that 6 suicide reports would be expected to be reported in the AERS by chance compared with the 37 actually reported. In Canada, out of the 222 isotretinoin adverse events archived in the Health Canada adverse drug reaction database between 1983 and 2003, 56 (25%) were psychiatric.[16]

These reports have prompted several governments to modify their isotretinoin package labeling to include depression as a possible side effect of the drug. These modifications were first introduced in France in March 1997,[17] the US in February 1998 and Canada in May 2000.[15] In 2001, a Dear Health Care Professional Letter was sent to Canadian physicians advising them to closely monitor patients presenting with depression or depressive symptoms during the course of an isotretinoin treatment.[18]

Given the contradictory results in the current literature and the repeated signals reported in adverse drug reaction databases, the association between isotretinoin and depression warrants further investigation. Therefore, the objective of the present study was to determine whether there is an association between isotretinoin and depression in patients with acne vulgaris.

5.3.3 METHODS

5.3.3.1 DATA SOURCES

Data were obtained from the Régie de l'Assurance Maladie du Québec (RAMQ) and Quebec's hospital discharge (Med-Écho) administrative databases. All Quebec residents are covered by the RAMQ for medical services. Prior to January 1, 1997, the RAMQ drug plan covered those who were 65 years and older and welfare recipients and their children. After

January 1, 1997, the RAMQ drug plan was changed to also include workers and their spouses/children who do not have access to a private insurance program. The RAMQ drug plan covers approximately 50% of Quebec residents.[19]

The medical and pharmaceutical databases of the RAMQ were linked by a unique patient identification number. The medical claims database includes information on the date and type of services received, and diagnoses are classified according to the International Classification of Diseases, Ninth revision (ICD-9).[20] The pharmaceutical claims database contains information on the date medications were dispensed, formulations, doses, duration of prescriptions, and quantities dispensed. Medications prescribed during hospitalizations are not included in the database. Both the medical and pharmaceutical claims databases have been validated and shown to be accurate for certain diagnoses.[21,22]

The unique patient identification number was also used to link the RAMQ to the Med-Écho administrative databases. Med-Écho contains hospitalization data on all Quebec residents. This data includes patient demographic information, physician characteristics, admission diagnostic, length of stay, as well as all services received during the hospitalization. Medical diagnoses recorded in Med-Écho have been shown to be valid and precise.[23]

The study protocol was approved by the CHU Sainte-Justine Ethics Committee and the Commission d'accès à l'information du Québec.

5.3.3.2 STUDY DESIGN

We employed a case-crossover design first introduced by Maclure in 1991.[24] In the case-crossover design, cases serve as their own controls by assessing exposure at different time intervals. The time intervals in which exposure is assessed are the risk and control periods. The risk period is a time interval immediately prior to the event. The control periods are time intervals that are prior and equal in length to the risk period, and provide an expected baseline frequency of exposure for each study subject in the absence of the outcome. Since cases serve as their own controls, time-independent confounders (known and unknown) are automatically adjusted by design. Confounders that change over time must be adjusted for in the analyses.

5.3.3.3 CASE DEFINITION

Cases were selected from a cohort of subjects who received at least one isotretinoin prescription between January 1, 1984 and December 31, 2003. Incident cases of depression were defined according to the following algorithm. We identified all subjects with a first diagnosis or hospitalization for depression (ICD-9 codes: 296.2, major depressive disorder, single

episode; 298.0, depressive type psychosis, 300.4, neurotic depression; 309.0, brief depressive reaction; 309.1 prolonged depressive reaction; 311, depressive disorder, not elsewhere classified) during the study period (1984-2003). In addition to having been diagnosed or hospitalized for depression, cases were required to have filled an antidepressant prescription (American Hospital Formulary System code: 28:16.04) in the 30 days following their diagnosis or hospitalization. The index date was defined as the calendar date of the diagnosis or hospitalization for depression.

Furthermore, cases had to be covered by the RAMQ drug plan for at least 12 months prior to the index date. This was deemed necessary to ensure that drug exposure information was available during the time periods of interest. In addition, cases had to have at least one diagnosis of acne vulgaris (ICD-9 code: 706.1) at any time in the 12 months prior to the index date. This criterion ensured that cases had acne and thus had an exposure opportunity to receiving isotretinoin. Finally, cases were excluded if they had received an antidepressant prescription in the 12 months prior to the index date. Since the index date was defined as the subject's first diagnosis or hospitalization for depression in their entire recorded medical history, none had any diagnoses or hospitalizations for depression at any time prior to the index date. That time period ranged from a minimum of 12 months up to 20 years.

5.3.3.4 TIME WINDOWS

The risk period was hypothesized to be a total of 5 months based on data found in the literature.[6,25,26] A five-month control window was separated from the risk window by a two-month washout period (Figure 1). A two-month washout period was chosen because product guidelines suggest initiating a second course of isotretinoin in those who have not responded to the treatment only eight weeks after the completion of a first course.[27] This is because improvements continue to occur during that time period despite having terminated the treatment.

5.3.3.5 POTENTIAL CONFOUNDERS

By design, the case-crossover method adjusts for time-independent confounders, such as socioeconomic status or gender. However, the following potential time-dependent confounders were recorded in each time window and adjusted for in the models: dermatologic visits, non-dermatologic visits, ≥1 hospitalization, ≥1 emergency department visit, and comorbidity. Dermatologic visits were defined as consulting a dermatologist and/or being diagnosed with acne vulgaris (ICD-9 code: 706.1). Comorbidity was assessed using the total number of different types of medications prescribed, other than isotretinoin. The number of different types of medications has been shown to be a very good predictor of healthcare utilization, similar to other comorbidity measures.[28]

5.3.3.6 STATISTICAL ANALYSES

Descriptive statistics were used to describe the characteristics of the cases. Relative risks (RR) along with 95% confidence intervals (CI) were estimated using conditional logistic regression with the individual case as the stratifying variable. In a first analysis, exposure to isotretinoin was entered as a dichotomous variable in the models (exposed at least once during each specific time window, yes or no). In a second analysis, we determined whether there was a dose-response of isotretinoin on the incidence of depression. The cumulative dose in milligrams of isotretinoin dispensed was calculated in each time window and entered as quartiles in the models. Crude and adjusted models were calculated for all situations. Analyses were two-sided and $p \leq 0.05$ was considered significant. SAS version 8.2 (SAS Institute, Cary, NC) was used to conduct the analyses.

5.3.4 RESULTS

Of the 30,496 subjects in the initial cohort, 126 (0.4%) cases met the inclusion criteria. This corresponded to 126 risk periods matched to 126 control periods. The mean age of cases was 28.1 (SD: 9.0) years, over 60% were males, and most were urban dwellers (Table 1).

Most cases were diagnosed with neurotic depression (65%), followed by brief depressive reaction (15%), depressive disorder (9%), major depressive

disorder (6%), depressive type psychosis (3%), and prolonged depressive reaction (2%). The most frequently prescribed antidepressants were selective-serotonin reuptake inhibitors (48%), tricyclics (37%), New Antidepressants (13%) and monoamine oxidase inhibitors (2%). Depression was diagnosed by psychiatrists (49%), general practitioners (47%) and other physicians (4%) (data not shown).

5.3.4.1 ISOTRETINOIN AND DEPRESSION

The number of cases exposed to isotretinoin in the 5-month risk and control periods were 41 (32.5%) and 28 (22.2%), respectively. Twenty-six cases were exposed in the risk and not the control period, versus 13 exposed in the control and not the risk period (crude RR = 26/13 = 2.0) (Table 2). The adjusted RR of isotretinoin associated with depression was 2.68 (95% CI: 1.10, 6.48) (Table 3).

