Appendix 13
Review of All Spontaneous Reports of Psychiatric Conditions

SAFETY ISSUE WORK-UP

Author(s):	Robert C. Nelson, Ph.D.
Department(s):	Pharma Development Clinical Science; Safety Risk Management F. Hoffmann-La Roche Ltd., 4070 Basel, Switzerland/340 Kingsland Street Nutley, New Jersey
Drug Preferred Name(s):	RoAccutane (Isotretinoin)
SOC(s): 500	Psychiatric Disorders
ADR(s): (Preferred term or verbatim)	See Attachment
Reporting Period:	Market Introduction (1982) through April 30, 1999.
Date Issue written:	May 31, 2000.
Request Source:	Food and Drug Administration

Hoffmann-La Roche Inc. 340 Kingsland Street Nutley, New Jersey 07110-1199 Pharma Development Clinical Science Safety Risk Management

QJ918 ROACCUTAN - SOC 500
FIRST EVENT LISTED (LOWEST AESN)

Events (AE) and Comanifestations (CO) of 2348 cases.

DATA STATUS: 2 MAY 99

		EVENT_TYPE			PDF-FILE
SOC	PREFERRED_TERM	AE	CO	Grand Total	
500	ABNORMAL BEHAVIOUR NOS	49	2	51	QJ918A1
	ADJUSTMENT REACTION	1	1	2	QJ918A2
	AGGRESSIVE REACTION	36		36	QJ918A3
	AGITATION	33		33	QJ918A4
	AMNESIA	64	8	72	QJ918A5
	ANOREXIA	82	33	115	QJ918A6
	ANOREXIA NERVOSA	1		1	QJ918A7
	ANXIETY	61	7	68	QJ918A8
	APATHY	8	1	9	QJ918A9
	APPETITE INCREASED	14	1	15	QJ918A10
	ATTENTION DEFICIT/HYPERACTIVITY DISORDER	1		1	QJ918A11
	CATATONIC REACTION		1	1	QJ918A12
	CONCENTRATION IMPAIRED	31	3	34	QJ918A13
	CONFUSION	39	6	45	QJ918A14
	DELIRIUM	5		5	QJ918A15
	DELUSION	6		6	QJ918A16
	DEPERSONALIZATION	5	2	7	QJ918A17
	DEPRESSION	898	8	906	QJ918A18
	DEPRESSION PSYCHOTIC	7		7	QJ918A19
	DREAMING ABNORMAL	3		3	QJ918A20
	DRUG ABUSE	5		5	QJ918A21
	DYSPAREUNIA	6	6	12	QJ918A22
	EMOTIONAL INSTABILITY	19		19	QJ918A23
	EMOTIONAL LABILITY	167	5	172	QJ918A24
	EMOTIONAL PROBLEMS	1		1	QJ918A25
	EUPHORIA	3		3	QJ918A26
	HAIR PLUCKING	1		1	QJ918A27
	HALLUCINATION	13	1	14	QJ918A28
	HYSTERIA	3		3	QJ918A29
	ILLUSION	1		1	QJ918A30
	IMPOTENCE	74	1	75	QJ918A31
	INSOMNIA	62	8	70	QJ918A32
	LIBIDO DECREASED	35	2	37	QJ918A33
	LIBIDO INCREASED	1		1	QJ918A34
	MANIC REACTION	6		6	QJ918A35
	NERVOUSNESS	44	8	52	QJ918A36
	NEUROSIS	10		10	QJ918A37
	PARANOID REACTION	11		11	QJ918A38
	PARONIRIA	11		11	QJ918A39
	PERSONALITY DISORDER	41		41	QJ918A40
	PICA	1		1	QJ918A41
	PSYCHIATRIC DISORDER NOS	3		3	QJ918A42
	PSYCHOSIS	47		47	QJ918A43
	PSYCHOSIS MANIC-DEPRESSIVE	7		7	QJ918A44
	SCHIZOPHRENIC REACTION	15		15	QJ918A45
	SLEEP DISORDER	8	1	9	QJ918A46
	SOMNAMBULISM	1		1	QJ918A47
	SOMNOLENCE	71	24	95	QJ918A48
	SUICIDAL IDEATION	45		45	QJ918A49
	SUICIDE (ACCOMPLISHED)	62		62	QJ918A50
	SUICIDE ATTEMPT	75		75	QJ918A51
	THINKING ABNORMAL	20	5	25	QJ918A52
	YAWNING	1		1	QJ918A53
Grand Total		2214	134	2348	

RoAccutane/Accutane (Isotretinoin)-Psychiatric Disorder Issue Work-up

Table of Contents:

1. CONTEXT

1.1 Labeling History

Since June 1985, the U.S. package insert for Accutane in the Adverse Reactions section stated that:

> "The following CNS reactions have been reported and may bear no relationship to therapy – seizures, emotional instability including depression, dizziness, nervousness, drowsiness, malaise, weakness, insomnia, lethargy and paresthesias."

In August 1986, the Package Insert was amended to state:

> "Depression has been reported in some patients on Accutane therapy. In some of these patients, this has subsided with discontinuation of therapy and recurred with reinstitution of therapy."

In late 1997, the nature of an association between the administration of Accutane for severe, recalcitrant nodular acne and the onset of various psychiatric disorders and suicide was queried by the U.S. Food and Drug Administration. Roche conducted reviews and a product relabeling was initiated on February 23, 1998 in the US.

The Current U.S. label contains the following wording:

> WARNINGS Section - "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".
>
> ADVERSE REACTIONS section – "In the postmarketing period, a number of patients treated with Accutane have reported depression, psychosis and, rarely, suicidal ideation, suicide attempts and suicide. Of the patients reporting depression, some reported that the depression subsided with discontinuation of therapy and recurred with reinstitution of therapy".

The 1998 relabeling was based on receipt of spontaneous reports. These spontaneous reports were mixed in content and nature, and provided an unclear and unconvincing picture of the risk. The nature, extent, and public health importance of these unconfirmed adverse experience reports continue to be of concern. Accordingly, Roche and the FDA agreed that it was important to make the prescribing professionals and the consuming public aware of these issues.

Under "Precautions" in the Core Data Sheet, version 1.1, April 8, 1999, the following is found:

"Depression, psychotic symptoms and rarely suicide attempts and suicide have been reported in patients treated with Roaccutane. Although a causal relationship has not been established, particular care needs to be taken in patients with a history of depression and all patients should be monitored for signs of depression and referred for appropriate treatment if necessary.

1.2 Comprehensive Review

This review was commissioned by Roche in the second quarter of 1999 to examine the nature and content of the spontaneous reports it has received from 1982-1999, relating all psychiatric events that were temporally related to the administration of RoAccutane/Accutane. An extensive literature review was also conducted to provide context to this complex set of issues. Epidemiological analyses from the literature examined competing and attributable risks relevant to the reported events. Adverse drug reaction (ADR) reports represent those of both RoAccutane and Accutane, trade names for isotretinoin capsules. They are used interchangeably in this report.

Upon commissioning and initiating this review, there was no misunderstanding of the limited value of spontaneous reports in resolving these issues. It was clear 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. For example, was there a characteristic symptom or set of symptoms, consistent comorbidity, persistent proximal factors, a time-course, a dose threshold, common external risk factors, a unique pattern of resolution?

If clear hypotheses could be raised by this review, Roche was prepared to study the issues further in hopes of testing and, if appropriate, quantifying the risk, and possibly elucidating a mechanism of action.

2. PRINCIPAL FINDINGS

After a comprehensive review of the spontaneous reports, literature, and epidemiology of the relevant factors the following conclusions have been reached:

Mood Disorders:

There are a small number of reported cases that imply causality between depressive symptoms, 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 these kinds of data do not allow any potential risk factor to be completely ruled out, no matter how unlikely it may appear.

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 these kinds of data do not allow any potential risk factor to be completely ruled out, no matter how unlikely it may appear.

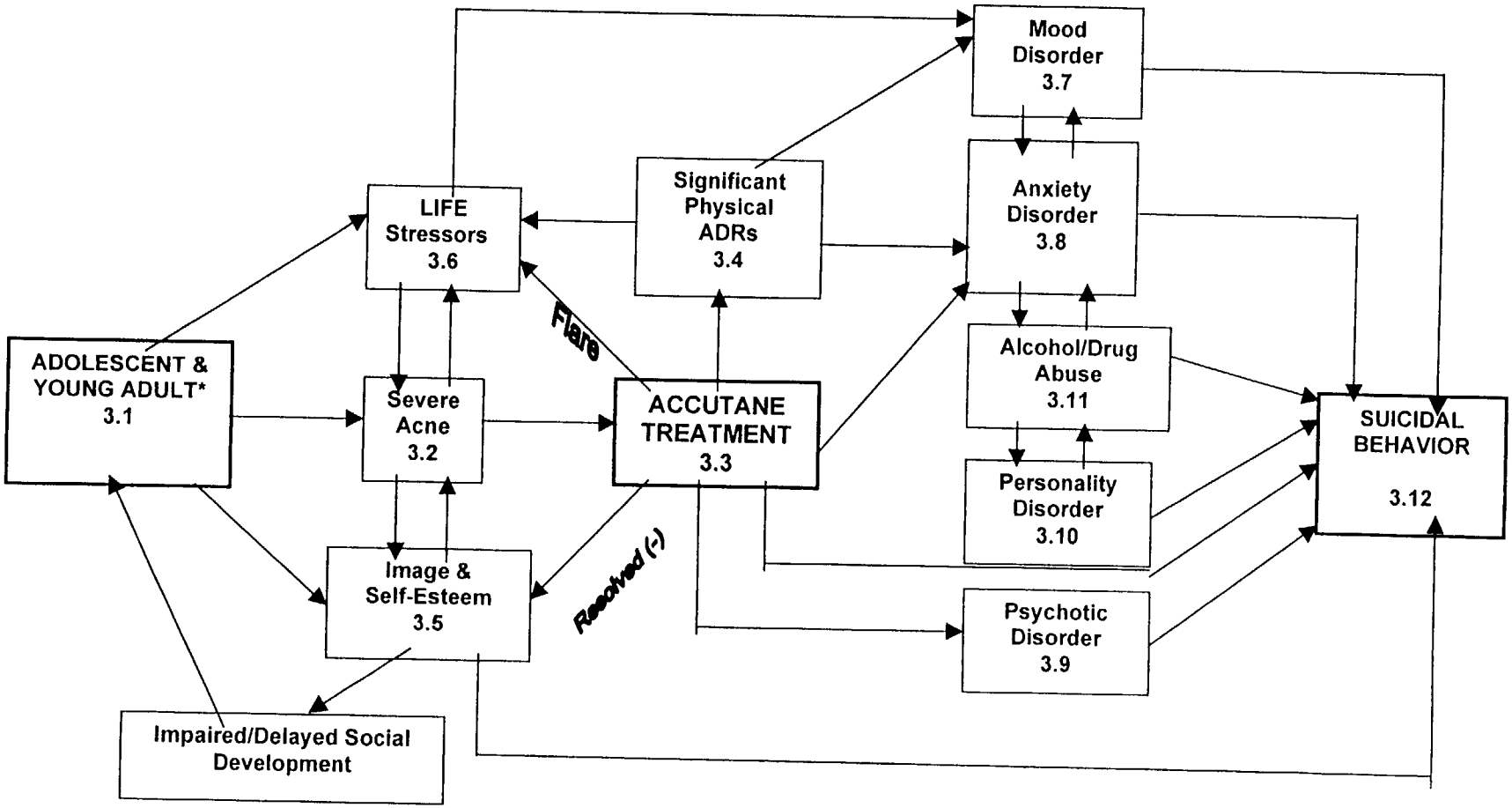
Suicidal Behavior:

There are no reports amongst the 168 reviewed that would imply causality between suicidal behavior and Accutane. 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

3. MODEL

The diagram presented in Figure 1 greatly simplifies the complex contextual framework for the relationship under investigation..

