

5. PSYCHIATRIC CONDITIONS

5.1 Overview

- *Analysis of all available data (pharmacoepidemiological, retrospective, and prospective), failed to verify the signal for an association between Accutane and psychiatric conditions, which had been suggested by the number of spontaneous reports received.*

To clarify if there is an association between Accutane and psychiatric conditions, Roche initiated a risk assessment program. The cornerstone of this program was a pharmacoepidemiological analysis of spontaneous reports, whose objective was to evaluate these reports within the context of the etiology and epidemiology of psychiatric conditions, including suicidal behavior. This report failed to confirm any causal association between Accutane and psychiatric conditions. Rather, psychiatric events reported in association with Accutane therapy reflect the multiple risk factors in the population of adolescent and young adults afflicted with the disfiguring disease of acne. This conclusion was confirmed by an independent expert clinical review of all reports of suicide. In addition, an exploratory analysis of data from a large prospective clinical trial comparing two isotretinoin formulations showed no evidence of increased incidence of psychiatric morbidity using a validated screening instrument. Additional epidemiological analysis of other databases found no elevated relative risk of psychiatric conditions associated with Accutane, when compared to other acne therapies such as antibiotics. A review of the literature on retinoids and the central nervous system revealed no evidence of a plausible mechanism for isotretinoin-induced psychiatric adverse events.

5.2 Risk Assessment Program

Based on the number of spontaneous reports of psychiatric conditions in association with Accutane therapy, Roche in discussion with the FDA amended the labeling in February 1998 to include the following bolded warning:

"Psychiatric Disorders: Accutane may cause depression, psychosis, and rarely, suicidal ideation, suicide attempts, and suicide. Discontinuation of Accutane therapy may be insufficient; further evaluation may be necessary. No mechanism of action has been established for these events (see ADVERSE REACTIONS: Psychiatric)."

At the same time, as part of its overall risk assessment program Roche undertook a number of studies to attempt to confirm the signal these spontaneous reports constituted. The goal of these studies was to:

1. evaluate the natural history of the psychiatric conditions reported
2. evaluate all spontaneous reports in the context of the natural history of these conditions
3. evaluate the spontaneous reports from a clinical perspective
4. analyze other databases to try if possible to confirm and quantify the signal
5. review literature to assess the biological plausibility of the signal

The following sections provide the details of each step of this risk assessment program.

5.3 Adolescence, Acne, and Psychiatric Conditions

- *Every prescriber of acne therapy must be concerned about psychiatric conditions, regardless of treatment choice, because patients suffering from acne are at increased risk for some forms of psychosocial disturbance.*
- *Acne patients are at increased risk for psychiatric conditions because of developmental changes and comorbidity associated with adolescence, and their cosmetically disfiguring disease.*

This section summarizes key findings from the literature to clarify the multiple risk factors in the adolescent and young adult population which comprises the majority of Accutane patients.

5.3.1 Adolescence as a Risk Factor

- *Adolescence is a time of great psychosocial, cognitive, and biological changes.*
- *The increased prevalence of mood and psychotic disorders coincides with the age of onset of acne.*

Acne is usually associated with the changes in endocrine hormones that accompany puberty. The age groups most affected with acne are: 14-17 years for females and 16-19 years for males [Cunliffe, 1989]. Adolescents and young adults also represent the majority of patients treated with Accutane, with approximately 70% of male Accutane users below the age of 20 years.

Adolescence is a time of profound developmental changes: cognitive, psychological, physiological, and social. Factors such as the transition from elementary school, the increasing importance of peers, decreasing social support due to the desire for increased autonomy, and cognitive changes that allow adolescents to envision the future and consider alternatives have the potential to overwhelm vulnerable individuals [Elkind, 1981; Goldman and Beardslee, 1999; Hauser and Bowlds, 1990]. Adolescents experience not only transient and age-appropriate periods of psychosocial disruption, but some also suffer from clinical psychiatric disorders. While the former call for parental patience, the latter require professional treatment.

Unfortunately psychological disorders often are undiagnosed in this age group. Indeed, mood disorders in both children and adolescents represent one of the most under-diagnosed groups of illnesses in psychiatry [Offer, 1992]. One reason for this phenomenon is the challenge of differentiating normal and abnormal behavior. Adolescents tend to present with symptoms other than depressed mood, which makes diagnosis difficult. Additionally, mood changes in adolescents are often assumed to be normative [Rendleman and Walkup, 1997]. Because adolescents have developed the cognitive capacity to mask their emotions and symptoms, they are also more likely to hide depression and other psychological problems from family and friends [Elkind, 1981; Rendleman and Walkup, 1997].

Psychiatric disorders have potentially serious consequences, however, especially if left undiagnosed. The MECA Study (Methodology for Epidemiology of Mental Disorders in Children and Adolescents) estimated that almost 21% of U.S. children ages 9-17 had a diagnosable mental or addictive disorder with at least minimum impairment, 11% with significant functional impairment, and 5% with extreme functional impairment. Others have found 12-month prevalence rates of mental disorders in adolescents of 17.5% [Wittchen et al., 1998]. The prevalence of depression in adolescents has been reported to be anywhere from 5%-28%, with a greater prevalence among females than males [Rendleman and Walkup, 1997]. In addition, the age of onset of depression has decreased since World War II [Clark and Goebel-Fabbri, 1999]. Early onset mood disorders are associated with more prolonged episodes and the development of more severe disorders [Keller and Russell, 1996; Rendleman and Walkup, 1997]. Plainly, then, adolescents must be considered a population at appreciable risk for psychological disorders.