To assess whether our results could be explained by surveillance bias due to increased physician awareness of isotretinoin's possible psychiatric effects, we stratified the cases according to the calendar date of Canadian label change addressing isotretinoin's possible psychiatric risks. There were no differences in the RRs of cases diagnosed or hospitalized for depression after the label change (after May 2000) than cases diagnosed or hospitalized for depression before the label change (before May 2000) (data not shown).

5.3.4.2 CUMULATIVE DOSE

Although the effect sizes were large, none of the cumulative doses of isotretinoin in the adjusted model reached statistical significance (Table 4).

5.3.5 DISCUSSION

To our knowledge, the present controlled study is the first to detect an association between isotretinoin and depression in patients with acne vulgaris. The risk of depression in subjects with no previous history of the condition increases close to 3-fold after being exposed to isotretinoin. Because depression could have serious consequences, our results advocate for close monitoring of patients undergoing isotretinoin therapy. This may be done by administering psychiatric assessments prior and during therapy.

To date, Jick et al.[11] conducted the largest population-based study investigating the association between isotretinoin and depression, psychotic symptoms and suicide. They used data collected between 1983 and 1997 in the Saskatchewan database and the United Kingdom General Practice Research Database. In their primary analysis, the authors compared a cohort of patients with acne treated with isotretinoin to another cohort treated with systemic antibiotics. No association was found between isotretinoin and depression, psychotic symptoms or suicide. Unlike the study conducted by Jick et al.,[11] it was not possible to determine whether there is an association

between isotretinoin and suicide, given that we had access only to inpatient and outpatient medical visits. However, with regards to depression, there are several reasons why our results differ from that study. First, we used a strict case definition where cases were required to have both a diagnosis or hospitalization for depression and an antidepressant. This led to the inclusion of 126 cases. Despite this small sample size, the associations obtained were large enough to be statistically significant. In contrast, Jick et al.[11] identified cases of depression using diagnostic codes alone, and thus it is possible that some cases were misclassified as non-cases which could have biased the RRs towards the null. Second, we identified incident cases of depression. The cases identified in the present study had no diagnoses or hospitalizations for depression for a minimum of 12 months up to 20 years prior to the index date. In contrast, Jick et al.[11] adjusted for previous psychiatric history using data recorded 6 months up to 5 years before the first isotretinoin prescription. Therefore it is likely that some residual confounding occurred, which would have once again biased the RRs towards the null. Finally, one of the strengths of the case-crossover design is that cases serve as their own controls. As such, known and unknown time-independent confounders are automatically adjusted by design.

In claims data, the length of the risk and control periods necessitates knowledge of the duration of exposure required to alter the risk for an outcome, to become noticed by the physician, and then be recorded in the

administrative database.[29] Depression has been reported as early as 1 day and up to 4 months after initiating an isotretinoin treatment.[6,25,26,30] Therefore, the maximum induction time was hypothesized to be 4 months. Furthermore, patients undergoing isotretinoin treatment are typically seen by their treating physicians at 1-month intervals. As such, if depressive symptoms do appear, physicians would be expected to diagnose them at one of the follow-up visits. For these reasons, the risk period was set to be 5 months in length. This time window also concords with the recommended duration of an isotretinoin treatment.[31,32]

5.3.5.1 DOSE-RESPONSE RELATIONSHIP

Although the effect measures relating cumulative dose of isotretinoin to depression were large, none reached statistical significance. This is likely due to the small number of cases in each cumulative dose stratum. Studies with greater sample sizes would be needed to determine the exact dose-response relationship between isotretinoin and depression.

Acne has been associated with depression, suicidal ideation, and suicide in patients.[33,34] Acne is thus an important confounder of the isotretinoin-depression association. The presence of acne was intrinsically controlled by requiring cases to have at least one acne diagnosis in the 12 months prior to the index date. Due to the retrospective nature of the study and lack of

clinical data, it was not possible to directly adjust for acne severity. However, the possibility of confounding by acne severity is unlikely for the following four reasons. First, all cases had at least one acne diagnosis in the 12 months prior to their index date. This indicates that cases received medical attention for their acne, and were thus likely to have received an anti-acne medication. Receiving an anti-acne treatment should to the very least stabilize the severity of acne, and it is therefore unlikely that it may have worsened during the study period. Second, although there is a correlation between acne and depression, previous studies found no correlation between acne severity and depression,[35,36] thus putting into question whether severity is a true confounder. Third, isotretinoin is a highly effective medication whose utilization is associated with drastic reductions in acne lesions. In theory, the clearing of acne lesions should be associated with improvements in depressive symptoms and quality of life. Fourth, there is evidence that isotretinoin is being prescribed to patients with mild or moderate acne,[37] or as a first line treatment.[27,38] Thus, not all patients receiving isotretinoin have severe nodular acne. We nonetheless attempted to control for acne severity by adjusting our models for dermatologic visits in the risk and control periods, although such analyses would have been subject to some residual confounding.

The present study has limitations inherent in the use of administrative databases. Variables such as smoking, alcohol consumption, and illicit drug

use are not available in administrative databases. Although these variables are likely to be associated with depression, it is unclear how they would be related to the use of isotretinoin. Furthermore, these variables are unlikely to have changed over a 12-month period. Given their time-independent nature, they would be automatically adjusted by design in a case-crossover study. Administrative databases report only on medications dispensed, and therefore it is unknown whether medications are actually taken by patients. However, given that isotretinoin is typically prescribed for 30-day intervals, renewals between successive prescriptions is indicative of patient adherence.[38] One major advantage of administrative databases is that they are not prone to recall bias. As such, they provide accurate information on the number, types and dosages of medications dispensed over a specific time period. Coding errors may be present in administrative databases. If that were the case, non-differential misclassification of the outcome would result biasing the RRs towards the null. If coding errors did occur in our data, then the estimates obtained would actually be underestimates of the true RR.

There are several studies that have pointed to a possible biological association between isotretinoin and depression. Isotretinoin and vitamin A share similar chemical structures, as such many side effects of isotretinoin are similar to Vitamin A when taken in large doses.[39] Hypervitaminosis A has been shown to induce irritability and depressive symptoms.[40-42] One study

found that exposure to retinoic acid results in hippocampal cell loss in mice.[43] In humans, hippocampal volume has been shown to be inversely related to depression,[44] indirectly supporting the hypothesis that isotretinoin may cause cell loss in this region of the brain. Another study found that daily intake of 1 mg/kg of isotretinoin for 6 weeks in young male mice (similar doses used in humans) was associated with depression-like behavior.[45] Recently, Bremner et al.[46] assessed brain function in patients with acne treated with isotretinoin and antibiotics. They found that isotretinoin decreased metabolism in the orbitofrontal cortex, a region of the brain known to be involved in depression. This effect was not observed in patients treated with antibiotics. More research is needed to elucidate the exact mechanisms through which isotretinoin may induce depression.

Depression is likely to be a rare side effect of isotretinoin therapy. The present study supports close monitoring of patients during the treatment for possible signs of such symptoms. Current guidelines should possibly be modified to include psychiatric assessments of patients prior and during isotretinoin therapy.