FIGURE 1: MODEL OF THE INVESTIGATION OF PROPOSED RELATIONSHIPS BEING EVALUATED



**without psychiatric disorder*

Arrows represent hypothetical relationship for the purpose of this analysis only

In the leftmost box of the model diagram are the young adults and adolescents who represent the majority of Accutane-consuming patients with their hypothetical relationship to the major categories of mental disorders: mood, anxiety, and psychosis, as well at suicidal behavior. Accutane is prescribed to individuals suffering from the medical disease of severe recalcitrant nodular acne, and who comprise only a small percentage of the population. This is a very simplified diagram of a complex set of variables that are constantly changing in intensity. Between the population of interest and the outcome of interest are the variables of interest. Each box on the diagram will be discussed briefly in turn in this section.

3.1 Adolescents, Young Adults and their Developing Brain

For many young people, the development of emotional coping mechanisms enables the control of aggression and irritability. Since this development is progressive and variable, frequent changes in mood are extremely common event in adolescents. The concept of "Normal Adolescent Turmoil" is used both in the sociological and psychological literature to describe these turbulent times.

The adolescent brain is not fully developed either physiologically or psychologically. Its development is uneven, much like that of the adolescent body. For example, the myelin development to coat the nerves in white matter is not complete. Along with the biological development of the body and the brain, the personality traits continue to develop. Maturation can vary considerably from person to person. Male and female patterns vary markedly with females developing at an earlier age.

Social maturation is partially a product of experience. Impaired or delayed social development can occur and extend well into the third decade. The wide fluctuations in sex and other endocrine hormones during adolescence affect all parts of the young life, body and mind. Acne is associated with the onset of change in endocrine hormones that first appear during adolescence. Acne, and the social isolation it produces, can delay the psychological maturity that comes with life experience and thus extend this period of emotional immaturity.

A young person's perception of body image is extremely important both socially and psychologically and is often a source of considerable stress and anxiety. During the teenage years, self-esteem is universally in doubt. Numerous published studies have described the psychological effects of a disfiguring disease such as acne (Gupta et al, 1990; Gupta and Gupta, 1998; Cotterill and Cunliffe, 1997; Kellett and Gawkrodger, 1999), which only exacerbates the problems with self-image. These factors contribute to underlying disorders in some individuals. This topic will be addressed in detail in section 3.5.

As will be discussed in this document, many of the mental disorders are just beginning to surface, often as isolated symptoms, during these years of maturation.

3.2 Severe Acne

Acne vulgaris is a chronic inflammatory disease of the pilosebaceous follicles in which the major etiological factors are increased sebum production, hypercornification of the pilosebaceous duct, abnormal microbial flora, and inflammation. Clinically, acne is characterized by the presence of comedones (open blackheads containing melanin and closed whiteheads), papules, pustules, nodules and scars. Onset is predominately during adolescence, although late onset acne (particularly in females) is becoming increasingly recognized. Resolution usually occurs by mid-20s, although in some patients acne can persist a good deal longer. (Lowe, 1993). Rademaker et al (1989) surveyed 2014 Glasgow schoolchildren and found a prevalence of 85% in girls and 93% in boys by the age of 17 in that group. Epidemiological surveys indicate a 95% lifetime prevalence of acne, mostly noninflammatory and mild or moderate in severity.

Lowe (1993) reminds us that acne is not confined to teens. While the epidemiology is not clear, we can determine that less than 45% of Accutane use in females is in persons over 25 years of age (though only 15% of use in males is for the groups older than 25 years of age) (IMS, 1998).

Onset of acne correlates with the sex hormone rush of puberty, with androgens serving as the precipitant. While mild acne is ubiquitous and therefore equal across gender, it is not so for the more severe forms. Females often begin to develop acne at earlier age than males. Males have a greater prevalence of moderate/severe disease (some estimates are four-fold)(White, 1998). The lifetime prevalence of severe nodular acne is unknown but has been estimated to be about 4%.

The relationship of stress to many dermatological diseases, such a chronic urticaria and generalized pruritus, is well established (Garrie and Garrie, 1978; Koblenzer, 1983). Its relationship to acne is less clear. Koo (1991) contends that emotional stress can exacerbate acne. The literature is sparse on the topic of stress as a cause of acne. Wu and colleagues (1988) found that acne patients internalized their anger more than controls and felt this suppression of anger may lead to more severe acne. There was little additional research in the literature that confirmed or supported this potentially important concept. A recent report (Schulpis et al, 1999) indicated that patients with severe acne had higher levels of stress-related hormones (catecholamines) than age-matched non-acne subjects and had higher scores on various mood disorder scales. After treatment with isotretinoin and resolution of the acne, the hormone levels and mood disorder scores were reduced.

3.3 RoAccutane/Accutane Treatment

3.3.1 Mechanisms of Action

Accutane is indicated for severe recalcitrant nodular acne. Inhibition of sebum production with alterations in skin surface lipid chemistry may represent an important mechanism of action of isotretinoin leading to clinical improvement in acne. Inhibition is roughly dose-dependent, and doses of 0.5 to 1.0 mg/kg per day lead to an 80-90% inhibition of both sebum excretion rate and reduction in lesion counts after 12-16 weeks of therapy. The sebaceous glands appear to atrophy during treatment with isotretinoin but gradually recover after discontinuation of therapy. The efficacy of Accutane is secondary to daily dose and perhaps to total dose. Its side-effect profile is somewhat dose-dependent over the range of efficacy. The efficacy of Accutane in acne can be to a large extent understood from the mechanism of action of isotretinoin in epithelial cell proliferation and differentiation. Documented pharmacological effects of isotretinoin would not be predictive of an association between Accutane and psychiatric disorders.

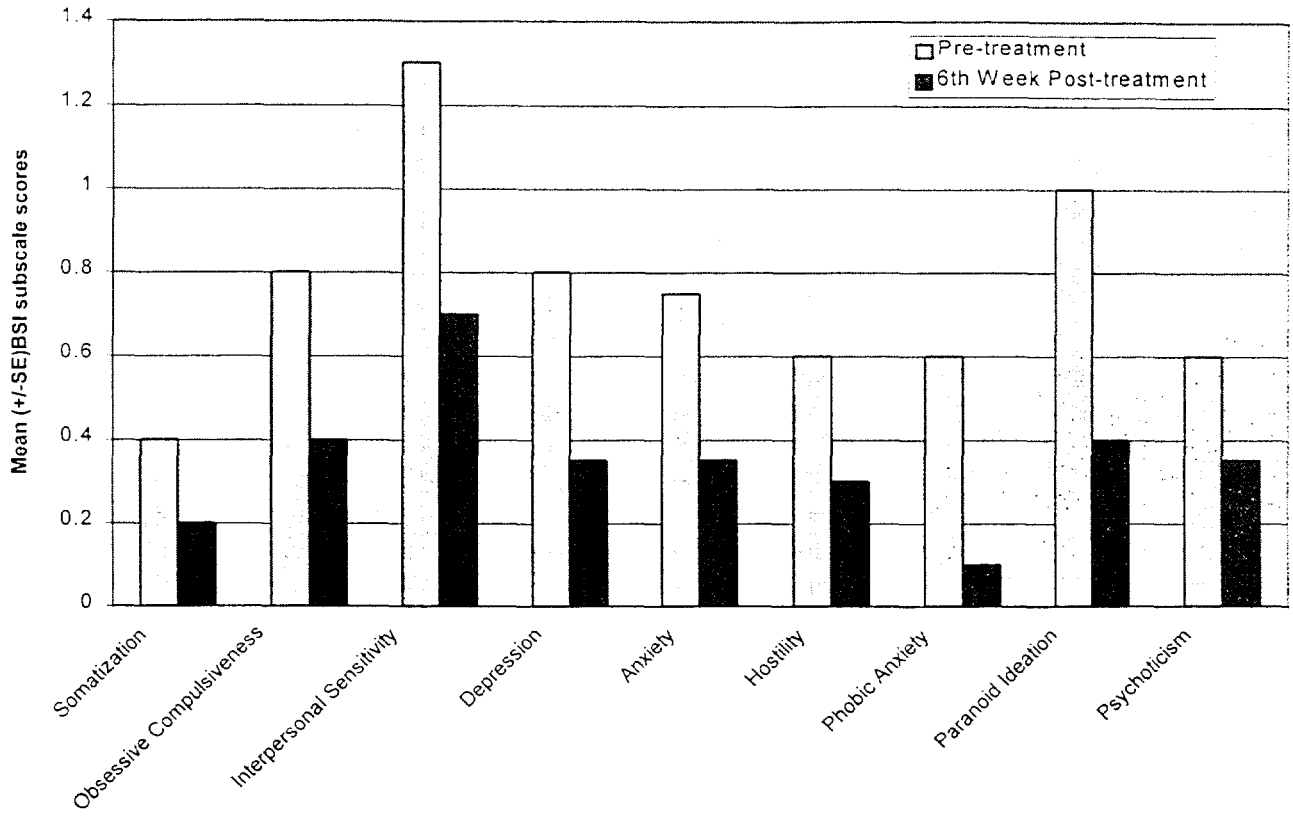
Please refer to Appendix A for more background and to Appendix B for the epidemiology of Accutane use.