The increased prevalence of both depression and suicidal behavior from childhood to adolescence is believed to be due partially to the increased cognitive abilities of adolescents. Newly developed capabilities allow them to consider the future, to think about alternative solutions to problems, to anticipate the reactions of others, and to plan and execute a suicide [Goldman and Beardslee, 1999; Harter, 1999]. With these changes comes the ability to envision the future, and therefore, the possibility of feeling hopeless about what the future holds. Because hopelessness is a risk factor for suicide, the risk of suicidal behavior increases during adolescence. However, it has typically been found that adolescents who are at risk for significant psychological turmoil, depression, and/or suicidal behavior suffer from a combination of risk factors including family instability or crisis, abuse, personal losses, low self-esteem, social isolation, and access to lethal methods [Goldman and Beardslee, 1999].

5.3.2 Alcohol and Substance Abuse as Cofactors

- *Alcohol and substance abuse are cofactors in adolescent psychiatric conditions*

Alcohol and substance abuse exacerbate adolescent risk for psychiatric conditions. Adolescents and young adults often drink socially, but many abuse the drug. Data from the 1995 National Household Survey on Drug Abuse (NHSDA) indicate that 11.6% (18.4% males, 4.9% females) of the 18-25 year old age group are considered heavy alcohol users. Approximately the same number in this age group abuse illicit drugs. Extensive comorbidity between these two groups of abusers must be assumed, although precise estimates are not available. Alcohol and substance abuse are major risk factors for psychiatric conditions. By measuring comorbidity with depression, anxiety and aggressive behavior, the NHSDA survey reveals that adolescents with psychosocial problems are more likely to be substance users and abusers. In adolescents aged 12-17 years old reporting substance abuse in the past month, 24.3% of males and 21.9% of females showed high levels of psychosocial difficulty. Of alcohol abusers, specifically, 15.4% of males and 13.1% of females showed high levels of difficulty. Alcohol abuse is of particular concern with regard to suicidal behavior. Psychological autopsy studies indicate that approximately 25% of suicides in the general population suffered from an alcohol use disorder. In addition, as many as 50% of suicide victims were drinking at or near the time of their death. Plainly, then, alcohol and substance abuse accompany and contribute to psychological difficulties, sometimes with tragic outcomes.

5.3.3 Acne as Contributor to Psychological Distress

- *Even mild to moderate acne is associated with psychological distress, including depression and suicidal ideation.*

An adolescent's perception of his or her body is extremely important both socially and psychologically. During adolescence self-consciousness increases with the development of formal operational thought, which allows the adolescent to think about not only his or her own thoughts but also to consider the thoughts of others. These new introspective abilities initially lead to egocentric thinking on the part of the adolescent [Elkind, 1981]. This heightened self-awareness can be detrimental if the adolescent has a negative self-perception. Because individuals incorporate other peoples' attitudes about them into their own perceptions of themselves [Cooley, 1902; Mead, 1934], a belief that others view one negatively can lead to feelings of low self-worth. In addition, discrepancies between what we perceive ourselves to be versus what we want to be can lead to dejection-related emotions [Higgins, 1987]. Self-worth and self-esteem are directly linked to adolescents' perceptions of their own competency in domains that are considered important to them [Harter, 1990; Harter, 1999]. Studies have consistently shown that physical appearance tops the list of important domains for adolescents [Harter, 1990; Harter, 1999]. Because low self-esteem and negative self-attributions are correlates of depression [Harter, 1990], adolescents who have negative perceptions of their own appearance may be at risk for depression-related symptoms.

Because of this relationship between perceived physical attractiveness and self-esteem, acne patients have significantly higher anxiety scores than controls [Garrie and Garrie, 1978] and

exhibit elevated stress hormones [Schulpis et al., 1999]. There may be a vicious circle between acne severity and emotional stress because a large study (n=571) showed that 55% of patients associated acne flares with times of emotional stress in their lives [Griesemer, 1978]. Several published studies describe the psychological effects of a disfiguring disease such as acne [Cotterill and Cunliffe, 1997; Gupta et al., 1990; Kellett and Gawkrödger, 1999]. Pearl and colleagues [1998] studied the impact of acne in 847 adolescents and found that the severity of acne determined the extent of embarrassment and the lack of enjoyment of and participation in social activities. Importantly, Gupta and Gupta [1998] showed that even mild to moderate dermatological disease, especially facial acne, can be associated with significant depression and suicidal ideation. Others have documented that psychosocial stressors, self-esteem, and interpersonal difficulties are common issues for dermatologic patients [Folks and Kinney, 1995].

Conversely, and consistent with these findings, several studies have shown that successful acne treatment with isotretinoin reduces anxiety and depression scores. In the largest study to date, Rubinow and colleagues [1987] demonstrated that in treating 72 cystic acne patients with isotretinoin, even patients with a minimum response (<50% reduction in lesion counts) had improved scores for anxiety, depression, and interpersonal sensitivity. Table 16 shows that before-treatment and after-treatment comparisons of these patients showed statistically significant improvements.