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Table 1. Characteristics of cases (n=126)

Characteristics	
At the index date	
Age, years, mean (SD)	28.1 (9.0)
Males, n (%)	47 (37.3%)
Welfare recipients, n (%)	88 (70.0%)
Urban dwellers, n (%)	106 (84.1%)
In the 12 months prior to the index date	
Dermatologic visits[¶], mean (SD)	1.1 (1.3)
Non-dermatologic visits, mean (SD)	6.2 (7.1)
At least one visit to the emergency department, n (%)	42 (33.3%)
At least one hospitalization, n (%)	24 (19.1%)
Number of different medications other than isotretinoin, mean (SD)	5.5 (4.0)

Abbreviations: SD, standard deviation.

[¶]Defined as consulting a dermatologist and/or being diagnosed with acne during a visit to the MD (ICD-9 code: 706.1).

Table 2. Two-by-two table of cases exposed in the risk and control periods

		Control period	
		Exposed	**Not exposed**
Risk period	**Exposed**	15	26
	Not exposed	13	72

Crude RR = 26/13 = 2.0

Table 3. Risk of depression associated with exposure to isotretinoin using 5-month risk and control periods

	Crude relative risk (95% confidence interval)	Adjusted relative risk[†] (95% confidence interval)
Exposure to isotretinoin	2.00 (1.03, 3.89)	2.68 (1.10, 6.48)
Non-dermatological visits	1.21 (1.10, 1.34)	1.13 (1.01, 1.25)
Dermatologic visits[¶]	1.09 (0.90, 1.30)	0.81 (0.62, 1.05)
At least one hospitalization	2.44 (1.13, 5.31)	1.73 (0.65, 4.58)
At least one emergency department visit	1.81 (0.98, 3.34)	0.94 (0.43, 2.04)
Number of different medications other than isotretinoin	1.40 (1.20, 1.63)	1.34 (1.11, 1.61)

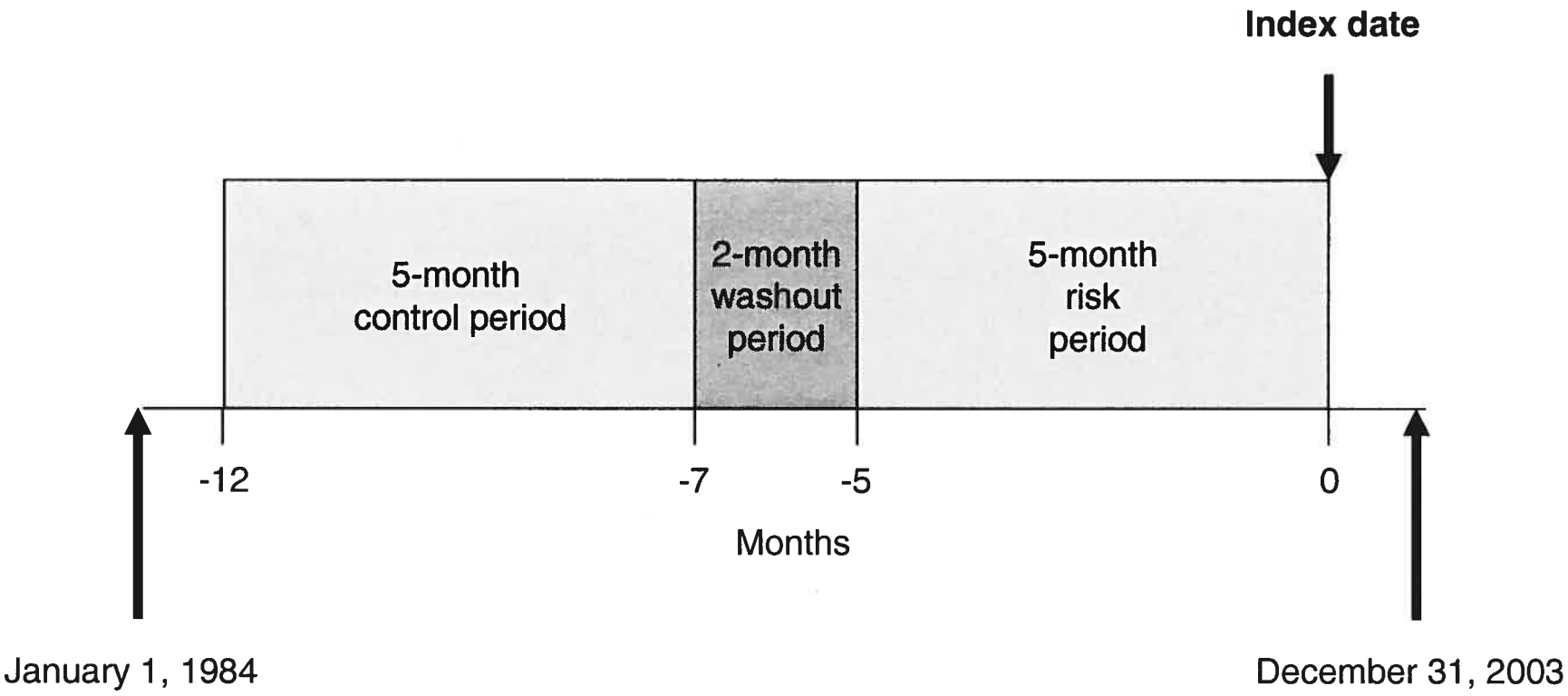
[†]Adjusted for the covariates in the table.
[¶]Defined as consulting a dermatologist and/or being diagnosed with acne during a visit to the MD (ICD-9 code: 706.1).

Table 4. Risk of depression associated with isotretinoin cumulative dose using 5-month risk and control periods

	Crude relative risk (95% confidence interval)	Adjusted relative risk[†] (95% confidence interval)
Cumulative dose of isotretinoin		
0 mg	Reference (1.00)	Reference (1.00)
300 – 1200 mg	0.52 (0.05, 5.42)	0.79 (0.05, 13.86)
1200 – 2400	3.09 (1.04, 9.15)	3.24 (0.89, 11.79)
2400 – 4800 mg	2.55 (0.81, 8.01)	3.13 (0.84, 11.64)
≥ 4800 mg	1.46 (0.53, 4.00)	2.14 (0.62, 7.43)
Non-dermatological visits	1.21 (1.10, 1.34)	1.13 (1.01, 1.26)
Dermatologic visits[¶]	1.09 (0.90, 1.30)	0.82 (0.62, 1.07)
At least one hospitalization	2.44 (1.13, 5.31)	1.69 (0.63, 4.53)
At least one emergency department visit	1.81 (0.98, 3.34)	0.92 (0.42, 2.02)
Number of different medications other than isotretinoin	1.40 (1.20, 1.63)	1.33 (1.10, 1.60)

[†]Adjusted for the covariates in the table.
[¶]Defined as consulting a dermatologist and/or being diagnosed with acne during a visit to the MD (ICD-9 code: 706.1).