3.3.2 Acne Treatments and Diminished Depression

The clearance or improvement of acne has been shown to relieve some of the pre-existing psychological effects. In the largest study to date, Rubinow demonstrated that in treating 72 severe recalcitrant acne patients with isotretinoin, even patients with a minimum response, less then 50% reduction in lesion counts, had significant improvements in their anxiety, depression and interpersonal sensitivity. The most significant effect on all patients after treatment was in depression and anxiety scores (Rubinow et al. 1987). In other studies, the improvement in the skin condition had a direct association with decreased depression and anxiety due to the improvement in the patient's overall body image (Gupta et al. 1990 and Layton et al. 1997).

Figure 2, taken from Gupta et al, 1990, presents the subscale scores for various psychological constructs at an Accutane pretreatment point and then at the 6th week, post-treatment. All indices are lower in the post treatment point. Prevention of further scarring by isotretinoin therapy has led to clear improvement in the psychological perception of the patient (Layton et al. 1997). However, in other reports, some individual patients who developed depressive symptomatology months after completing isotretinoin therapy suggest that clearance of a disfiguring disease may force patients to confront and directly suffer from failures previously attributed to his/her appearance (Gupta et al. 1990).

Figure 2: Pre- and Post-treatment questionnaire findings



In a very recent study by Kellett and Gawkrodger (1999), 34 patients were administered a battery of validated measures of psychological and emotional functioning before, during and after treatment of chronic acne with RoAccutane. They found 44% of patients (mean age 24.5 years) reported clinically significant anxiety and 18% clinical depression at baseline. Scores on a variety of scales, such as embarrassment, self-esteem, locus of control, etc. improved as the skin improved with therapy. However, the emotional status of the patients appeared to be more resistant to change in the timeframe of the study.

3.4 Significant Adverse Drug Reactions Reported in Accutane therapy

This section describes adverse events reported in Accutane patients that may have had some effect on their mood, overall energy level, or feeling of well-being during therapy.
The adverse drug reaction (ADR) profile of Accutane has been summarized by Peck and DiGiovanna (1993) as follows: "The acute toxicities commonly observed with the synthetic retinoids, isotretinoin and etretinate, are well tolerated, not life-threatening, are dose dependent in incidence and severity, treatable with bland therapies, and reversible on

discontinuation of treatment. The acute toxicities of synthetic retinoids mimic many of the findings of Vitamin A intoxication but are less severe than those seen with the high doses of Vitamin A required for clinical efficacy; they involve primarily the skin and mucous membranes".

Most mucocutaneous side effects are not severe enough to cause discontinuation of the drug. Several adjuncts may be used to minimize the discomfort of these mucocutaneous effects, such a white petrolatum for dry, chapped lips, glycerin swabs for dry oral mucosa and saline drops for dry eyes (Millan, et al, 1987)

See Table P-1 in Appendix P for dose response data from original U.S. NDA.

However there are a number of additional adverse reactions that occur in smaller numbers of patients that contribute to the discomfort and stress. They are:

- Pseudotumor cerebri
- Muscle and/or joint pain
- Hair Loss
- Acne Flare

Benign intracranial hypertension (BHI, pseudotumor cerebri) involves headaches, nausea, vomiting and visual disturbances. To avoid cumulative risk of this disorder, tetracyclines and Accutane should not be used concomitantly (Mills and Marks, 1993).

Chronic pain and soreness in muscles and joints can significantly impair daily functioning and color one's perception of the world. There is extensive literature on the psychological impact of chronic pain (not reviewed here). Up to 15% of Accutane treated patients report arthralgia and muscle stiffness (Mills and Marks, 1993).

Hair loss or changes in texture have been reported in a small percentage of patients, and, in some instances the hair loss was reported to be extensive. There is no known mechanism of action.

Hair loss and acne flare have direct impact on the acne sufferers' already lowered body image and self-esteem. The acne flare, which appears at about 2-4 weeks after initiating therapy, is particularly devastating to some individuals because it appears that their "last hope", i.e., Accutane has not only failed, but also made the bad situation worse. The mechanism by which mood disorders and/or depression are risk factors for exacerbation of acne is unclear and has not been well studied. However, in a large study of several thousand dermatology patients, 55% of the acne patients associated periods of emotional stress with flare up of acne lesions (Griesemer, 1978).

Similarly, the lack of effect from a course of therapy can have severe impact on any degree of hopefulness that the individual held. Accutane treatment is often, if not always, regarded as the last chance for resolution of severe recalcitrant nodular acne.

These specific ADRs were examined, as confounders and as component risk factors in this review.

3.5 Image and Self-Esteem

Skin is a major organ of social and sexual communication. Acne complicated skin disease, when severe, can be disfiguring and demoralizing (Ginsberg, 1993)

In late 1940's, Sulzberger and Zaidems stated that "There is no single disease which causes more psychic trauma, more maladjustment between parent and children, more general insecurity and feelings of inferiority and greater sums of psychic suffering than does acne vulgaris" (Koo, 1995). Since then, it has been consistently demonstrated that dermatological conditions, although not generally life-threatening have a major impact on patients' psychological state, social relationships and everyday activities (Krowchuk, 1991 and Koo, 1991/1995).

The interactions between acne and psychological problems are complex and potentially circuitous (Koo, 1991). A psychological condition can exacerbate acne because of the emotional stress (psychophysiological) and conversely, the disfiguring acne condition and the consequent lack of self esteem or social phobias can lead to mood disorders and possibly depressive conditions (Rubinow, 1987).

Dermatology quality of life scales (DQOLS) have been developed to assess the impact of skin conditions on psychological state and patient perceived impacts (Girman, 1996 and Morgen, 1997).

The interrelationship between acne and depression may be demonstrated by a report on psychosomatic treatment (biofeedback relaxation) in which patients' acne lesions improved with treatment and became more severe when therapy was withdrawn (Hughes, 1983). In a more recent observation, improvements in psychological well being by psychotherapy also resulted in improved dermatology conditions in four patients with recalcitrant acne vulgaris (Koblenzer, 1997).

The most severe forms of acne produce conspicuous changes in personal appearance, which in turn can have profound effects on self-esteem and social interactions (Koo, 1991). Sixty-six patients with cystic acne in a systematic study on psychiatric morbidity and mood characteristics had significantly increased psychological test scores for depression and anxiety than normal subjects (Rubinow, 1987). In an earlier study of 40 patients with severe acne, these patients were found to be more neurotic, had a lower self-defensive attitude and were more anxious than people in a normal population (van der Meeren, 1985). There is a deterioration of self-image in patients suffering from certain skin diseases which is related to severity, sex, and site of disease. Pearl and colleagues (1998) studied the impact of acne in 847 adolescents. The severity of acne determined the extent of embarrassment and the lack of enjoyment of and participation in social activities. This was true for both genders. Thus the presence of acne itself may increase the severity of the mood disorder in adolescents.

Several studies have reported that, apart from any involvement of Accutane therapy, the psychological symptoms of acne patients may range from a mild feeling of anxiety to depression, including a variety of degrees of embarrassment or self-consciousness, lack of self-confidence and perceived social rejection (Cohen, 1991; Gupta, 1994; Girman, 1996). A number of factors such as concern about prognosis of the disease may be a source of

anxiety (Jowett, 1985) and the matter is complicated by the fact that 30% - 50% of people aged 12 - 20 years worry "a lot" or "have some health concern" with acne (Feldman, 1986). In rare cases, the severity of the acne or the perception of the severity may lead subsequently to suicide (Cotterill, 1997).

One of the more human stories that discuss the psychological consequences of acne with adverse events reported during treatment with Accutane appeared in Lancet in 1996. A patient described his misery due to side effects from Accutane but went on to describe them as a small price to pay to get relief from the blanketing impact of severe acne on a young persons life (James, 1996).

The individual feeling of disfigurement may find its expression in self-consciousness, lack of trust, conception of self vs. ideal of self and Welp concludes that individual experience of wanting physical attractiveness, associated with predominantly neurotic depressive personal structure, may play a central part in a disturbed process of interaction with the environment (Welp, 1990).

Barth et al (1993) studied the self-image of hirsutism in females. They found that 27% hirsute subjects had significant symptoms of psychiatric disturbance and that 68% avoided some social situations.

Body Dysmorphic Disorder is a grossly excessive preoccupation with an imagined defect in physical appearance or slight physical anomaly in a normal-appearing person. One etiologic theory places trauma in adolescence, a time of physical and physiological change, as contributory. (Phillips, 1991). Adolescents with cystic acne have a real disease but that disease, in and of itself, does not qualify them for the criteria for BDD. However, some of the same symptoms may come into play: trauma, social isolation etc.

Finally, Gupta and Gupta (1998) found a 5.6% prevalence of active suicidal ideation amongst non-cystic facial acne patients versus 2.4-3.3% in general medical patients. This is one of the few studies that document an association between psychological symptoms and moderate acne.

3.6 Life Stressors

Stressors are an unavoidable consequence of life. A comprehensive list of all possible life stressors would be enormous. Some that are more specific to the adolescent and young adult are: parents, significant others, school, high school graduation, dating, marriage, PMS, post-partum period, moving, and the hormone flood.

The nature and timing of stressors vary from person to person. Also variable are the coping mechanisms required to handle life's stressors. Coping mechanism development usually parallels biological, psychological, and social development. Delayed maturation delays mature coping mechanisms. Kendler (1993) studied pairs of female twins and found a strong genetic core, with life stressors setting longitudinal variability, but that variability was transient. That is, different genetic makeup set a tolerance for handling life stressors. Once above that level of tolerance, clinical disease may occur. Many of the stressors are non-specific.

Non-specific life events or stressors precede and accumulate toward Major Depressive Episodes (MDE) and Generalized Anxiety Disorder (GAD). MDE only patients tend to have a greater burden of stressful events and comorbid disorders, than persons with GAD only (Newman, 1994).

Life stressors can be distal or proximal causes of mental disorders. The same stressor could be either depending on timing and cumulative load.