Table 16 Significant Treatment-Related Changes in Psychologic Factor Scores: Before-Treatment versus After-Treatment Comparisons (from Rubinow et al., 1987)

	Paired t-value	p-value
Whole Group (n=66)		
Anxiety (HSCL)	2.99	<0.01
Anxiety (MS)	2.24	<0.05
Male Patients (n=58)		
Anxiety (MS)	3.30	<0.005
Predominantly Facial (n=15)		
Anxiety (MS)	2.44	<0.05
Depression (POMS)	3.14	<0.01
Responders (n=22)		
Anxiety (MS)	4.56	<0.001
Depression (POMS)	2.19	<0.05
Minimal Responders (n=13)		
Interpersonal sensitivity (HSCL)	2.42	<0.05
Factor V (POMS)	2.64	<0.05

HSCL: Hopkins Symptoms Checklist; MS: Mood Scale; POMS: Profile of Mood Scale

5.4 Natural History of Psychiatric Disease

- *To evaluate the phenomena described in spontaneous reports, it is important to understand the etiology and epidemiology of psychological conditions and the clinical terminology used to describe them: many terms that have precise clinical meanings have varying denotations and connotations in everyday usage.*

5.4.1 Terminology

If, as the preceding section shows, adolescents and young adults have multiple risk factors for psychiatric conditions, the etiology and epidemiology of these conditions is confused by a plethora of imprecise descriptive terms. Most notably, the term “depression” is commonly used to describe an array of mood phenomena ranging from “everyday ups-and-downs” and “the blues” to various forms of clinical depression. The former pair should be understood as constituting *symptoms* of varying intensity and duration that may be present, but do not themselves constitute a clinically diagnosable *syndrome*. To lend precision to this terminological challenge, the psychiatric community has developed a uniquely refined lexicon that is codified in the Diagnostic and Statistical Manual of Mental Disorders, which is now in its fourth edition (DSM-IV). The following material draws on DSM-IV terminology to provide an overview of the nature and prevalence of psychiatric disorders that confront the acne population.

5.4.2 Depression and Other Mood Disorders

- *Mood disorders are often underdiagnosed and are not uncommon in adolescents and young adults.*
- *Mood disorders are often cyclic—ranging from manifest and intense to imperceptible and mild as part of their natural course.*

5.4.2.1 Presentation

Mood disorders involve a disturbance of mood that is not due to any other physical or mental disorder. Mood here refers to prolonged emotion that colors the whole psychic life. Moods are generally distinguished in terms of lowered or elevated affect and disorders are sustained over a period of weeks to months and are often periodic or cyclic.

Clinically diagnosable mood disorders are slightly less prevalent in the young than in adults. The age of onset of mood disorders and the typical treatment age for acne are similar. Mood disorders develop in the young, appearing first as prodromal depressive symptoms. Mood disorders are transient and often periodic or cyclic, but can be sustained over a period of weeks to months.

5.4.2.2 Depression

While there are many kinds of clinical depression (ranging from brief recurrent depression to dysthymia to mild, moderate, and major depression) that are differentiated by intensity, array, and duration of symptomatology, there is substantial overlap in these categories. Generally speaking, depression as a clinical disorder usually refers to dysthymia or to major depressive disorder (MDD). As Table 17 shows, the DSM-IV uses nine criteria to define MDD, which is diagnosed

when individuals present depressed mood or diminished interest in daily activity (symptoms 1 or 2) and at least four of the remaining symptoms. These symptoms must be present for at least two weeks.

Table 17 DSM-IV Criteria for Major Depressive Disorder (adapted)

1.	Depressed mood
2.	Diminished interest or pleasure in daily activities
3.	Significant weight loss without dieting or weight gain
4.	Altered sleep patterns
5.	Psychomotor agitation or retardation
6.	Fatigue or loss of energy
7.	Feelings of worthlessness or guilt
8.	Inability to concentrate or indecisiveness
9.	Thoughts of death, including suicidal ideation

While major depressive episodes typically follow a psychosocial stressor with variable onset and duration, 50% of major depressive episodes occur without a recognizable stressor. Adolescents with depression are often also experiencing problems with family functioning, peer relations, or academics [Rendleman and Walkup, 1997]. Low self-worth is also highly correlated with depression in adolescents [Harter, 1999]. The onset and duration of major depressive episodes vary immensely. Importantly, depression—mild, moderate, and major—is a *cyclic* disorder whose symptoms can appear and disappear as part of its natural course.

The prevalence rate of major depressive disorders for males and females in the age group of 15-24 years is shown in Table 18.

Table 18 Prevalence Rates* of Major Depressive Disorders for 15-24 Year Olds (Males and Females)

	Males	Females	Total
30 days	4.3%	8.2%	6.1%
12 months	9.5%	16.3%	10.3%

*Derived from the National Comorbidity Study

5.4.3 Symptomatology of Psychotic Disorders

- *Psychotic disorders are rare, chronic, and debilitating.*
- *The age of onset of psychotic disorders and of severe acne are similar.*

Psychotic disorders are defined as mental disorders that comprise major disturbances in affect, thinking, and behavior. They cause gross distortion or disorganization of mental capacity, affective response, and capacity to recognize reality, communicate, and relate to others to the

degree of interfering with ability to cope with ordinary demands of everyday life. Psychotic disorders may present with several psychotic symptoms including delusions, hallucinations, incoherence or marked loosening of associations, disorganized speech and other thought disorders, blunted or inappropriate affect, odd beliefs or magical thinking, catatonic symptoms, ambivalence, and autism. The most common psychotic disorder is schizophrenia.