Figure 1. Case-crossover analysis using 5-month risk and control periods separated by a 2-month washout period



5.4 ISOTRETINOIN AND THE RISK OF DEPRESSION: A COMPARISON OF SELF-MATCHED DESIGNS

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5.4.1 ABSTRACT

Isotretinoin is the most effective treatment for severe nodular acne. Over the years however, it has been associated with depression, suicidal ideation, and suicide. Using a large cohort of subjects who received ≥1 isotretinoin prescription from 1984 to 2003 in the province of Quebec, the authors identified 126 incident cases of depression on which they conducted a case-crossover study. There was 2- to 3-fold increase in the risk of depression in subjects exposed to isotretinoin. This was the first study to find a statistically significant association between isotretinoin and depression. However, this association may have been confounded by exposure time-trends. The case-time-control design is an extension of the case-crossover which was developed to correct for such exposure time-trends. Thus, the objective of the present study was to determine whether there was an exposure time-trend, and adjust for it using the case-time-control design. This required selecting a control group with no previous history of depression. A total of 1149 controls were matched to cases on age, sex, and calendar year. The adjusted odds ratio of depression related to isotretinoin exposure in the case-time-control design was 1.56 (95% confidence interval: 0.66, 3.73). Although it did not reach statistical significance, the relatively large odds ratio is suggestive of an association. Several assumptions and conditions inherent to the use of the case-time-control design are emphasized.

5.4.2 INTRODUCTION

Isotretinoin is the most effective treatment for severe nodular acne, capable of inducing long-term remissions (1-3). However, it is a well known teratogen (4, 5), and has been associated with a number of side effects (6). Over the years, case reports and adverse reaction databases have signaled a possible association with depression (7-10). This was reported as early as 1983 (7), a year after the medication was marketed in the US, and the same year it was introduced in Canada.

Although several observational studies have investigated whether there was an association between isotretinoin and depression, none found a link (11-14). However, these studies were either uncontrolled, had small sample sizes, or suffered from methodological problems such as case ascertainment. Using a case-crossover design, we were the first to find a statistically significant association between isotretinoin and depression (Azoulay et al., University of Montreal, in press). The case-crossover design offered two important methodological advantages. First, there was no need to select a separate control group, since patients served as their own controls. This eliminated the possibility of control selection bias. Second, the design automatically adjusted for known and unknown time-independent confounders.

Despite these advantages, the case-crossover design does have a few limitations. First, it does not adjust for confounders that change over time. Thus known time-dependent confounders must be adjusted for in analyses. Second, an assumption of the case-crossover design is the absence of a time-trend in the exposure. Often this is not the case, such as when a medication is aggressively marketed leading to an increase in its utilization, or during pregnancy for example, a time when there is a decrease in the prescribing of certain medications (15). In either situation, a bias is introduced in the model because of the exposure time-trend. Thus, time-trend alone can explain an association or lack of association between an exposure and an outcome. With regards to isotretinoin, its prescribing has been shown to have significantly increased over the years (16). Its utilization outside its intended indication (16), and the fact that it is being used as a first line treatment for acne might explain such increases (17, 18). As a result, the association observed with the case-crossover design may have been biased by an exposure time-trend. This would have overestimated, and possibly explained the association observed between isotretinoin and depression.

The case-time-control introduced by Suissa in 1995 (19), is an extension of the case-crossover design whose goal is to correct for any exposure time-trend. Therefore, the objective of this study was to determine the impact of an exposure time-trend on the association between isotretinoin and

depression by comparing the point estimates from the case-crossover and case-time-control designs.

5.4.3 MATERIALS AND METHODS

5.4.3.1 DATA SOURCES

Data for the isotretinoin cohort studied here were obtained from the Régie de l'Assurance Maladie du Québec (RAMQ) and Quebec's hospital discharge (Med-Écho) administrative databases. The RAMQ covers all Quebec residents for medical services. In addition, prior to January 1, 1997, the RAMQ also covered those who were 65 years and older, and welfare recipients and their children for their medications. After January 1, 1997, the RAMQ drug plan was modified to also include workers and their spouses/children who did not have access to a private medication insurance program (adherents). Approximately 50 percent of all Quebec residents are covered by the RAMQ drug plan (20).

A unique patient identification number was used to link the medical and pharmaceutical databases of the RAMQ. The medical database includes information on the date and type of services received, and diagnoses are classified according to the International Classification of Diseases, Ninth revision (ICD-9) (21). The pharmaceutical database contains information on the subject's socioeconomic status (welfare recipient or adherent), characteristics of the prescribing physicians, date medications were dispensed, formulations, doses, duration of prescriptions, and quantities dispensed. Medications prescribed during hospitalisations are not included in the database. Both the medical and pharmaceutical claims databases have been validated and shown to be accurate (22, 23).

The RAMQ databases were also linked to the Med-Écho databases via the unique patient identification number. Med-Écho contains hospitalisation data on all Quebec residents. This database includes patient demographic information, physician characteristics, admission diagnoses, length of stay, as well as all services received during the hospitalisation. Medical diagnoses (ICD-9 codes) recorded in Med-Écho have been shown to be valid and precise (24).

The study protocol was approved by the CHU Sainte-Justine Ethics Committee and the Commission d'accès à l'information du Québec.

5.4.3.2 STUDY POPULATION

The study population was composed of subjects from the province of Quebec who received at least one isotretinoin prescription, in either the 10 mg or 40 mg formulation (drug identification numbers 582344 and 582352, respectively) between January 1, 1984 and December 31, 2003.

5.4.3.3 CASE-CROSSOVER DESIGN

The case-crossover design was first introduced by Maclure in 1991 (25). In this design, cases serve as their own controls by determining exposure at different time intervals. Thus, this design removes the need of selecting a separate control group. The time intervals in which exposure is assessed are the risk and control periods. The risk period is a time interval immediately prior to the event. The control period is a time interval prior and equal in

length to the risk period, and provides an expected baseline frequency of exposure for each study subject in the absence of the outcome. This design was originally designed to study transient exposures with acute effects. However, it is possible to use the case-crossover for prolonged exposures and insidious outcomes by increasing the length of the risk and control periods (26, 27). Given that cases serve as their own controls, time-independent confounders (known and unknown) are automatically adjusted by design. Confounders that change over time must be adjusted for in analyses.

Case definition has been described previously (Azoulay et al., University of Montreal, in press). Briefly, within our study population, we identified all subjects with a first diagnosis or hospitalization for depression (ICD-9 codes: 296.2, 298.0, 300.4, 309.0, 309.1, 311) during the study period (1984-2003). Subjects had to have received at least one antidepressant prescription in the 30 days following their diagnosis or hospitalization. Their index date was defined as the calendar date of the diagnosis or hospitalization for depression. They were required to be covered by the RAMQ drug plan at least 12 months prior to index, and have at least one acne diagnosis (ICD-9: 706.1) during that same period. Those with who filled an antidepressant in the 12 months prior to the index date were excluded.

We hypothesized the risk period to be a total of 5 months based on data found in the literature (7, 28, 29). That time window also corresponds to the recommended duration of an isotretinoin treatment (30, 31). The risk period immediately followed the index date which was separated from a 5-month control period by a 2-month washout period.

We adjusted for non-dermatologic visits, dermatologic visits, all-cause hospitalizations, emergency department visits, and comorbidity measured in the risk and control periods independently. Dermatologic visits were defined as either consulting a dermatologist, or being diagnosed with acne vulgaris (ICD-9 code: 706.1) by a general practitioner. Comorbidity was assessed using the total number of different types of medications prescribed, other than isotretinoin.

5.4.3.4 CASE-TIME-CONTROL DESIGN

The case-time-control requires selecting a control group around the same calendar period as the cases. Using these controls, a control-crossover is performed using the same time window scheme as in the case-crossover, to determine whether there is an exposure time-trend. Thus, the odds ratio (OR) obtained with the case-crossover is divided by the OR of the control-crossover to produce an OR adjusted for exposure time-trend (case-time-control). This design implicitly makes the assumption that the OR obtained

from the case-crossover is a product of the OR relating the exposure to the outcome and the OR produced by exposure time-trend. It also assumes that the exposure time-trend is the same in the cases and controls.