3.7 Mood Disorders

Mood (affective) disorders are best considered as syndromes (rather than discrete diseases). They are defined as disturbance of mood, accompanied by a full or partial manic or depressive syndrome, that is not due to any other physical or mental disorder. Mood refers to prolonged emotion that colors the whole psychic life; it generally involves depression or elation. They are sustained over a period of weeks to months and are often periodic or cyclic.

Mood disorders are diagnosed by the pattern of mood episodes (major depressive, manic, hypomanic). The symptoms observed during manic episodes are inflated self-esteem, talkativeness, decreased need for sleep, distractibility, and psychomotor agitation. The essential features of a major depressive episode are depressed mood or loss of interest or pleasure in all, or almost all, activities for a period of at least 2 weeks. The associated symptoms include appetite disturbance, change in weight, sleep disturbance, psychomotor agitation, decreased energy, feelings of worthlessness, difficulty thinking, recurrent thoughts of death, or suicidal ideation and attempts. Major depressive episodes typically follow a psychosocial stressor and the onset and the duration is extremely variable.

Mood disorders are divided into two sub-categories: bipolar disorders and major depressive (unipolar depression) disorders. Refer to Appendix C for a brief Background on Psychiatric disorders with DSM-IV classifications and to its Figure C1 for a visual of the "Mood Tree", then Table C1 for full definitions for the various mood disorders.

Also, very importantly, refer to Appendix D for the epidemiological parameters of mood disorders and other forms of psychiatric morbidity. The special section on mood disorders in the young demonstrates the very different, and critically important for this analysis, patterns of mental disease in this young population.

Depression in adolescence is a matter of public concern. The occurrence and the manifestations of depressive illness in adolescence have been the focus of considerable controversy and conflicting data. There appear to be two schools of thought: first, what appear to be depressive symptoms are simply markers of normal adolescent turmoil with no implications for subsequent pathology. In part, this thesis is supported by the fleeting nature of many of these symptoms in this age group, in contrast to the long-lasting symptomatology of adults. The second school suggests that depressive illness does occur in adolescence with considerable frequency but that it manifested differently and therefore is often unrecognized. The consistent understanding in both is that different and varied symptoms with their rapid onset-offset timecourse occur in the adolescent/young adult.

The dividing lines of the mood disorders are soft with much shared symptomatology but as time progresses, symptoms stabilize, and there is increasing comorbidity. A continuum would follow this flow: Adolescent behavior -> Depressive symptoms -> Subclinical depression and/or Brief recurrent depression -> Dysthymias -> Co-morbid depression and mixed symptomatology -> Mild depression -> Moderate depression -> Severe depression. However, this is a continuum with substantial variance and overlap. In addition, there are also empirical data to demonstrate that severe form of the disease is qualitatively different than the less severe form (Jorm,1987).

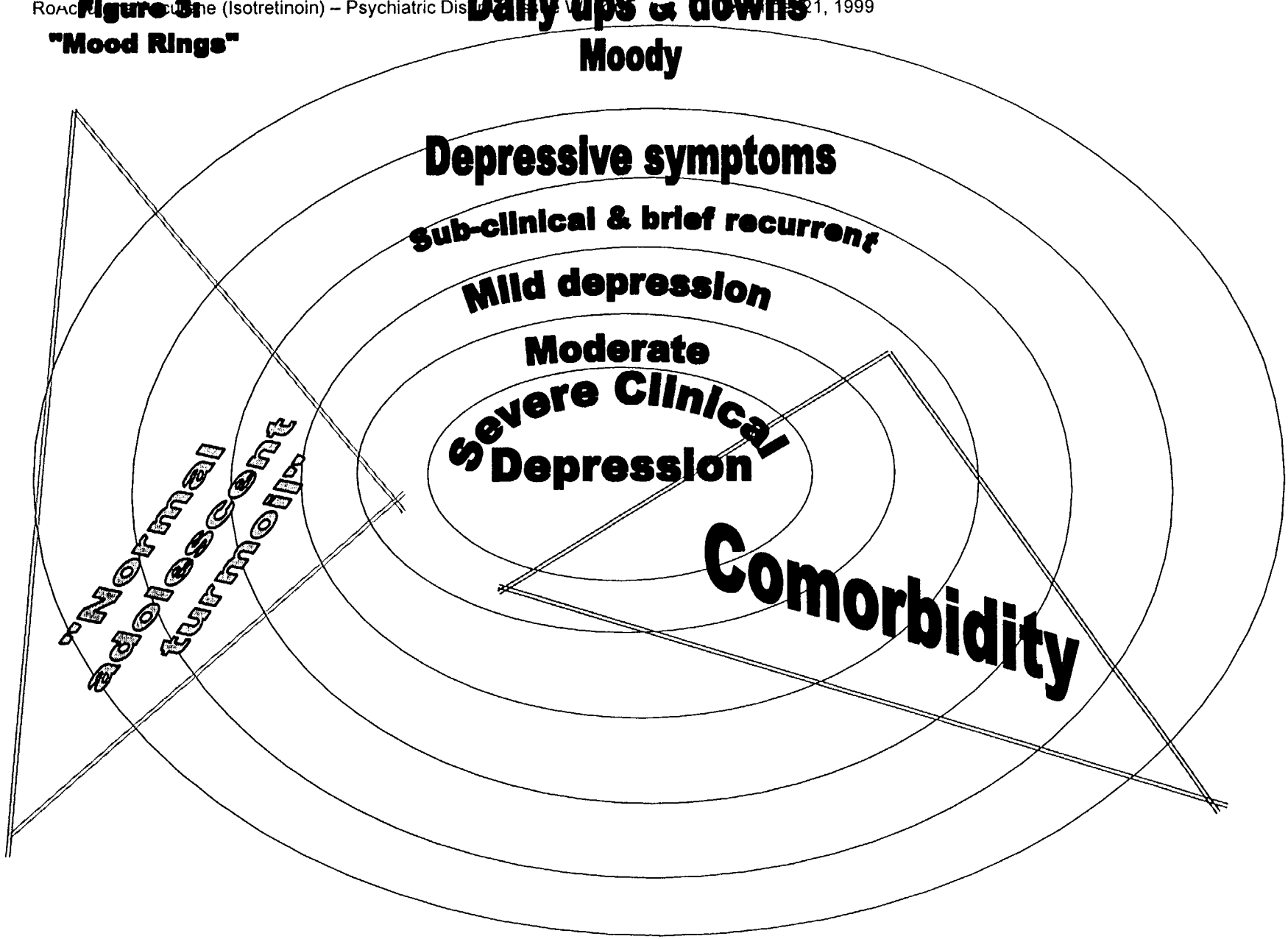
Figure 3 is a graphical representation of the various mood disorders and depressive symptoms with rate relative to circle position . This is an illustration and not drawn to real scale. Data (Kessler, 1993, Blazer 1994) that would be included in the center three circles, ie, major depressive disorder prevalence rates, for the 15-24 age group are:

- 6.1% (4.3% M:: 8.2% F) - 30 days
- 10.3%(9.5% M::16.3% F) - 12-month
- 17.1% (11.0% M::20.8% F) – lifetime

Thus, the prevalence of major depressive disorder in any 12-month period averages 10.3% and prevalence of symptoms increases with each circle toward the outside. The triangle on the left represents the prevalence of symptoms in normal adolescent turmoil The triangle on the right represents the prevalence of additional comorbid mental disorders .

(An overview of the epidemiology of psychiatric disorders can be found in Appendix D)

Figure 3:
"Mood Rings"



Mood disorders in both children and adolescents represent one of the most under-diagnosed groups of illnesses in psychiatry (Offer, 1992). Murphy (1989) considers anxiety and depression as clinical processes of considerable time depth. Some 'normal adolescent turmoil' involves developing psychopathology too fluid to permit definitive nosological classification. Symptoms, isolated or in smaller clusters, that occur earlier are prodromes to affective disorders. They remain subclinical until the proximal event or cause occurs. Anxiety and depressive symptoms are often mixed in adolescents (Strober, 1981).

Non-specific life events such as mood disorders and life stressors precede and accumulate toward Major Depressive Disorder (MDD) and Generalized Anxiety Disorder (GAD). Persons with MDD only tend to have a greater burden of stressful events and comorbid disorders than persons with GAD only (Newman, 1994). Distal causes may be the same or similar. Accumulating life stresses of loss may direct one toward depression, whereas life stresses of danger may direct one toward anxiety disorders. Major depression, including bipolar affective disorder, often appears for the first time during the teenage years (Murphy, 1989). Dysthymic disorders also have this earlier onset.

Jorm (1987) considers severe and less severe depression as different clinical modalities with different risk factors. The less severe disorder is more dependent on external risk factors. The severe form is more chronic, comorbid and less responsive to new external stressors. The social and personal impact of mood disorders and other psychological problems are immense and may lead to difficulties in school, in work, and in personality development that often continue into adulthood.

There are four major relevant points regarding mood disorders:

- ***Clinically diagnosable mood disorders are slightly less prevalent in the young than in the decades to follow, but depressive symptoms are very common***
- ***Age of onset of mood disorders and the typical treatment age for Accutane are similar***
- ***Disorders of mood develop in the young ages, and first appear as prodromal depressive symptoms, which include irritability and aggression, usually with a short time-course***
- ***Many of the characteristics of "normal adolescent turmoil" overlap with those of the emerging disorder. Duration of symptoms is a key discriminating factor.***

3.8 Anxiety Disorders

Anxiety disorders are divided into panic, phobias, and generalized anxiety disorder.

Panic Disorder: the occurrence of three or more panic attacks within a 3-week period. These attacks cannot be precipitated by exposure only to a feared situation and must be accompanied by at least four of the following symptoms: dyspnea, palpitations, chest pain, smothering or choking, dizziness, feelings of unreality, paresthesias, hot and cold

flashes, sweating, faintness, trembling or shaking (American Psychiatric Association (APA), 1980).

Agoraphobia: defined as a fear and avoidance of being in places or situations from which escape might be difficult or in which help might not be available in the event of sudden incapacitation (APA, 1980).

Social Phobia: the central feature is the persistent, irrational fear of situations in which a person may act in a humiliating or embarrassing way while under scrutiny of others (APA, 1980),

Generalized Anxiety Disorder (GAD): the DSM-III criteria for GAD require the presence of unrealistic or excessive anxiety and worry, accompanied by symptoms from three of four categories: (1) motor tension, (2) autonomic hyperactivity, (3) vigilance and scanning, and (4) apprehensive expectation. The anxious mood must continue for at least 1 month, and the diagnosis is not made if phobias, panic disorder, or obsessive-compulsive disorder are present or if the disturbance is due to another physical or mental disorder, such as hyperthyroidism, major depression, or schizophrenia (APA, 1980).