Psychotic symptoms are not confined to psychotic disorders, but also can be observed in the dementia of Alzheimer's disease, substance-induced delirium, and other amnesic and cognitive disorders or major depressive disorders. Psychoactive substances, drugs or alcohol can also cause psychotic symptoms by excessive or chronic use. Psychotic symptoms can be observed either during the entire course of the above listed disorders or as a single symptom appearing occasionally. Thus, the diagnosis of a specific psychotic disorder requires consideration of the appearance of specific psychotic symptoms during a certain period of time.

Psychotic disorders are relatively rare, but they are chronic and debilitating. The age of onset of psychotic disorders coincides with the development of severe acne. Many of the early characteristics or symptoms of these disorders can be mistaken for "normal adolescent turmoil" or other psychological disorders, such as mood or substance abuse disorders. The 12-month prevalence of psychotic disorders is 0.5% in males and 0.6% in females as shown in Table 19.

Table 19 **Prevalence Rates* of Psychotic Disorders for 15-24 Year Olds (Males and Females)**

	Males	Females	Total
12 months	0.5%	0.6%	0.5%

*Derived from the National Comorbidity Study

5.4.4 Suicidal Ideation and Suicidal Behavior

- *The majority of suicidal ideators do not attempt suicide and the majority of suicide attemptors do not go on to commit suicide.*
- *Although reports of suicide sometimes make the act appear impulsive, it is the result of an accumulation over a substantial period of time of factors that become apparent only during detailed psychological autopsy.*

Narrowly defined, *suicidal ideation* goes beyond thoughts of death to include active consideration of taking one's own life, possibly including a specific plan. Some studies have found that anywhere from 15%-40% of adolescents think about suicide in a given year while others report suicidal ideation in 3%-14% of adolescents with a greater prevalence in females than males [Goldman and Beardslee, 1999]. Suicidal ideation is best understood as a feature of depression, rather than a risk factor for imminent suicidal activity. In fact, ideation very infrequently leads to suicide attempts or completions. It is estimated that over five million people in the U.S. have suicidal ideation each year [Mościcki, 1989], while approximately thirty

thousand people die by suicide each year [Mościcki, 1997]. While suicidal ideation is, therefore, a risk factor for suicide, it does not have strong predictive power in identifying who will eventually commit suicide.

Suicidal behavior includes both suicide attempts and suicide completions. While there is no standard, widely accepted definition of ***attempted suicide***—and hence no reliable national data on prevalence—it can be understood as “a potentially self-injurious action with a nonfatal outcome for which there is evidence, either explicit or implicit, that the individual intended to kill himself or herself” [O’Carroll et al., 1996]. Broader definitions, particularly in Europe where the term “parasuicide” is used, include self-destructive behavior generally without regard to lethality or intent. In terms of this narrow definition, it is estimated that 0.3-0.8 adults per 100 and 0.2-2.6 adolescents per 100 attempt suicide in a 12-month period [Andrews and Lewinsohn, 1992] and that for every completed suicide there are 18-23 attempts [Goodwin and Runck, 1992]. Although 90% of those who attempt suicide do not go on to complete suicide [Clark and Fawcett, 1992], 56% of adolescents who commit suicide have made previous attempts or threats [Hauser, 1990].

Suicide, or completed suicide, is multifactorial. Contrary to common perception, suicide is not a sudden, impulsive act, but rather the result of cumulative experiences and risk factors over a substantial period of time. It is disturbing, but not uncommon, for close friends and family not to be aware of suicidal tendencies before a suicide attempt; these only become plain after psychological autopsy. Risk factors for suicide include: possession of firearms, family history or previous episodes of psychiatric conditions, personality disorders, and life stresses. The strongest known risk factor for completed, as for attempted, suicide is a history of psychiatric disorders. Psychological autopsy studies consistently show that over 90% of all completed suicides in all age groups are associated with psychopathology—most commonly mood disorders, followed by substance abuse. While psychiatric history is thus all but a necessary, though not a sufficient, cause of suicide, it is important to realize that 5%-10% of suicides have no apparent psychopathology and thus appear to “come out of the blue” [Brent et al., 1993]. Key risk factors become apparent only upon psychological autopsy. (The detailed investigative analysis involved in a psychological autopsy is provided in Appendix 12 that presents a representative autopsy report form.) Figure 3 attempts to illustrate the array of potential risk factors of suicide, without regard to scale.



Figure 3 Suicide: A Multi-Factorial Event (adapted from Jacobs DG, 1997)

The U.S. suicide rate in the general population has remained relatively stable over time at approximately 11.2 completed suicides per 100,000 people annually [Mościcki, 1997]. However, as Figure 4 shows, there has been an alarming increase in the reported rates of suicide among adolescents and young adults. The suicide rate in the 15-24 year old age group nearly tripled between 1952 and 1996, and now exceeds 13.8 per 100,000. As a result, suicide has become the third leading cause of death in the U.S. in the 15-24 year old age group; for Caucasians in this age group, it is the second leading cause of death.