In the case-time-control design, we used the same cases that were used in the case-crossover design. As for controls, they were selected according to the following algorithm. We first identified all subjects who were non-cases in the study population. For each subject in the non-case pool, we generated a random index date between the first and last day of their coverage in the RAMQ drug plan. Subjects had to be covered at least 12 months prior to the index date, and have at least one acne diagnosis (ICD-9: 706.1) during that same time period. Subjects were excluded of they had received an antidepressant prescription in the 12 months prior to the index date, or a diagnosis or hospitalization for depression (ICD-9 codes: 296.2, 298.0, 300.4, 309.0, 309.1, 311) at any time prior to the index date. Up to 10 controls were matched to each case on age (±3 years), sex, and calendar year (±1 year).

Exposure to isotretinoin was assessed using the same time window scheme as in the case-crossover design. Similarly, we adjusted the model for non-dermatologic visits, dermatologic visits, all-cause hospitalizations,

emergency department visits, and comorbidity measured in the risk and control periods, independently.

5.4.3.5 STATISTICAL ANALYSIS

Descriptive statistics were used to summarize the characteristics of cases and controls. For the case-crossover design, odds ratios (OR) with corresponding 95 percent confidence intervals (CI) were estimated using conditional logistic regression using the individual subject as the stratifying variable. For the case-time-control, a conditional logistic regression was fitted with time (risk versus control periods) as the dependent variable and the exposure and an interaction term (the product of the exposure and case group) as the independent variables. Crude and adjusted ORs were estimated for both study designs. SAS version 8.2 (SAS Institute, Cary, NC) was used to carryout the analyses.

5.4.4 RESULTS

5.4.4.1 CASE-CROSSOVER DESIGN

In the original case-crossover analysis, 126 cases met the inclusion criteria. In the present study, 2 cases could not be matched to suitable controls, leaving 124 cases for analysis. This corresponded to 124 risk periods matched to 124 controls periods. The characteristics of the cases are presented in Table 1. The number of cases exposed to isotretinoin in the 5-month risk and control periods was 41 (32.5 percent) and 28 (22.2 percent), respectively. Twenty-six (21.0 percent) cases were exposed in the risk and not the control period, versus 13 (10.5 percent) exposed in the control and not the risk period (crude OR = 26/13 = 2.00) (Table 2). After adjusting for time-dependent confounders, the OR (95 percent CI) was 2.47 (1.06, 5.75) (Table 2).

5.4.4.2 CASE-TIME-CONTROL DESIGN

A total of 1149 controls met the inclusion criteria. Despite matching on age, sex, and calendar year, controls appeared healthier than cases (Table 1).

In the control-crossover, the number exposed to isotretinoin in the 5-month risk and control periods in the control-crossover analysis was 403 (35.1 percent) and 311 (27.1 percent), respectively. Two-hundred-ninety-eight (25.9 percent) controls were exposed in the risk and not the control period,

versus 206 (17.9 percent) exposed in the control and not the risk period (crude OR = 298/206 = 1.45) (Table 2). The adjusted case-time-control OR (95 percent CI) determined by dividing the adjusted case-crossover OR by the adjusted control-crossover OR was 1.56 (0.66, 3.73) (Table 2).

5.4.5 DISCUSSION

In the present study, we compared the point estimates obtained in the case-crossover design to the ones obtained in the case-time-control design. A case-time-control OR close to unity would have been expected if the association between isotretinoin and depression was solely due to an exposure time-trend. The OR obtained using the case-time-control design was 1.56, although it did not reach statistical significance. This indicates that trends in isotretinoin prescribing cannot account for the entirety of the association. However, controls used in the case-time-control appeared healthier than cases, and may have thus overestimated the exposure time-trend. These results emphasize the important assumptions and conditions implicit in the use of the case-time-control design.

The case-time-control design revealed an exposure time-trend in the use of isotretinoin during the time periods of interest. This could be due to the increasing prescribing of isotretinoin to patients with mild or moderate acne (16), or the fact that it is increasingly being prescribed as a first line agent

(17, 18, 32). The exposure time-trend however, did not fully explain the association between isotretinoin and depression. Although the point estimate of the case-time-control was relatively high (OR=1.56), it did not reach statistical significance. Two factors can explain this lack of statistical significance. The first is the small sample size resulting in a lack of statistical power to detect an OR of this magnitude. The second is that in the case-time-control design, there is loss in precision caused by within-subject correlations. This reduces the effective study size (19). In fact, the standard error of the case-time-control design was larger than the one produced by the case-crossover design.

The case-time-control design is only valid under certain conditions (33, 34). Greenland showed that adjustment for exposure time-trend cannot be universally valid (33). A caveat of the case-time-control design is that unmeasured confounders are not different between cases and controls. However, if any unmeasured confounder is differential between cases and controls, so would be their use of the study medication. In such situations, using controls to correct for an exposure time-trend would introduce a new bias, which may be larger than the original time-trend bias (33). Although we matched controls to cases on age, sex, and calendar year, there were differences in their healthcare utilization in the 12 months prior to the index date. The general health of the cases appeared to be worse than that of controls. Therefore, it is possible that controls were more likely to use

isotretinoin than cases because of their better health status. This corroborates with our findings, where 22.2 percent of cases versus 27.1 percent of controls were exposed in the control period. Thus, using healthier controls is likely to have overestimated the exposure time-trend, and biased the case-time-control OR towards the null.

The bidirectional case-crossover is another method for correcting exposure time trends that does not require selecting separate controls (35). Using this approach, exposures are determined both before and after the outcome in cases. The premise of this approach is that any time-trend before the outcome would cancel out with the time-trend after the outcome. This design has been frequently used in environmental epidemiology to determine the seasonal variation of pollutants on health outcomes (36). However, an important assumption of this model is that the outcome does not affect subsequent exposure. This may not be the case for all outcomes, such as death, where subsequent exposure to a medication will not occur. We did not perform a bidirectional case-crossover for the following two reasons. First, isotretinoin is an effective medication where only 26 percent of subjects require a second treatment course (3, 18). As such, it is unlikely for subjects to have more than one treatment course. Second, if it is suspected that isotretinoin triggered or caused depression, it is unlikely that it would be prescribed again even if the subject's acne relapsed. It is more likely that the treating physician would consider other treatment options. Because of the

methodological limitations of the bidirectional case-crossover in investigating our study question, we used the case-time-control to adjust for possible time trends in the exposure (19).

The present study is an illustration of how self-matched designs can be easily implemented using administrative databases. Provided the research question is appropriate, self-matched designs may be particularly useful when using administrative databases. First, there is no need to adjust for time-independent confounders that are not recorded in administrative databases. This net advantage over other conventional designs makes self-matched designs attractive alternatives when using these data sources. Second, self-matched designs conducted by interviewing subjects are prone to differential misclassification of exposure, which is a result of fading memory over time (37). That is, subjects are more likely to remember their exposure immediately prior to the outcome than any other time in their exposure history. Thus exposure during the control periods is typically underestimated, biasing the association away from the null. On the other hand, self-matched designs conducted using administrative databases use accurate information on the date medications were filled, their formulations and dosages, duration of prescriptions, and quantities dispended. Therefore, differential misclassification of exposure in self-matched designs is minimized when using administrative databases.