Panic Attacks and the Phobias are discrete diagnostic entities that are fear based. For the most part, these are disorders that form fixed symptoms with clear triggering events. They are not considered endpoints for any form of chemical toxicity. There is no literature that supports substance-induction.

GAD, however, is a disorder that shares much with mood disorders. In adolescents symptomatology of anxiety and depression are usually mixed. While phobias are common by this age, GAD and panic attacks are uncommon. Adolescents and young adults have symptoms but rarely clinical GAD.

The role of panic disorder and panic attacks in adult suicidal ideation and attempts was thoroughly investigated by Weissman et.al. (1989). Subjects who had panic disorder, when compared to a group with other psychiatric disorders, had more suicidal ideations and suicide attempts. Twenty percent of subjects with panic disorder (lifetime prevalence 1.5%) and 12 percent of those with panic attacks (estimated lifetime prevalence is 2-3 times that of panic disorder) had made suicide attempts. These results could not be explained by the coexistence of major depression or of alcohol or drug abuse. Female gender and coexisting alcohol abuse were associated with the highest risk in all diagnostic study groups. These data were for adults, and their relevance to younger persons is unclear except that full panic disorder is relatively rare (10% of total; prevalence unknown) in the younger group. A recent analysis of these data, which were controlled for comorbid disorders in the aggregate rather than one at a time, showed that panic disorder was not associated with an increased risk of suicide attempt (Hornig and McNally, 1995). A psychological autopsy by Henricksson et al (1996) on 1397 cases of suicide in Finland showed that panic disorder was comparatively rare (17 of 1397 or 1.2%) and the authors concluded that suicides in these cases were associated with superimposed major depression, substance abuse, and personality disorders.

There are four major relevant points regarding anxiety disorders and any claimed association with Accutane:

- ***Age of onset of many of these disorders and the typical treatment age for Accutane are similar***
- ***Disorders of mood and anxiety may share the same distal risk factors***
- ***Irritability and aggression in the young are symptoms of "normal adolescent turmoil", or mood, or anxiety, or substance abuse disorders***
- ***Many of the characteristics of "normal adolescent turmoil" are shared by these disorders. Time-course (duration) of symptoms is key.***

3.9 Psychotic Disorders

Psychotic disorders are defined as mental disorders that comprise major disturbances in affect, thinking and behavior. They cause gross distortion or disorganization of a person's mental capacity, affective response, and capacity to recognize reality, communicate, and relate to others to the degree of interfering with capacity to cope with ordinary demands of everyday life. According to the Glossary of the American Psychiatric Association, "the term psychotic means grossly impaired in reality testing. The term may be used to describe the behavior of a person at a given time or a mental disorder in which at some time during its course all people with the disorder have grossly impaired reality testing. With gross impairment in reality testing, people incorrectly evaluate the accuracy of their perceptions and thoughts and make incorrect inferences about external reality even in the face of contrary evidence." 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 main psychotic disorder is schizophrenia. Schizophrenia is characterized by the presence of the following characteristic symptoms: gross impairment in reality testing and marked loosening of associations as evidenced by delusions and/or hallucinations, disorganized speech, grossly disorganized or catatonic behavior and other negative symptoms of a certain duration and in the absence of organic factors. In addition, the definition incorporates dysfunction in interpersonal relations, work, education or self-care.

Psychotic symptoms are not only confined to psychotic disorders (schizophrenia, schizoaffective or schizophreniform disorders, delusional disorders, and brief reactive psychosis). They can be observed in several other psychiatric disorders such as dementia of the Alzheimer's type, substance-induced delirium or other amnesic and cognitive disorders or major depressive disorders. Patients can also present transient psychotic symptoms during the course of some affective disorders (e.g. bipolar psychosis with mania), organic mental disorders, subgroups of personality disorders (e.g. borderline personality disorder). Psychoactive substance use, 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 duration of time.

There are four major relevant points regarding psychotic disorders and any claimed association with Accutane:

- ***Age of onset of disorders and the typical treatment age for Accutane are similar***
- ***Psychotic disorders are rare***
- ***Psychotic disorders are chronic and debilitating***
- ***Many of the early characteristics or symptoms of these disorders can be mistaken for "normal adolescent turmoil" or mood, or anxiety, or mixed disorder, or substance abuse disorders.***

3.10 Personality Disorders

Personality traits are enduring patterns of perceiving, relating to, and thinking about the environment and oneself that are exhibited in a wide range of social and personal contexts. Only when personality traits are inflexible and maladaptive and cause significant functional impairment or subjective distress do they constitute Personality Disorders. A personality disorder is an enduring pattern of inner experience and behavior that deviates markedly from the expectations of the individual's culture, is pervasive and inflexible, has an onset in adolescence or early adulthood, is stable over time, and leads to distress or impairment. There are 10 specific Personality disorders: Paranoid, Schizoid, Schizotypal, Antisocial, Borderline, Histrionic, Narcissistic, Avoidant, Dependent, Obsessive-Compulsive, and NOS (APA, 1994). The discussion of each type is not required for this report.

Beginning with the DSM-III in 1980, a multiaxial diagnostic system was established. It involves an assessment on several axes, each of which refers to a different domain of information that may help the clinician plan treatment and predict outcome. The multiaxial system is as follows:

Axis 1 – Clinical disorders
Other conditions that may be a focus of clinical attention
Axis II – Personality disorders
Mental retardation
Axis III – General medical conditions
Axis IV – Psychosocial and environmental problems
Axis V – Global assessment of functioning

Personality Disorders were assigned their own axis (axis II) in the diagnostic nomenclature. Personality Disorders are conceptualized as long-term characteristics of individuals that are likely to be evident by adolescence and continue through adulthood. The diagnosis of Personality Disorder should not be made if the characteristics only occur during episodes of an axis I disorder.

There have been five major epidemiological studies conducted post-DSM-III era that had a focus on personality disorders:

1. Nestadt (1993) detailed the results of a follow-up assessment for personality disorders of the Epidemiologic Catchment (ECA) study. Of the 1,086 subjects that 'screened positive' for psychopathology in the Baltimore ECA site, 810 agreed to further interviews. A prevalence of 5.9% for a definite diagnosis of personality disorder and a prevalence of 9.3% for their combined definite plus provisional diagnostic categories.

2. Zimmerman and Coryell (1989) reported rates among a nonpatient convenience sample of 797 individuals. Some subjects where assessed face-to-face, others via telephone. The prevalence of any DSM-III personality disorder, including mixed personality disorder, was 17.9%.

3. Casey and Tyrer (1986) carried out a study in 200 randomly selected community residents in the United Kingdom. Personality disorders were diagnosed in 13% of their subjects.

4. Reich and colleagues (1989) conducted a random mailed survey of the adult population of Iowa City. Two hundred forty surveys (62%) were returned. The rate for receiving any axis II disorder was 11%.

5. Maier (1994) studied a sample of 452 subjects in the mixed urban/rural Rhein-Main area of Germany. Face-to-face structured diagnostic interviews were conducted. The rate of receiving any personality disorder diagnosis was 10%.

Overall, the Male-to-Female ratio was around one, but there is variance by disorder type. There are little firm data on age of onset by type. Most epidemiological studies were conducted in adults. However, all these disorders have their external onset in adolescence or early adulthood.

Diagnosis in persons under 18 year requires 1 full year of symptomotology. Antisocial personality, by definition, cannot be diagnosed in individuals less than 18 years.

In summary, by their nature alone, true personality disorders are likely to play no role in this relationship model other than a potential source of misclassification.

There are four major relevant points regarding personality disorders and any claimed association with Accutane:

- ***Age of onset of these traits as disorders and the typical treatment age for Accutane are similar***
- ***Disorders of personality have been* establishing themselves from very young ages**
- ***Many of the characteristics and symptoms of these disorders can be mistaken for new (incidence cases) axis I disorders***

- ***Lastly, a reported 'change in personality' cannot be a personality disorder, for they are innate and long term***

3.11 Alcohol and Drug Abuse

Alcohol and drug abuse are major risk factors in this model. Data from the 1995 National Household Survey on Drug Abuse indicate that a 11.6% (18.4% males: 4.9% females) of the 18-25 age group are considered heavy alcohol users. Table O2 contains the relevant data. Heavy is defined by SAMHSA as five or more drinks for each of five days in the last 30 days (SAMHSA, 1995). Table O3 show the rates of substance abuse (here, ages 12-17) by type and problem score. It clearly shows that adolescents with psychosocial problems are more likely to be substance users or abusers.

These are the age groups that consume both alcohol and illicit drugs at rates above average and who are often not prepared for the consequences. The consequence of alcohol use and abuse is also seen in the number one cause of mortality in this young age group: automobile accidents. These years, 15-24 encompasses both high school and college years. Both are environments and times for experimentation and testing of ones limits. The extent of the background prevalence of these risk factors is presented in Section 5.3 of this report.

3.12 Suicidal Behavior

The central questions being examined in this review is whether there is either a direct or indirect relationship between Accutane and suicide.

Appendix E to this report contains the relevant overview of the etiology and epidemiology of suicidal ideation and behavior, attempts and completions.

The review of the etiology or risk factors reveals a distinction for both ideation and behavior amongst the young adult, the adult and the elderly adult. Most importantly for this research are the data describing the risk factors for the young (usually 15-24 years). Mental and addictive disorders are the major risk factors for suicide and suicidal behavior. Their attributable risk is estimated to be greater than 90% (Moscicki, 1995). Mental disorders are considered a necessary condition for suicide. They are not sufficient however, since a majority of individuals with mental disorders do not die from suicide. However, serious suicide attempts are indicative of severe psychiatric illness.

The model displayed in Figure 1 displays some of the potential risk factors for suicide attempts and completions.

In summary

- ***Suicide in the young (<15 years of age) is rare***
- ***Suicide is the 3rd leading cause of death in 15-24-year olds (second in caucasians)***

- ***It is multifactorial and the result of cumulative experiences and risk factors over a substantial length of time. Most mental disorders themselves are outcomes based on cumulative events over a substantial time.***
- ***On the whole, suicides are non-impulsive***
- ***A mental disorder is a necessary condition***
- ***Alcohol is found, on autopsy, in 50% of completers***
- ***The availability of a lethal method often decreases the attempt to completion ratio***

4. INDIVIDUAL CASE REVIEW

4.1 Scope of the Review

All spontaneous reports for adverse events received by Roche between 1982 and April 30, 1999 and classified with any preferred term into WHO SOC 500 Psychiatric Disorders, then placed in the ADVENT database. A MEDLine search for literature on acne, psychiatric disorders, and suicide were requested and selected results were reviewed.