Figure E6: Suicide rates for all persons and persons aged 15 to 24, U.S., 1900-1990

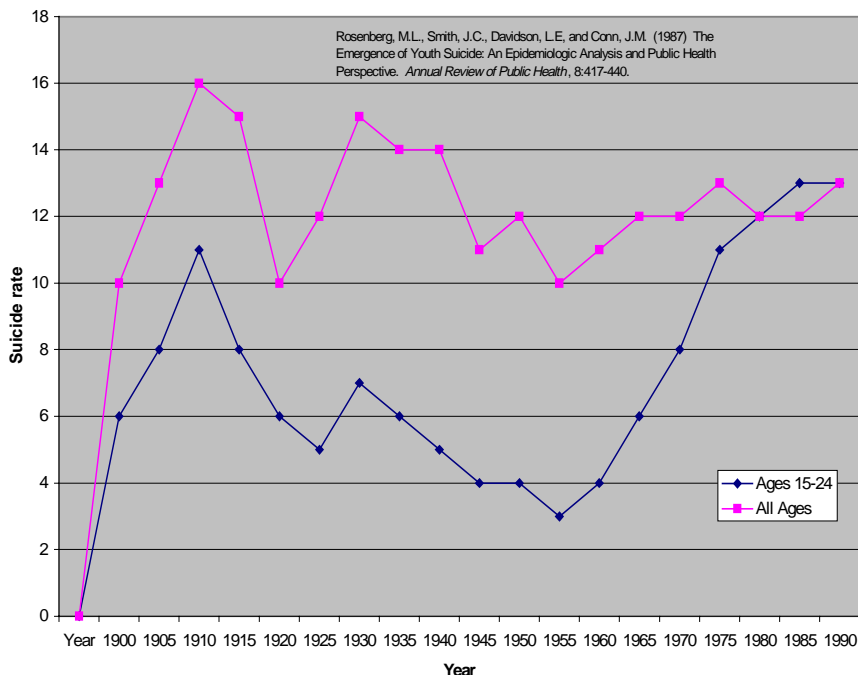


Figure 4 Suicide Rate (Per 100,00 Persons) for All Persons and Persons Aged 15 to 24 Years from 1900-1990 (U.S. Data)

5.5 Pharmacoepidemiological Analysis of Spontaneous Reports

- *Assessment in the context of natural history and alternative risk factors provides strong supporting evidence that psychiatric symptomatology and disorders described in spontaneous reports are much more likely to be due to factors other than Accutane*

A comprehensive review of all spontaneous reports of psychiatric conditions Roche received worldwide between 1982 and April 30, 1999 was submitted to the FDA in March 2000. Appendix 13 presents the body of this report. The material below summarizes the objectives, methodology, and principal findings.

5.5.1 Objectives

The analytical goal of this review was to assess the nature of any association between the use of Accutane and consequent psychiatric conditions (mood disorders, psychoses, and suicidal behavior). The objectives were to determine the nature and extent of any relationship between Accutane therapy and psychiatric morbidity, specifically:

1. Describe the types of reported psychiatric conditions

2. Identify all associated risk factors
3. Assess the magnitude of the identified risk factors
4. Evaluate causality within the pharmacoepidemiologic framework

The comprehensive review included an extensive literature review to provide context to this complex set of issues.

5.5.2 Methodological Overview

The methodology used to evaluate the spontaneous reports consisted of three parts:

- Literature Review
 - Determine scope of work and related disciplines
 - Comprehensively review and evaluate literature (250 citations)
 - Review etiology and epidemiology of psychiatric conditions (including suicidal behavior)
 - Conceptualize proposed relationships
- Review Spontaneous Reports
 - Evaluate spontaneous reports for category, quality, and content
 - Determine the value of spontaneous reports in explaining proposed relationships
- Review Epidemiology
 - Evaluate relative likelihood of all risk factors identified
 - Derive relevant conclusions

The preceding section (Section 5.4) summarized key findings on the etiology and epidemiology from the first step, the literature review. The methodology for the second step, the evaluation of individual spontaneous reports, consisted of a review of the individual cases followed by an assessment of the coded/reported term and then of the quality and consistency of the data. The review assessed all spontaneous reports for psychiatric adverse events received worldwide by Roche Global Drug Safety between 1982 and April 30, 1999. The reports were classified with any preferred term into WHO-ART SOC 500 Psychiatric Disorders, and then placed into the Roche Drug Safety database. The reports (2,346) were sorted into one of eight functional diagnostic categories: mood disorders (53.1%), anxiety disorders (10.6%), psychotic disorders (5.1%), cognitive disturbances (7.4%), sleep disorders (3.5%), personality disorders (1.7%), suicidal behavior (7.1%), and excluded terms (11.3%). These excluded terms incorporate dyspareunia, appetite increased, drug abuse, attention deficit, pica, libido decreased, libido increased, impotence, hair plucking, yawning, anorexia nervosa, and anorexia. Suicide and suicidal attempts were both placed into the suicidal behavior category. However, suicidal ideation was clustered with mood disorders.

The findings from both of these steps reinforced important caveats. Spontaneous reports are not clinical data and they are often extremely difficult to interpret. The vast majority of the spontaneous reports were for depressive symptoms and other mood disorder symptoms, not for the syndromes themselves. No attempt was made to reclassify any of the spontaneous reports with the exception of suicidal behavior reports, which are much less subject to interpretative variation. The key step in the analysis of the spontaneous reports was the classification in terms

of the strength of the kind of evidence of the presence or absence of causality. The strongest evidence for the presence or absence of causality were the reports of positive dechallenge or positive dechallenge with positive rechallenge. These reports were the most important for the assessment of causality.