The association between isotretinoin and depression has been a controversial issue. This is part due to the fact that acne itself can cause depression, suicidal ideation and even suicide. Although our case-crossover design intrinsically controlled for the presence of acne, increasing trends in isotretinoin prescribing could have explained the observed association. Our results revealed a moderate exposure time-trend, but which did not explain the entirety of the association. Furthermore, since controls appeared to be healthier than cases, the exposure time-trend may have been overestimated, biasing the case-time-control OR towards the null.

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Figure 1. The interrelationship between the case-crossover, case-time-control and case-control designs using 5-month time windows.

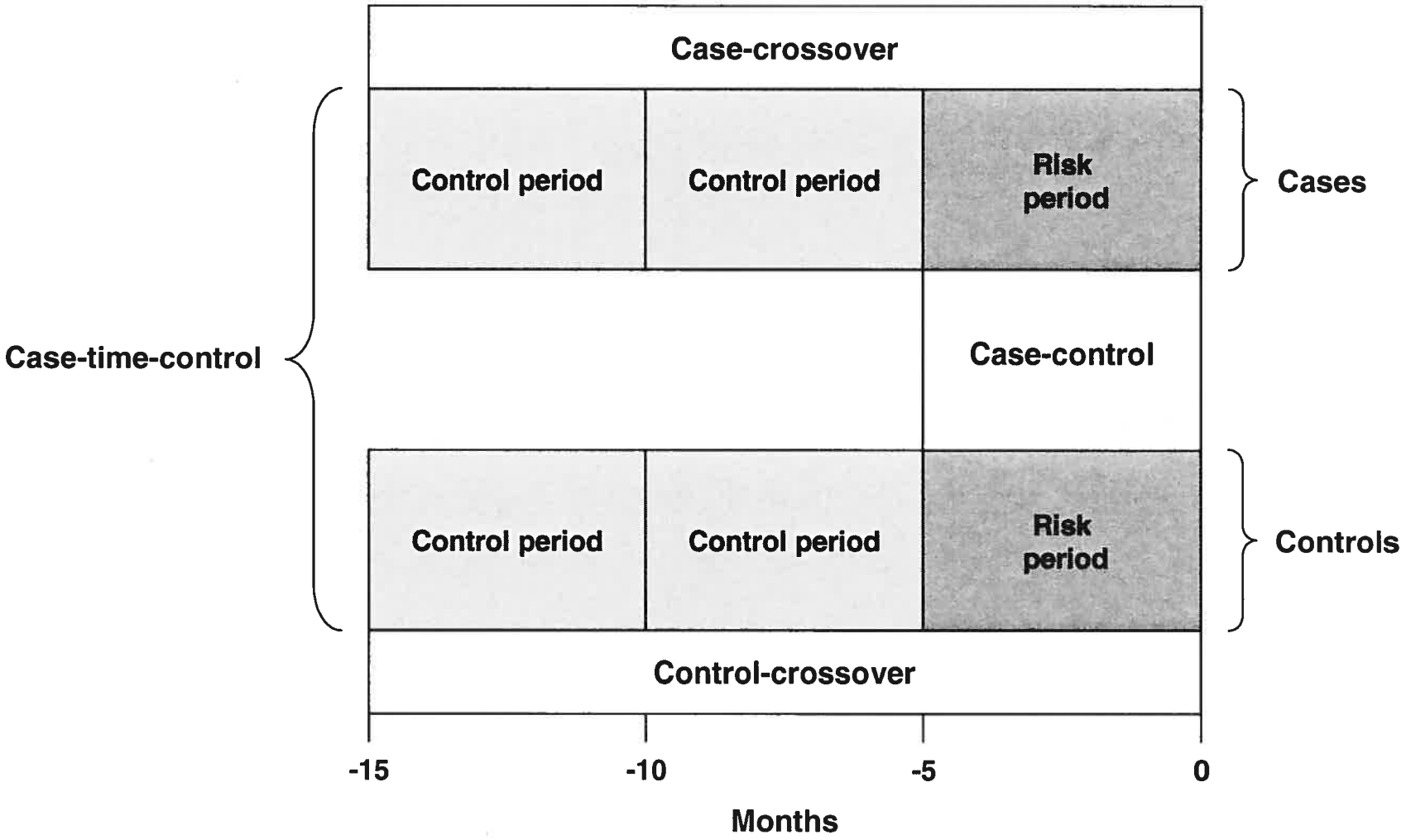

Table 1. Characteristics of cases and controls

	Cases (n=124)	Controls (n=1149)
At index date		
Age, years, mean (SD)	27.7 (8.6)	26.3 (7.7)
Males, n (%)	46 (37.1%)	412 (35.9%)
Welfare recipients, n (%)	86 (69.4%)	662 (57.6%)
Urban dwellers, n (%)	104 (83.9%)	927 (80.7%)
In the 12 months prior to the index date		
Dermatologic visit (>2)‡, n (%)	44 (35.5%)	510 (44.4%)
Non-dermatologic visits (>5)‡, n (%)	72 (57.1%)	372 (32.4%)
All-cause hospitalizations (≥1), n (%)	42 (33.3%)	133 (11.6%)
Emergency department visits (≥1), n (%)	24 (19.1%)	290 (25.2%)
Number of different medications other than isotretinoin, mean (SD)	5.5 (4.0)	3.7 (3.5)

‡Variables dichotomized on the median number of visits.

Table 2. Relative risks of depression associated with the use of isotretinoin in the case-crossover and case-time-control designs

Study design	Exposed only in the risk period n (%)	Exposed only in the control period n (%)	Crude RR (95% CI)	Adjusted RR‡ (95% CI)	Standard error
Case-crossover	26 (21.0%)	13 (10.5%)	2.00 (1.03, 3.89)	2.37 (1.04, 5.41)	0.4208
Control-crossover	298 (25.9%)	206 (17.9%)	1.45 (1.21, 1.73)	1.58 (1.29, 1.93)	0.1031
Case-time-control	26 (21.0%) and 298 (25.9%)	13 (10.5%) and 206 (17.9%)	1.38 (0.69, 2.75)	1.50 (0.64, 3.51)	0.4332

Abbreviations: RR, relative risk; CI, confidence interval.
‡Adjusted for non-dermatologic visits, dermatologic visits, all-cause hospitalizations, emergency department visits, and number of different medications used other than isotretinoin.

CHAPTER 6: DISCUSSION

Isotretinoin is the most effective medication for the treatment of severe nodular acne. However it is a potent human teratogen (2), and has been associated with several other important side effects (3). These side effects have led to several label changes by regulatory agencies, and the issuing of new guidelines that were meant to improve its utilization (209). Over the years, case reports and signals from adverse reaction databases have fueled concerns that isotretinoin may cause depression. Several observational studies have been conducted on the subject, but failed to find an association. However, these studies were either uncontrolled, had small sample sizes, or suffered from other methodological limitations that rendered their results inconclusive. Using a case-crossover design, the present study is the first to find a statistically significant association between isotretinoin and depression.