4.2 Methods

The approach toward the spontaneous report case review for this issue work-up was different than the specific methods used in previous issues by this reviewer. Those methodological decisions were due both to the sheer volume of reports (2376), and the tremendous diversity of symptoms, syndromes, and disorders manifested within those reports. However, the general logic of post-marketing surveillance (PMS) risk assessment was followed (Appendix S).

Incoming reports to Roche Global Drug Safety Department are given WHO-ART classification terms based on the reporter's verbatim language. If the reporter, health professional or consumer uses terms loosely and does not use them as recognized by the psychiatric community, confusion arises. For example, a parent who reports that her child appears depressed may be describing something very different from a DSM-IV Major Depressive Episode. Given that reports are entered based on reporter verbatim term, it was felt that all reports required individual review in this effort.

4.3 Distribution of Cases

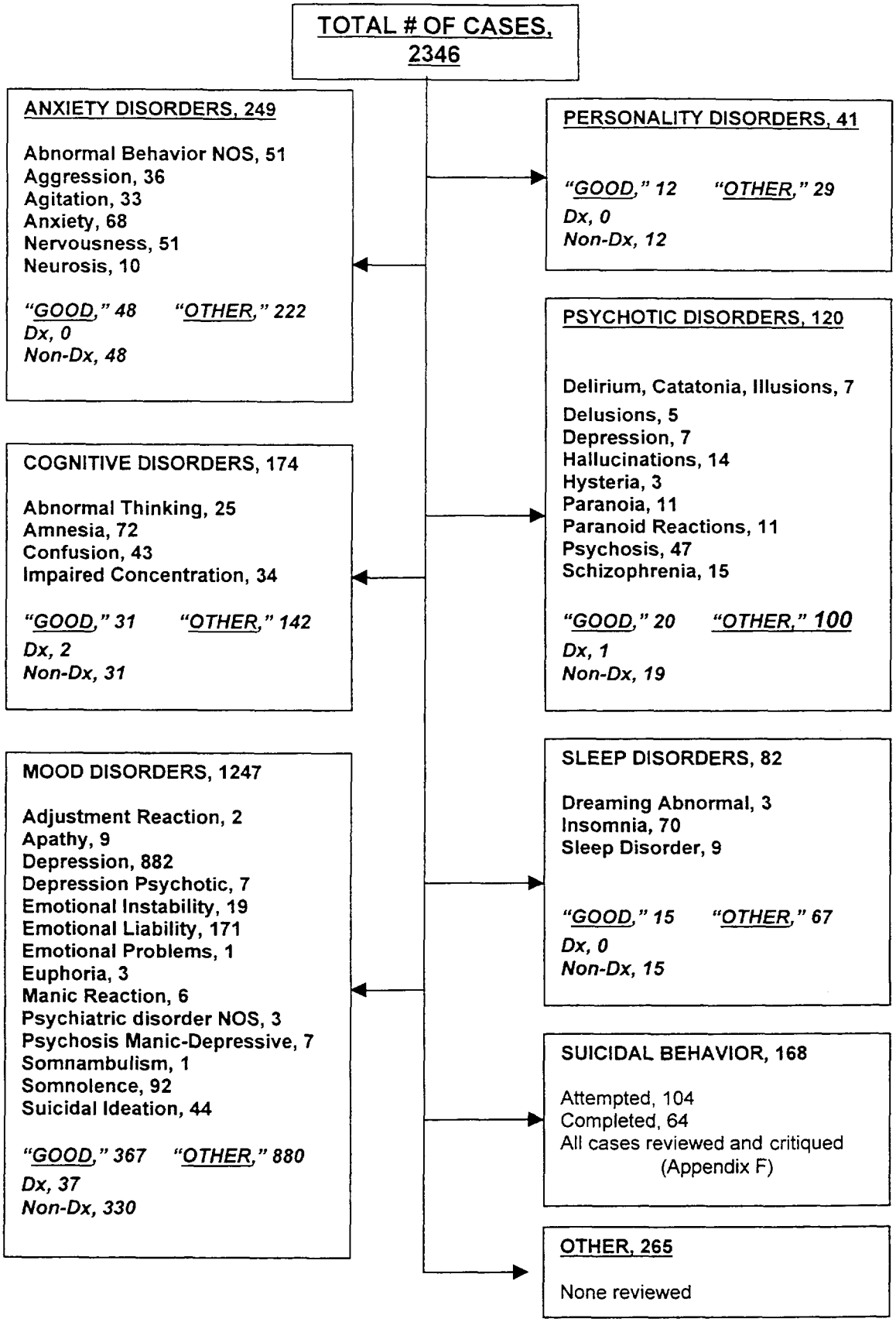
The ADVENT database search was made to include all terms in WHO-ART SOC.500. 2376 reports were retrieved by first preferred term. The following major psychiatric disorder types then divided the reports: mood, anxiety, psychotic, personality disorders, cognitive, sleep disturbances. Groupings approximated DSM-IV groupings. Suicide and suicidal attempts were placed together into the Suicidal Behavior category. However, suicidal ideation alone was clustered with the mood disorders. The SOC.500 reports sorted out by Categories A-H, as below.

The Functional Diagnostic Categories:

Category A – Mood Disorders (N=1276)
Category B – Anxiety Disorders (N= 268)
Category C – Psychotic Disorders (N=121)
Category D – Cognitive Disturbances (N=176)
Category E – Sleep Disorders (N=82)
Category F- Personality Disorders (N=41)
Category G – Suicidal Behavior (N=137)
Category H – Excluded terms WHO-ART SOC 500 (N=265)

- Dyspareunia (12)
- Appetite increased (15)
- Drug abuse (5)
- Attention deficit (1)
- PICA (1)
- Libido Decreased (37)
- Libido increased (1)
- Impotence (75)
- Hair Plucking (1)
- Yawning (1)
- Anorexia Nervosa (1)
- Anorexia (115)

Full Preferred terms and their counts are displayed in Figure 4. The 31 case difference in counts represents to cases moved from their initial classification into suicidal behavior classification.



NOTE: 31 cases moved from diagnostic categories to Suicidal Behavior.

The terms in Category H were judged to be outside the framework of this effort and excluded before any individual case review was conducted. It is acknowledged that some small amount of relevant reports may have been misclassified into the components of Category-H.

Each remaining category of included reports (N= 2111) was subsequently reviewed at the individual report level. Assessments were made on report quality (see below for a description of the five quality classes). Reports of events listed in Figure 4 were categorized as either "good" (class 2, or 3A), or "other" (class 1, 3B, or 4). Reports were also assessed for the appropriateness of psychiatric disorder category. Suicide behavior cases were moved prior to inventory and analyses. Other reports that were felt to be misclassified (e.g. an emotional liability cases that is more likely, depression) were not moved If the case was of high quality then it would be considered as part of the overall evidence in that later category.

Basic descriptive data for these Categories A->G appear in Appendix O. Tables O1-O7 contain a distribution of the reports by reporter type, then age group and gender. Tables O8 – O14 provide these categories by Reporter Type and Presence of Psychiatric History. Tables O15-O20 provide these categories by Preferred Term and Quality Class. Note: the Tables 1-14 in Appendix O contain a slightly higher case count because it includes cases that occurred before the data lock point, but had been entered after.

Quality class is a triage tool. Upon individual review every case must be triaged into one of five quality categories:

Class 1 – Insufficient data to assess
Class 2 – Positive Dechallenge with Positive Rechallenge
Class 3A – Positive Dechallenge
Class 3B – Default category when more than one cause is as likely
Class 4 – Outside inclusion criteria for this review.

Each case receives a quality ranking and these appear in the category spreadsheets in Appendix Q.

The presence of a new psychiatric diagnosis (made by a physician of any medical subspecialty) and psychoactive drug treatment was cataloged. Therefore, it was determined which reports were from consumers, including parents, reported by health professionals, and amongst those, which had mention of a diagnosed, or diagnosed and treated psychiatric disorder. Those important data are on Table O-21. A collapsed display of these data is Table O-22.

All cases in the final Suicide Behavior (attempts and completions) category received individual write-ups that appear as Appendix F. Quality class determinations were not made for these reports. All reports were reviewed and analyzed. Unfortunately, the available data are scanty and do not allow for much value and insight during the in-depth content analyses.

All cases with a positive dechallenge-positive rechallenge (Quality class 2) also received individual write-ups that appear as Appendix G.

Additionally, listings were made of "Diversity Cases". These cases were extracted and individual write-ups produced to highlight the diversity of symptoms, situations, or outcomes amongst them. These appear as Appendices I – N .

All 'good' cases were also catalogued. Again, a 'good' case had either a positive dechallenge or a positive dechallenge and positive rechallenge. These cases were considered the most important in terms of assessing causality. A full listing of all 'good' psychotic cases appears as Appendix H .

4.4 Literature Cases

All case reports in the literature were reviewed. Although, many of these events were also recorded amongst the reports from the Accutane Drug Safety ADVENT Database, they are reviewed here in the context of the published text.

An early correspondence by Hazen, et al, (1983) reported 6 of 110 patients (5.5%) experienced depressive symptoms while in some unspecified form of Accutane trial. Only one patient claimed a prior history. One patient had severe symptoms of depression and forgetfulness and was withdrawn. The other five continued on treatment. The onset was within two weeks and all symptoms resolved rapidly upon discontinuation.

One important publication which was reviewed is a report by Scheinman, Peck and colleagues (1990). During the conduct of a series of clinical trials they collected retrospectively seven (of 700 participants) patients who reportedly developed depression. This rate is not unexpected but the reported timecourse is noteworthy inasmuch as all had resolution within 2-7 days. Three of the seven were diagnostically confirmed. The remaining four had resolved before an assessment could be done. All patients had symptoms severe enough to interfere with normal function and were discontinued. One patient was subjected to a positive rechallenge. Headache was reported in three of seven, all of which also had a positive dechallenge. Funduscopic examination of four was negative. Onset was not related to dosage or time. Again regardless of time to onset, dose or severity, all symptoms resolved with a week for discontinuation.