When spontaneous reports are well documented and for rare adverse drug reaction (ADR) reports that have low background rates, the spontaneous reports yield the most defensible data. However, spontaneous reports are of very diminished value when the outcome has a common background rate. Thus there was no misunderstanding of the limited value of spontaneous reports in resolving the nature of any relationship between Accutane and psychiatric morbidity. It was clear from the start that they could not give definitive answers, but could possibly provide insight into the relationship. In addition, they could potentially illuminate the circumstances surrounding these reports and could possibly generate testable hypotheses.

5.5.3 Principal Findings and Conclusions

5.5.3.1 Depression and Other Mood Disorders

- *There are a small number of reported cases that imply causality between depressive symptoms and mood disorders and Accutane administration at the individual case level.*
- *However, an assessment in the context of natural history and alternative risk factors provides strong supporting evidence that the described symptomatology and disorders are much more likely to be due to factors other than Accutane. Unfortunately, the analyses of this type of data do not allow any potential risk factor to be completely ruled out no matter how unlikely it may appear.*

Of the 1247 reports of mood disorders, 367 were reports of dechallenge. Twenty-three of the 367 reports indicated positive dechallenge and rechallenge, and 37 reports indicated a diagnosis of mood disorder subsequent to exposure. There was a high level of diversity and inconsistency even within the reports of dechallenge.

5.5.3.2 Psychotic Disorders

- *There are a very small number (3) of reported cases that imply causality between a described psychotic disorder and Accutane administration at the individual case level.*
- *However, an assessment in the context of natural history and alternative risk factors provides strong supporting evidence that the described symptomatology and disorders are much more likely to be due to factors other than Accutane. Unfortunately, the analyses of this type of data do not allow any potential risk factor to be completely ruled out no matter how unlikely it may appear.*

There were 120 reports indicating psychotic disorders. Of these, 20 were reports of dechallenge. Five of the 20 reports indicated positive dechallenge and rechallenge, and three reports had a diagnosis of psychotic disorder.

5.5.3.3 Suicidal Behavior

- *There were no reports among the 168 cases reviewed that imply direct causality between suicidal behavior and Accutane administration.*
- *An assessment in the context of natural history and alternative risk factors provides strong supporting evidence that the reported cases are much more likely to be due to factors other than Accutane.*

There were a total of 168 reports of suicidal behavior worldwide: 104 reports of suicide attempts and 64 reports of completed suicides. In the U.S., there were 38 reports of completed suicides. All suicide reports were poorly documented; none had psychological autopsies performed. The cases of completed suicide were examined for duration of therapy, dose, and covariates. No pattern emerged. The suicides were distributed randomly all through the course of treatment and for long periods of time (up to 10 years) thereafter. There was an abundance of alternative risk factors for each reported suicide.

The number of suicides observed in the U.S. in the Accutane-exposed cohort is much less than would have been predicted. Conservative calculations on 1997 data from the National Center for Health Statistics lead to a prediction of 310 (262 males + 48 females) completed suicides among adolescents and young adults (15-24 years old) in the U.S. during their Accutane therapy (Table 20). There is plainly no excess of observed suicides in the Accutane-exposed population (32) compared to what would be predicted in the age-matched general population.

Table 20 Observed vs. Predicted Suicides for 15-24 Year Olds in an Accutane-Exposed Cohort (U.S. Data and Estimates)

Observed						
Male (33)			Female (5)			
Under 25 Years	Over 25 Years	Unknown	Under 25 Years	Over 25 Years	Unknown	Total
27	4	2	5	0	0	38
Predicted						
Male (319)			Female (79)			
Under 25 Years	Over 25 Years		Under 25 Years	Over 25 Years		Total
262	57		48	31		398

5.6 Complementary Analyses

5.6.1 Analysis in a Prospective Clinical Trial, NR15645

- *An exploratory analysis of data from a large prospective clinical trial comparing two isotretinoin formulations showed no evidence of increased incidence of psychiatric morbidity using a validated screening instrument.*

5.6.1.1 Study Design

The clinical trial NR15645 was a double-blinded, randomized, parallel-group, multi-center study in which 602 patients were randomized to receive either 0.4 mg/kg Accutane NF once daily without food or 1.0 mg/kg Accutane in two divided doses daily with food for a period of 20 weeks to demonstrate that the two formulations were clinically equivalent.

5.6.1.2 Beck Depression Inventory

The Beck Depression Inventory [Beck et al., 1996], which is now in its second edition (BDI-II), is a validated screening instrument that was used to detect changes in depressive symptoms during the clinical trial (see Appendix 14). To monitor the possible occurrence of depression during the course of the clinical trial, a BDI-II was recorded at baseline and at the end of treatment (Week 20). In addition, at each visit, a four-item Mood/Depression Assessment Questionnaire (see Appendix 15) was given to test for the onset of depressive symptoms and to determine whether a BDI-II should be administered. A BDI-II score of ≥ 31 , signifying severe depression, was a criterion for exclusion from enrollment in the trial; patients who recorded such a score during the trial were to be immediately withdrawn from treatment and referred for psychiatric counseling.

The two treatment groups were essentially identical with an overall decrease in depression score of the course of the trial. The mean BDI-II scores at baseline were 3.5 ± 4.6 (range 0-24) and 3.6 ± 4.5 (range 0-29) for Accutane NF and Accutane patients, respectively. The values at Week 20 were 1.7 ± 3.1 (range 0-21) and 1.9 ± 3.7 (range 0-28) for Accutane NF and Accutane patients, respectively.