An association between isotretinoin and depression raises a number of questions regarding the way it is being utilized in the province of Quebec, and possibly the rest of Canada. Studies 1 and 2 presented in this thesis determined to whom, by whom, and how many times isotretinoin was prescribed. These studies also determined whether guidelines had any impact on prescribing patterns. In Study 1, we found that 45% of all isotretinoin prescriptions were written by non-dermatologists. Although it is relatively easy to diagnose severe acne, it is unknown whether non-

dermatologists are fully aware of isotretinoin's side effect profile. In the UK, only consultant dermatologists are authorized to prescribe isotretinoin because of their good knowledge of the medication. In the US, the iPLEDGE program requires prescribers to be registered in a computerized database in order to prescribe isotretinoin (131). Currently, there is no system in place in Canada that monitors by whom, to whom, and how isotretinoin is being prescribed. We also found that over 60% of patients did not receive any anti-acne medication in the year prior to their first isotretinoin treatment. This is contrary to product guidelines, and suggests that isotretinoin is either being prescribed as a first line treatment, or to patients with mild or moderate acne. In either situation, a large proportion of patients are unnecessarily exposed to a potent agent without consideration of other therapeutic options. The third finding was that the Dear Healthcare Professional letter issued by Health Canada regarding isotretinoin's possible psychiatric risks in March 2001 had no impact on prescribing patterns. This indicates that such warnings were either not adequately promulgated, or that physicians do not give them the attention that is required. Study 2 reinforced that notion, in that the different acne treatment guidelines published over the years had no impact on the incidence of acne relapse in patients initially treated with isotretinoin.

The results described above could be a result of Canada's passive approach to dealing with the prescribing of isotretinoin. As an example of this troubling trend, our research team recently published a study investigating the

incidence of pregnancy during an isotretinoin treatment, and the impact of the Pregnancy Prevention Program (PPP) on this incidence. The study showed that the PPP had no impact on the incidence of pregnancies, as would have been expected. Furthermore, the pregnancy rates were four times greater than what has been published previously in the US (129). Despite these alarming figures, officials from Health Canada continue to believe that there is no problem in Canada (222). Their belief is that there is no need to implement a stringent program such as iPLEDGE (222). This view was shared by the Canadian Dermatology Association (223).

Although isotretinoin's teratogenecity can have grave consequences on the mother and her unborn child, its psychiatric risks should theoretically push for more rigorous regulations. This is because both men and women, young and old can be affected by this side effect. Furthermore, depression can have an important socioeconomic burden. It can lead to household strain, financial loss, occupational limitations, and impaired social relationships (224). Thus more needs to be done to better regulate and monitor the use of isotretinoin. This is likely to get complicated with the introduction of new generics in the market. Their cheaper price and thus greater availability will most likely increase the use of isotretinoin.

The studies presented in this thesis have limitations inherent to the use of administrative databases. Administrative databases, such as the RAMQ, provide data on prescriptions filled. As such, it is unknown whether medications were actually taken, or whether the patient correctly followed the treatment regimen. However, administrative databases are not prone to recall bias and thus provide accurate information on the type, formulation, dosage, duration, and quantity of the medications prescribed. Furthermore, the administrative databases we used allowed us to create the largest isotretinoin cohort to date. This enabled us to conduct the largest studies on isotretinoin utilization. This also enabled us to have sufficient statistical power to detect a rare event such as depression in isotretinoin users.

This study generated new research questions that would need to be addressed in future studies. A limitation of the present study was that we lacked statistical power to determine whether there a dose-response relationship between isotretinoin and depression. This is due to the fact that there were not enough subjects in the cumulative dose strata. Thus, the exact dose-response relationship between isotretinoin and depression needs to be investigated in studies with larger sample sizes. Another limitation was that it was not possible to determine whether there was an association between isotretinoin and suicide. This is because the RAMQ and Med-Echo administrative databases provide information on inpatient and outpatient visits only. Thus, it was unknown how many patients committed suicide in

the cohort. Future studies should investigate whether there is an association between isotretinoin and suicide. Finally, our population was mainly composed of subjects of low to moderate socioeconomic status. Although the association between isotretinoin and depression is supported by some biological data, future studies would have to investigate whether the association is still present in individuals of higher socioeconomic status.

CHAPTER 7: CLINICAL IMPLICATIONS

Isotretinoin is the most powerful agent for the treatment of severe nodular acne. For this reason, it is likely to remain the mainstay treatment for severe acne for a long time to come. However, exposure to isotretinoin can lead to depression in certain patients. As a result, treating physicians need to be aware of this association and be prepared to terminate the treatment if symptoms appear. In some situations, termination of treatment may not be enough, and psychotherapy and/or pharmacologic treatments may be indicated.

Depression is frequently underdiagnosed and untreated (225). Therefore it may be difficult to diagnose it within the context of a dermatologic visit. Thus, psychiatric screening tests may be appropriate in patients undergoing isotretinoin therapy. This can be done by administering standardized assessments, such as the Beck Depression Inventory or Hamilton Rating Scale for Depression, before and during an isotretinoin treatment. Because depression can have serious consequences, current guidelines should possibly be modified to include these psychiatric assessments. Their effectiveness at reducing the incidence of depression in patients undergoing isotretinoin therapy should subsequently be evaluated in large prospective cohort studies.

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APPENDIX III: LIST OF ANTI-ACNE MEDICATIONS

List of anti-acne medications and their drug identification numbers	
Anti-acne medications	**Drug identification numbers**
Systemic antibiotics	
Minocycline	2084090, 2084104, 2230735, 2230736, 2173514, 2173506, 2154366, 2153394, 2108143, 2108151, 2239238, 2239239, 1914138, 1914146, 2237313, 2237314, 2242080, 2242081
Tetracycline	580929, 2169924, 717606, 156744
Doxycycline	740713, 874256, 817120, 860751, 742562, 887064, 725250, 2158574, 2091232, 2093103, 24368, 578452
Erythromycin	563854, 563854, 1925938, 726672, 682020, 637416, 545678, 688568, 583782, 893862, 607142, 704393, 704377, 2051850, 769991
Clindamycin	2245232, 2245233, 2248525, 2248526, 30570, 2182866, 2241709, 2241710, 2130033, 2192659, 2242409, 2242410
Azithromycin	2212021, 2231143, 2223716, 2223724, 2239952
Miscellaneous agents	
Benzoyl peroxide	406848, 370568, 187585, 1908871, 432938, 374318, 263699, 403571, 373036
Oral contraceptives (Diane-35®)	2233542
Topical retinoids	
Tretinoin	897329, 897310, 443794, 870021, 870013, 443816, 657204, 578576, 518182, 587958, 587966, 641863, 578568, 518174, 662348, 1926497, 1926500, 1926519, 1926527, 1926470, 1926489, 1926462
Tazarotene	2243895
Topical antibiotics	
Erythromycin	1910086, 1902628
Clindamycin	2230540, 2230535, 260436, 582301

APPENDIX IV: DERMATOLOGIC PROCEDURE CODES

Dermatologic procedure codes	
Dermatologic code	**RAMQ description**
9249	Dermatologie cabinet privé : consultation
9220	Dermatologie cabinet privé : supplément de durée
9182	Dermatologie cabinet privé : visite de contrôle
9180	Dermatologie cabinet privé : visite principale
9250	Dermatologie centre hospitalier de soins de courte durée : externe consultation
9187	Dermatologie centre hospitalier de soins de courte durée : externe visite de contrôle
9186	Dermatologie centre hospitalier de soins de courte durée : externe visite principale
9184	Dermatologie centre hospitalier de soins de courte durée : hospitalisation consultation
99	Dermatologie centre hospitalier de soins de courte durée : hospitalisation tournée des malades le week-end
9185	Dermatologie centre hospitalier de soins de courte durée : hospitalisation visite de contrôle
9183	Dermatologie centre hospitalier de soins de courte durée : hospitalisation visite principale
9181	Dermatologie en CHSLD (et centre d'accueil) : consultation (incluant la visite principale et le supplément de consultation)
9189	Dermatologie en CHSLD (et centre d'accueil) : visite de contrôle
425	Dermatologie infiltration intralésionnelle (une (1) ou plusieurs lésions)
468	Dermatologie injection de substance sclérosante, intralésionnelle (dermatologie) une (1) ou plusieurs
9190	Dermatologie domicile : visite principale
9188	Dermatologie en CHSLD (et centre d'accueil) : visite principale
9206	Dermatologie local sous gestion du gouvernement visite de contrôle
9251	Dermatologie local sous gestion du gouvernement consultation (incluant la visite principale et le supplément de consultation)