In a letter to the editor, Gatti followed-up the Scheinman report with a report of a 17 year-old male who began having substantial difficulties in social readjustment 30 days after completion of a successful course of Accutane therapy (Gatti, 1991). Two months later, after an attempt and psychiatric care, he committed suicide. The author was cautious in drawing conclusions but did suggest that clearing of an extremely disfiguring skin disease like acne made it more difficult for the patient to overcome deficiencies that were previously acceptable and attributable to his disfigured appearance. Peck (1991) replied, in a letter, reminding the reader that the Gatti case had an onset more than 30 days after therapy, but that the Scheinman cases had symptoms that occurred on therapy and had a rapid (within 2-7 days) resolution. Peck did concur that some

patients do have unrealistic expectations of life after a successful treatment. They suggest that dermatologists be diligent in monitoring the mood of their Accutane patients.

Duke and Guenther cite two distinct case reports in their 1993 letter. One was a teenage female who developed severe mood swings and bizarre behavior after about a month of therapy. Her skin was improving. She subsequently threatened to harm herself when the notified dermatologist discontinued her Accutane. Timecourse on discontinuation was not provided. In the second case, a teenage male also suffered intense mood swings (after about 30 days) that resolved within three days of discontinuation. He had no further problems in two years of follow-up. The authors alerted dermatologists to be aware of unusual behavior in their patients.

Byrne and Hnatko (1995) made one of the first reports in a psychiatric journal. They strongly suggest a specific syndrome and illustrate three cases. All three reported onset of the symptoms of anergia, headache, irritability and agitation during Accutane therapy. All responded to antidepressant therapy, but one only when her Accutane treatment was stopped. Two of the patients had been "actively suicidal". The author felt that the symptoms (irritability, headache) were similar to those reported with hypervitaminosis A and may be suggestive of raised intracranial pressure. They alerted prescribers to be diligent and watch for suicidal behavior.

Kovacs and Mallory (1996) cite the prior literature reports and provide one additional report. A 16 year-old male was described as angry, intolerant and difficult after being on Accutane for five months, and the drug was suspected. Upon dechallenge the symptoms abated and he returned to school. Months later he was rechallenged with the onset of the same symptoms. However, on follow-up the patient admitted to illicit drug use, which he attributed as the cause of his behavior. The authors suggest that his problems and subsequent drug abuse were related to his failure to adapt to social changes. They encouraged clinicians to probe for extraneous factors, especially in this age group.

In 1998, Byrne and her psychiatric colleagues evaluated the evidence from the literature on the potential association between Accutane and depression. She also reported the same three cases as her earlier report in a Canadian journal (Byrne, 1995), but now in the Irish journal and in more detail. She cites that these cases provide strong evidence of a unique syndrome that is much more variable in onset and offset then previously reported. They asserted caution on dermatologists' downplaying of this association and to focus on the young as high-risk patients.

There was one case report of psychosis in the literature (Villalobos 1989). He and his colleagues reported a 16 year-old male who completed therapy with Retin-A gel and tetracycline and developed psychotic symptoms 11 days after initiation of Accutane therapy. There appeared to be a dechallenge/rechallenge and severe disorder requiring a month-long hospitalization and antipsychotic medications. The author implied normal functioning after hospital discharge. This case is MCN#93035.

A recent report (Schulpis et al, 1999) indicated that patients with severe acne had higher levels of stress-related hormones (catecholamines) than age-matched, non-acne

subjects and had higher scores on various mood disorder scales. After treatment with isotretinoin and resolution of the acne, the hormone levels and mood disorder scores were reduced.

4.5 Case Assessment

4.5.1 Reports by Psychiatric Disorder

In clinical practice, psychiatric disorders are so classified by the recognized and reported signs and symptoms. Proper identification and diagnosis is a difficult task for even trained psychiatrists, more so for general practice physicians. A substantial number of these spontaneous reports were of signs and symptoms, many of those directly from consumers (often parents), without medical confirmation. Only a small minority of these spontaneous reports had a formal psychiatric diagnosis, and only a subset of those was from a psychiatric professional.

Therefore, if subsequent 'diagnoses' were made in cases from spontaneous reports, this review would be filled with errors of misclassification. However, if Accutane was affecting the dynamics of the host, there may be some recognizable patterns within these cases. If Accutane was a causative (necessary, sufficient or component) agent in the production of psychiatric disorders, patterns of symptoms, comorbidity, dose, duration and resolution could be expected. In a manner of speaking, we are searching for hypothetical threads of evidence.

In this report, cases with a positive dechallenge (my class 3A), or with both a positive dechallenge and positive rechallenge (my class 2), were considered "good" cases. The 'diversity' cases are those that represent the vast array of circumstances that can surround the reporting of an adverse event. They represent the opposite of the common thread that would point to a common cause.

Personality Disorder Reports: Upon review, the Personality Disorder (N=41) cases revealed themselves to be largely mood changes or 'changes in personality'. There were no cases of a true and permanent change in a personality trait. None should have been expected. The strict use of reporter verbatim led to "his personality changed and he became irritable" to be coded under personality disorders. Of these 41 cases, 12 had good content and a positive dechallenge. Unfortunately, none had any medical confirmation in the form of a psychiatric diagnosis. All reported symptoms were consistent with mood alterations. Appendix N contains a sample of the diversity of cases found in this category.

Sleep Disorder Reports: The Sleep Disorders cases (N= 82) also appeared, upon review, to be largely symptomatic of either anxiety or mood. Some manic-like episodes were also described. Of the 82 cases, only 15 had good content and a positive dechallenge. Unfortunately, none had any medical confirmation in the form of a psychiatric diagnosis. All reported symptoms were consistent with mood alterations or mixed symptomatology. Three of the cases (MCN#s 840200367001, 890500104001, 920201020001) were suicide attempts and were moved from the 'Somnolence'

subcategory to the Suicide Behavior category. Appendix M contains a sample of the diversity of cases found in this category.

Cognitive Disorder Reports: The Cognitive Disorder cases (N=174) also appeared to be largely due to mood. Impaired concentration is a hallmark and often the most prevalent symptom of depression. Of the 174 cases, 31 had good content and a positive dechallenge. Two cases (MCN#s 890100456001, 920201380001) had a diagnosis of increased intracranial pressure and severe chronic depression, respectively. Case MCN940201166001 had short-term memory loss with a positive dechallenge/positive rechallenge (See Appendix G). Two of the cases (MCN#96303, 102871) were suicide attempts and were moved from the 'Confusion' subcategory to the Suicide Behavior category. Appendix L contains a sample of the diversity of cases found in this category.

Therefore, one could argue that all of these above categories (Personality, Sleep, Cognitive) could have been added to the 'Mood' category. However, individual case review demonstrated that it was unlikely that any (with one exception, 920201380001) of these were full disorders.
In pharmacovigilance methodology, the case-series analyses are qualitative, not quantitative. Therefore, it is the content, not the number of reports that is important. Therefore, the reports from the personality, sleep and cognitive were not added to the, already diverse, Mood category. However, a search for commonality of covariates was performed.

Anxiety Disorder Reports: For the Anxiety Disorder category, there were a total of 286 reports, including 48 cases with good content and positive dechallenge. Of these 48 reports, there were none in which a formal diagnosis was made or where anxiolytics were prescribed. The strongest evidence of causality rests with positive dechallenge/positive rechallenge reports. There were only three (MCN#77234, 92242, 900200383001) such report amongst the 286 anxiety cases (see Appendix G). Appendix J contains a sample of the diversity of cases found in this category.

The intelligence from the literature reviewed in Appendix D strongly indicated that it is likely that anxiety and depression share the same proximal causes. Early in their development, mixed symptomatology is common and more often expected than GAD or panic in the cohort aged 15-24.

Therefore, while these reports should not be combined with those of mood, they do not represent a totally separate syndrome either. Unfortunately, most have little content value.

Mood Disorder Cases: The Mood Disorders are by far the largest psychiatric classification of events reported in Accutane patients. There were 1247 reports clustered into Category-A, of which 882 were originally coded as depression. As indicated in Section 4.3, many related preferred term groupings were added. Suicidal ideation reports are one of the components of this Category. However, as stated above, many of the anxiety reports had mixed symptomatology with depression, most personality disorder reports were mood changes, and many of the cognitive and sleep reports were related to changes in mood. Many cases described swings between depressive symptoms and anger, irritability or aggression. Therefore, if all reports with

'mood changes' were combined there would be 1792 (2346 minus 265 other, 168 coded as suicide, and 121 coded as psychosis).

Figure 2 shows the concentric layers of affect modification. This needs to be borne in mind when attempting to understand the content of these reports. What would be the array of these 1792 reports across these concentric circles? This could not be done with any degree of precision, but it was possible to show that very few cases fall within the inner three circles of depression.

Psychotic Disorder Reports: The Psychotic Disorder category was meticulously reviewed to assess the support of the causal statement in the current U.S. product label. There were a total of 121 reports, including 20 'good' cases. The 20 cases that are the strongest evidence of causality are listed in Appendix H. They include five cases with a positive dechallenge/positive rechallenge (See Appendix G or H). Of the 20 "good" Psychotic Disorder cases only five (MCN#95864, 109046, 880201083001, 900200749001, 940600114001) had a formal diagnosis. Nine other less documented cases also had formal diagnoses of psychosis and depression/hallucinations, respectively (see Appendix H).

Of the five dechallenge/rechallenge cases, one is a literature case (MCN#93035) with a negative dechallenge, one was a vague consumer case, and one was undergoing an intense divorce, but two had good information. Both (MCN#109046, 940600114001) were females who were diagnosed and treated with apparent resolution. Of the remaining cases in Appendix H, MCN#880201083001 is most substantial in severity and time-course but may point to an interaction with topical Retin-A.

Of the 101 cases with lower quality content, 85 are rated as possible, (ie, meaning that the existing content of the report does not support any risk factor as being more causally associated than any other) six were considered 'non-cases' by inclusion criteria, and an additional 10 cases had data too sparse to evaluate at any level. These 85 possible cases are composed of a broad array of symptoms and descriptions. As mentioned above, nine had a formal diagnosis. No conclusion about causality can be made for these cases. The only conclusion that can be made is that they are not reports of DSM-IV psychotic disorders.