No patients had a score of ≥ 31 on the BDI-II; therefore, all episodes of depression fell into the categories of minimal, mild, or moderate. Approximately equal numbers of patients from each treatment group had BDI-II scores that raised or lowered the grade by one or two units. (The Roche Briefing Document for Accutane NF [NDA 21-177] provides further details on analyses of psychiatric findings from this trial.)

5.6.2 Retrospective Analysis of Epidemiological Databases

- *A retrospective cohort study of other databases found no elevated relative risk of psychiatric conditions associated with Accutane, when compared to other acne therapies such as antibiotics*

5.6.2.1 Objectives

In 1998, as part of ongoing monitoring of isotretinoin users and to clarify the uncertainty regarding the proposed association between isotretinoin therapy and the risk of depression, psychotic symptoms, and suicide attempts and suicides, Roche, in collaboration with Susan S. Jick, D.Sc, from the Boston Collaborative Drug Surveillance Program, Boston University School of Medicine, conducted a retrospective cohort study using data from Saskatchewan Health in Canada and the General Practice Research Database (GPRD) in the United Kingdom. The objective was to determine the rates and relative risks of suicides, suicide attempts, psychotic

disorders, and neurotic disorders among users of oral isotretinoin compared to nonusers who had antibiotic-treated acne.

5.6.2.2 Definition of Cohorts

Oral isotretinoin users were identified from among all members of Saskatchewan Health and the GPRD. All recruited subjects had at least 6 months and up to 5 years of computer recorded history prior to their first isotretinoin prescription and 12 months of computer recorded history after their last isotretinoin prescription. The *current exposure* cohort was defined as the time from first prescription through the third month while the *recent exposure* cohort covered the time from 4 to 6 months after last prescription for either isotretinoin or antibiotics. Two *unexposed* comparison cohorts were identified. The first comparison cohort was comprised of acne subjects on antibiotic drug therapies diagnosed within the same time period (± 6 months) and within the same 10 years age bands as the isotretinoin patients but treated with oral antibiotics. The second cohort was comprised of isotretinoin users as their own comparison group for the 6 months period prior to receipt of the first isotretinoin prescription.

5.6.2.3 Results

Analyses of data from two separate sources yielded similar results. In total, data from nearly 9,000 isotretinoin users were identified and compared to different matched control cohorts. In no instance was there evidence that use of isotretinoin is associated with depression and other psychiatric conditions, nor suicidal behavior. The relative risk estimates for these outcomes were all around 1.0 regardless of the data source.

In Saskatchewan, where the largest quantity of information was available on isotretinoin users, the relative risk estimate for newly diagnosed psychiatric disorders was 1.1 (95% CI 0.8-1.6) for current isotretinoin exposure compared to acne patients with recent antibiotic exposure? The same analysis in the GPRD also yielded a relative risk estimate of 1.1 (95% CI 0.2-3.4). For suicide attempt and suicides, the relative risk estimate was 1.1 (95% CI 0.4-2.8) comparing current isotretinoin exposure to the non-exposed period in the Saskatchewan data. There was only one suicide attempt in the GPRD and that person was non-exposed.

In both the Saskatchewan data and the GPRD, the results of the newly diagnosed psychiatric conditions analysis restricted to isotretinoin users only yielded relative risk estimates of 1.2 (95% CI 0.9-1.7) and 1.3 (95% CI 0.2-5.7), respectively, for current isotretinoin use compared to the unexposed period 6 months prior to isotretinoin receipt.

Importantly, there are inherent limitations to this and other epidemiology study designs in relation to sample size, source of data, ascertainment of and the accuracy of psychiatric conditions, the severity of the psychiatric conditions, drug exposure definition, comparability of acne antibiotic cohort with the isotretinoin cohort, and prior and post drug exposure comparisons. The low number of suicides in the databases makes it difficult to assess relative risk. The psychiatric conditions are assessed by selecting a range of codes as recorded in the databases without strictly following the currently established diagnostic nosology.

Overall, the prevalence of psychotic disorders during or shortly after isotretinoin therapy is comparable to the prevalence in acne patients on oral antibiotic therapy. Prevalence is lower for the unexposed period following both therapy groups implying that successful treatment of acne reduces the occurrence of psychiatric disorders among acne patients. Analyses based on isotretinoin patients as their own comparison cohort also yielded no isotretinoin associated effect. These findings are consistent across different data sources which all included population based cohorts. Additional findings in relation to gender and age differences, effect of past psychiatric disorders, physical or psychiatric comorbidity are all consistent with the epidemiology of psychiatric disorders.

5.7 Review of Literature on Retinoids and the Central Nervous System

5.7.1 Overview

- *Although there are retinoid receptors in the adult brain, their function in regulating psychiatric conditions has not been established*

While all available data fail to confirm the initial signal for an association between Accutane and psychiatric morbidity, it is important to assess the theoretical possibility of such a relation. To do so, the literature on retinoids and the central nervous system was reviewed. This review revealed that, despite appreciable insight into the role of retinoic acid in the *developing* central nervous system (CNS), the question still remains whether such retinoic acid-sensitive systems are operative in the adult (or adolescent) brain and, if so, whether they are accessible to or modulated by exogenous isotretinoin. Absent such lines of evidence, a mechanistic association between retinoid administration and psychiatric disorders remains implausible.