APPENDIX I. ETHICS COMMITTEE APPROVAL CERTIFICATE

Le 21 avril 2005

Dre Anick Bérard
Centre de recherche
Étage A Bloc 7

CHU Sainte-Justine

Université de Montréal

OBJET: Titre du projet: Inappropriate management on isotretinoin therapy and its effects on pregnancy and congenital malformation outcomes, and health care costs

Responsables du projet: Anick Bérard Ph. D., principale investigatrice. Co-chercheurs: Dr Jacques Lelorier, Dre Lucie Blais, Dr William D. Fraser, Dre Sylvie Perreault, Dr Gideon Koren. Collaborateurs: Irma Ferreira, Pharm.D., Richard Dubue, M.D. et Laurent Azoulay, étudiant au Ph.D

Chère Docteure,

Votre projet cité en rubrique a été réapprouvé par le Comité d'éthique de la recherche en date du 14 avril 2005. Vous trouverez ci-joint la lettre de réapprobation du Comité.

Tous les projets de recherche impliquant des sujets humains doivent être réexaminés annuellement et la durée de l'approbation de votre projet sera effective jusqu'au 14 avril 2006. Notez qu'il est de votre responsabilité de soumettre une demande au Comité pour le renouvellement de votre projet avant la date d'expiration mentionnée. Il est également de votre responsabilité d'aviser le Comité de toute modification à votre projet ainsi que de tout effet secondaire survenu dans le cadre de la présente étude.

Nous vous souhaitons bonne chance dans la réalisation de votre projet et vous prions de recevoir nos meilleures salutations.

[redacted]

Jean-Marie Therrien, Ph.D., éthicien
Président du Comité d'éthique de la recherche

JMT/ic

APPENDIX II: COMMISSION DE L'ACCÈS À L'INFORMATION APPROVAL

Commission d'accès à l'information du Québec

Siège social
[illegible]

Bureau de Montréal
480, boul. St-Laurent, bureau 501
Montréal (Québec) H2Y 3Y7
Téléphone : (514) 873-4196
Télécopieur : (514) 844-6170

Québec, le 13 février 2004

Madame Annick Bérard
Centre de recherche
Hôpital Sainte-Justine
3175, Côte Sainte-Catherine
Montréal (Québec) H3T 1C5

N/Réf. : 03 20 70

Madame,

Nous avons bien reçu votre demande d'autorisation d'obtenir, pour votre étude, communication de renseignements nominatifs détenus par la Régie de l'assurance maladie du Québec (RAMQ) et le ministère de la Santé et des Services sociaux (MSSS). Votre projet vise à étudier l'utilisation de l'isotrétinoine auprès d'une cohorte d'hommes et de femmes, l'incidence de grossesse, l'incidence de malformations congénitales associé au médicament ainsi que les coûts pour le système de santé associés à un suivi inapproprié.

Après étude de cette demande et conformément à l'article 125 de la *Loi sur l'accès aux documents des organismes publics et sur la protection des renseignements personnels*, nous vous autorisons à recevoir de la RAMQ et du MSSS les renseignements nominatifs spécifiés ci-après et énumérés en annexe.

1re source : sélection par la RAMQ de la cohorte d'hommes et de femmes exposés à l'isotrétinoine et de leurs bébés :
tous les hommes (environ 18 000) et toutes les femmes (environ 27 000), assurés par la RAMQ, qui ont eu au moins une prescription pour l'isotrétinoine (code DIN 00582352, AHFS 84:36.00, ATC D10BA01) entre le 1er janvier 1982 et le 31 décembre 2002 ainsi que tous les bébés nés de ces femmes pendant la même période. Pour les

hommes, les femmes et les bébés identifiés, les renseignements autorisés sont énumérés à l'annexe 1.

2e source : appariement de la cohorte avec le fichier MED-ECHO :
la cohorte sélectionnée à la RAMQ sera appariée au fichier de MED-ECHO du MSSS par le numéro d'assurance maladie (NAM). La RAMQ transférera les NAM (brouillés et non brouillés) des sujets inclus dans la cohorte (soit les hommes et les femmes exposés à l'isotrétinoine et tous leurs bébés) ainsi que les dates de début des liens (dates d'obtention des NAM des bébés) à MED-ECHO. Le MSSS retournera au chercheur un fichier contenant le NAM brouillé pour chacun des sujets ainsi que l'information relative à toutes les hospitalisations que les sujets ont eues entre le 1er janvier 1982 et le 31 décembre 2003. Les renseignements autorisés sont énumérés à l'annexe 2.

3e source : appariement de cette cohorte avec le Registre des événements démographiques :
la cohorte sera ensuite appariée au Registre des événements démographiques. La RAMQ fournira à l'Institut de la statistique du Québec (ISQ), mandataire du MSSS, le NAM brouillé de la mère et le NAM brouillé des bébés, ainsi que les nom et prénom de la mère, la date de naissance de la mère et la date de naissance des bébés. Pour chaque bébé, l'appariement se fera à l'aide des quatre variables suivantes : les nom et prénom de la mère, la date de naissance de la mère et la date de naissance du bébé. L'ISQ remettra au chercheur un fichier contenant les NAM brouillés des mères, pères et des bébés ainsi que les renseignements concernant ces personnes, énumérés à l'annexe 3 pour la période du 1er janvier 1982 au 31 décembre 2003.

Cette autorisation est cependant assortie des conditions suivantes que vous devez respecter :

- vous devez assurer la confidentialité des renseignements nominatifs que vous recevrez;

- vous devez faire signer un engagement à la confidentialité aux membres de l'équipe de recherche qui n'ont pas signé le formulaire de demande d'autorisation et à toute autre personne qui s'ajoutera, par la suite, à cette équipe;

- vous devez utiliser les renseignements reçus uniquement pour cette recherche particulière;

- dans vos rapports, vous ne devez pas publier un renseignement permettant d'identifier un individu;

- vous ne devez pas communiquer un renseignement reçu à d'autres personnes que celles qui sont autorisées à le recevoir dans le cadre de cette recherche;

- vous devez détruire tous les renseignements reçus, énumérés en annexe, pour lesquels l'autorisation de la Commission vous est accordée, au plus tard le 28 février 2009.

Enfin, il est opportun de vous rappeler que la décision ultime de vous communiquer ou non ces renseignements nominatifs appartient toujours aux organismes détenteurs, en l'occurrence la RAMQ et le MSSS.

Veuillez agréer, Madame, l'expression de nos sentiments les meilleurs.

Le directeur général,

[redacted]

Denis Morency

DM/LB/lp

c.c. M. André-Gaétan Corneau, RAMQ
M^me^ Joanne Gaumond, RAMQ
M. Claude Lamarre, MSSS
M^me^ Louise Légaré, MSSS
M^me^ Louise Harvey, ISQ