5.7.2 Retinoid receptors in the brain

Retinoic acid receptors are abundant in the brain and whereas the retinoic acid receptor RAR- α is uniformly distributed, RAR- β and RAR- γ are restricted in their expression patterns. Likewise, the retinoic acid X receptors RXR- α and RXR- β are widely distributed but RXR- γ is localized specifically in the striatal region where dopaminergic neurons are also found [Ruberte et al, 1993]. The dopamine receptor D2 (D2R) has a retinoic acid response element (RARE) in the promoter region of the gene although this has not been shown to be activated by retinoids *in vivo* [Valdenaire et al., 1994].

Two recent studies tested the function of these retinoid receptors *in vivo* by using knockout mice. In both cases [Samad et al., 1997; Krezel et al., 1998], the double-null mutants, but not the corresponding single mutants, in RAR- β /RXR- β , RAR- β /RXR- γ , and RXR- β /RXR- γ exhibited significant locomotor defects together with a 30%-40% reduction in gene expression for dopamine receptors D1R and D2R in the striata. Since high levels of retinoid receptors are expressed in the brain and retinoic acid-synthesizing enzymes are localized in mesostriatal dopaminergic neurons [McCaffery and Drager, 1994], the authors suggested that altered retinoid signaling could be involved in the etiology of Parkinsonism and schizophrenia [Krezel, 1998].

A more subtle phenotype was found in double RXR- γ or RAR- β /RXR- γ knockout mutants, pointing to a role of retinoic acid in higher cognitive functions [Chiang et al., 1998]. These animals, while viable and fertile, were characterized by almost complete elimination of CA1 LTP (long-term potentiation) in double RAR- β and RAR- β /RAR- γ mutants, and complete but selective loss of LTD (long-term depression), while LTP was undiminished, in RAR- γ double mutants. This would imply that a significant decrease in exposure to endogenous retinoids may affect long-term memory function in higher animals but cannot be extrapolated to the effect of excess retinoids.

5.7.3 Prenatal and postnatal exposure to retinoids

Whereas prenatal exposure to retinoids has been well studied and periods of particular sensitivity identified, there are few studies on the effects of postnatal administration. Exposure of rats at postnatal days 3-5 to the relatively high dose of 20 mg/kg of retinoic acid did not affect survival or produce any changes in regional brain weights [Holson et al., 1997a]. In another study, however, a detailed histological study of rats, injected with retinoic acid when newborn, revealed the loss of a subpopulation of proliferating granule cells in the cerebellum 14 days later [Yamamoto et al., 1999]. It was concluded that sensitivity of cerebellar development to retinoic acid extends to the early postnatal period in rodents, which, interestingly, corresponds to the third trimester in humans. The teratogenic effects of isotretinoin in humans includes effects on cerebellar development, which may result from third trimester exposure.

Vitamin A (retinol) has profound effects on the developing embryo. Retinol must first be converted to retinoic acid to fulfill all of its roles in vertebrate development. The enzymes responsible for this conversion belong to families of alcohol dehydrogenases (ADH) and aldehyde dehydrogenases (ALDH) some members of which, for example ADH-IV, manifest a spatiotemporal expression pattern similar to that for retinoic acid during mouse embryogenesis [Duester, 1998]. Too much vitamin A is as harmful to the embryo as too little and a similar spectrum of developmental defects arises in the CNS and neural crest derivatives. This has been shown to be true in humans with the teratogenic appearance of cerebellar and craniofacial defects in babies born to mothers who had taken isotretinoin.

Retinoic acid induces pluripotent embryonal carcinoma cells to differentiate in culture into a variety of cell types, including neural cells, depending on the concentration that is applied [Edwards and McBurney, 1983]. In cells that are already neural, retinoic acid induces neurite extension both in dissociated cell cultures and tissue explants of spinal cord or sympathetic ganglia from a variety of sources, including human embryos [Maden and Holder, 1992]. In most organisms, it is the hindbrain that is specifically affected by retinoids. It appears that retinoic acid affects patterning and segmentation through its effects on *Hox* genes, such as *Hox B-1*, and *Krox-20* [Morriss-Kay et al., 1991]. Administration of retinoic acid at gastrulation causes alterations reminiscent of the cerebellar defects found in human retinoic acid embryopathy [Lammer and Armstrong, 1992] and suggesting that other cranial effects, such as facial nerve palsy and ear defects, could be the result of respecified neural crest. However, when rat embryos were exposed to levels of all-*trans*-retinoic acid and behavioral measurements conducted, there was a sensitive period at gestational days 11 to 13 when the homeobox changes were activated and cerebellar changes occurred resulting in some modest behavioral changes. Exposure to embryos

after this period, however, had very little effect on the cerebellar weight and little effect on the behavior of the animals when measured postnatally. For example, maze learning and avoidance behavior were not affected [Holson et al., 1997b]. The authors concluded that exposure to retinoic acid at doses near lethal for survival during a period of maximum sensitivity to retinoids does not cause severe learning deficits. This activity decreased for exposure at times after the sensitive period [Holson et al., 1997a].

In acute oral toxicity studies in 2-week old rats, no clinical signs were observed at doses less than 308 mg/kg [Hoffmann-La Roche data on file].

5.7.4 Summary

In summary, although the role of retinoic acid in the developing CNS is well characterized, extrapolation to effects on the mature brain seem unwarranted.

5.8 Overall Conclusions on Psychiatric Conditions

As the preceding sections demonstrate, analysis of all available data (pharmacoepidemiological, retrospective studies, and prospective studies), failed to confirm the initial signal of an association between Accutane and psychiatric morbidity.

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