Table O3 provides these reports by reporter type, then age group and gender. Males exceed females (72/44) for a ratio of 1.63 to 1. The ratio for the 29 cases in Appendix H cases is 19/10 or 1.9. The expected ratio for psychotic disorders is around one. An unknown covariate may be the determinant in many of these cases to account for this excess of males. Alcohol or substance abuse is only mentioned in 2 of the 29 (MCN#112316, 930201351001), and both of them have a history of chronic abuse. In this population expected alcohol/drug abuse may be as high as ¼ to 1/3 of total. Table O10 indicates that 27 (22.3%) of the total cases had a prior or active mental disorder (any type). As shown above, nine had a new diagnosis during Accutane therapy.

At the individual case level, one would need to critically question the sudden onset of diagnosed psychosis in a 40-year-old, and quickly suspect an exogenous toxin. There were three cases in this age group (MCN#109463, 870124185001, 930201351001) amongst the 29. The only one of the three with a confirmed diagnosis was a recurrence

of existing chronic disease. Another had intracranial hypertension , the third had an unspecified "psychogenic' disorder.

The epidemiology of psychotic disorders (Appendix D) demonstrates that, though the prevalence of psychotic disorders is low, the incidence of psychosis is relatively high in the 15-24 year age group compared to the older age group. Being a disorder with a gradual onset, individual symptoms manifest at different times and in differing intensities. The emergence of symptoms of psychosis is expected in a small fraction of the population in this age group. The true test for a causal relationship would have been in long-term follow-up with an in-depth probe of alcohol and drug use in these cases. If abuse was negative and a long-term pattern of symptoms leading to a psychotic disorder diagnosis was also negative, then Accutane-induced symptoms would have been a more likely cause. In contrast, little follow-up occurred in these cases and the mention of alcohol/drug abuse was minimal and below expected.

Substance-induced psychotic disorder, with delusions or hallucinations has been defined by DSM-IV to include symptomatic disease that abates (usually within four weeks) upon removal of the offending drug and does not recur in its absence. If alcohol/drug abuse covariate played no role in these three cases (109046, 880201083001, 940600114001), their details are not inconsistent with this new diagnosis.

Suicidal Behavior Reports: Suicidal Behavior includes attempts and completions. There were a total of 104 suicide attempts and 64 completed suicides. These cases were not classified on the same quality indices that are used in the psychiatric disorders, since dechallenge and rechallenge have little logical utility here. All 168 cases received a written summary, regardless of report quality (Appendix F contains a case description of each). That Appendix contains all cases of both attempts and suicides reported with Accutane exposure received by Roche between 1982 and May 1999, regardless of first term classification in ADVENT.

Forty-seven males and 52 females made the 104 attempts with 5 of unknown gender. Eighty-one of the 104 were under 25 years, including 40/44 of the males with known age.

The severity of these attempts was difficult to determine. Using hospitalization (either medical or psychiatric) as an index of severity, 23 (8 males and 15 females) of 104 (22%) were so treated. The attempted cases were examined for duration of therapy, dose and covariates without any patterns emerging. The suicide attempts were distributed randomly all through the course of treatment and for long period thereafter. Seventeen of the 104 occurred more than 30 days after therapy ended.

The reports of completed suicides were among the most poorly documented cases reviewed. In the typical case, very little detail was presented and nothing close to a psychological autopsy was performed on any case.

The duration of therapy was stated for 54 of the 64 cases. Five suicides occurred within 30 days, with one occurring on day 1 and one on day 5. Most (14) of those that did

occur on therapy had been on drug for greater than 90 days. Twenty-two of 42 (33.4%) occurred after therapy was completed. No dose pattern was observed.

Fourteen (14) of the 64 (22%) had a known history of psychiatric disorders. As stated before, these data may be substantial underestimates. Obviously, the rate of undiagnosed psychiatric morbidity is unknown, but is expected to be at least as high as the diagnosed.

Of the 64 cases of completed suicide, 53 were males and 11 were females, for a ration of 5-to-1.

Forty of the 64 (62.5%) were males under 25 years of age. This is consistent with suicide patterns, not Accutane exposure patterns.

Completed cases were examined for duration of therapy, dose and covariates. No patterns emerged. The suicides were distributed randomly all through the course of treatment and for long periods thereafter.

4.5.2 Cases with a Reported Psychiatric History

One important parameter in addition to the number of cases that received a new psychiatric diagnoses and/or treatment is the number of cases with a reported psychiatric history. The word "reported" is very critical here, because like all data in these spontaneous reports, it is likely to be under-reported if it is not actively probed for. Therefore, these data are likely to be underestimates. Table 1 provides a display of the data on both reported psychiatric history and on new diagnosis for the non-psychotic reports. Overall, 17% had a reported history of psychiatric disorder, ranging from 8.5% amongst Sleep to 18.8% amongst Mood category. New diagnoses were made in 7.8% of cases overall, with the most common category being Mood with 10.1%.

Table 1: Diagnosed Psychiatric Disease by History and New

Disorders	Total Reports	Consumer w/ Hist.	Medical Professional w/ Hist.	% of Reports w/ Hist.	"Good" Reports w/Diag.	Other Reports w/ Diag. (3B's)	% of Reports w/ New Diag.
Anxiety	249	10	27	14.90%	0	11	5.20%
Cognitive	174	6	16	12.60%	2	1	2.00%
Mood	1247	36	198	18.80%	37	65	10.10%
Personality	41	2	3	12.20%	0	0	0%
Sleep	82	1	6	8.50%	0	0	0%
Totals	1793	55	250	17%	39	77	7.80%

Only spurious conclusions could be reached if one tried to compare these rates to those expected in the population. One could say that the lifetime prevalence of 17% is absolutely consistent with the National Comorbidity Survey (NCS) (Kessler, 1993) rate, and that the 4-month incidence of 7.8% is higher than expected (1.2% in Murphy, 1989). That could be one explanation but one must always remember that these are spontaneously reported data. These events become cases because they were obvious enough to be detected. Therefore, these data are for descriptive purposes only.

Of those 1247 cases in the category originally labeled Mood Disorders, there were 367 good cases, including 344 cases with substantive content and a positive dechallenge, and 23 cases with a positive dechallenge/positive rechallenge. Thirty-seven (37) of these 367 cases had a psychiatric diagnosis subsequent to exposure to Accutane. While many of these 367 cases contained covariates and confounders, on the whole they represent the strongest suggestion of any causal association between Accutane exposure and mood symptoms or disorders.

The mood reports, divided by reporter type, and then age group and gender, are presented in Table O1. Interestingly, this distribution mimics that of Accutane use (Appendix B). Table O8 displayed these reports by reporter type, then by presence of a psychiatric history. 18.8% of reports were of an individual with a history of a psychiatric disorder. This is very difficult to compare to the epidemiologic data since type of disorder was not consistently recorded and alcohol/drug abuse disorders appear to be vastly under-reported.

4.5.3 Contribution of Other ADRs

Major physical adverse drug reactions (ADRs) potentially capable of negatively affecting one's mood (but not rising to the level of a "mood disorder"), such as joint & muscle pain, headache, acne flare, and hair loss were examined. They appeared in only about 2% in the cases each. These probably suffered from vast under-reporting, but did not appear to be a common covariate to the relationship under study. There were many case reports similar to the essay by James (1996) where the young patients strongly desired, and sometimes even ignored medical advice, to stay on Accutane regardless of his/her physical or psychological ADRs. The hope for Accutane as a cure for the disfiguring disease of severe recalcitrant nodular acne was high.

4.5.4 Test of the Model of Causality

The real test of the adverse drug reaction (ADR) model of causality lies in the consistency of the onset and offset data. Scheinman and Peck (1990) reported a variable onset that was dose-independent, but a rapid and definable offset upon discontinuation. One could suspect that an analysis of spontaneous reports for onset would likely yield valid data. However the offset data would be highly biased. That is because one of the main reasons that these ADRs are suspected IS the rapid resolution of symptoms. Therefore the index of suspicion would be expected to be negatively correlated with the time of offset. This leads to a biased set of data that can be misleading if their detection environment was not understood. Nevertheless, these analyses were performed and the results are displayed on Figures O1 – O3, for all 'good' cases, and their subcategories. These data clearly show a majority resolving within 30 days and most of those within 15 days. Table O23 displays the data for the 25 of these cases that had both an onset within 15 days and a offset or resolution within 15 days of discontinuation. Again, if these data had come from a known subpopulation of patients, as in a clinical trial, one could contend that these data are unbiased, calculate a rate, and use this as an indication of drug effect. Given that these reports represent the biased sample that was detected and attributed to Accutane at the individual level, neither can a rate be calculated nor an attribution be made at the population level. Therefore, while these highlighted reports appear to support the observations of Scheinman and Peck, that conclusion cannot be made with any degree of certainty. This, unfortunately, is always the case when an outcome is a disorder of high prevalence in a population.

Comorbidity is common in persons having major depressive disorder. It is more common in severely depressed. It is also common in suicides. These spontaneous reports were not cross-tabulated to count comorbid conditions since actual diagnoses were so few. Literature does indicate that often more than one disorder (axis II or I) can be underlying and that the most severe cases are also the most comorbid (Table D2).

The preliminary conclusions based only on the review of these spontaneous reports are:

- ***Upon individual case review, it became clear that the vast majority of these reports were for signs and symptoms rather than full psychiatric syndromes that met current diagnostic criteria for a disorder. Many of these were reported in lay terms, even when reported by physicians. While it was important to focus on and assess the most severe, it also was important to characterize the nature of the reported symptoms. These were examined along three major lines: mood, anxiety and psychosis. Also examined were sleep, cognitive and personality disorder categories.***
- ***Upon individual case review, a small number of reports imply that depressive and mixed symptoms as well as diagnosable mood disorders are an infrequent (undetermined rate) and probably idiosyncratic (not related to dose or duration) outcome of Accutane therapy.***
- ***Upon individual case review, a very small number (3) of reported cases imply that psychotic symptoms (but probably not full disorders) have been associated with Accutane use***
- ***The content of the suicidal behavior cases provides no support of an association.***

5. EPIDEMIOLOGIC REVIEW

Spontaneous reports yield the most defensible data when they are well documented and for rare ADRs with outcomes that are also rare. Spontaneous reports are of very diminished value when the outcome has a common background rate. The diversity and lack of diagnostic rigor of most of the case definitions in these reports further amplify their weakness.

Ideally, the age/gender-specific incidence and prevalence rate for well defined diseases would be known; ideally, the known background prevalence would be very low. Under these circumstances, spontaneous reports may be able to provide a sense, though not a quantified answer, as to whether those reported appear to be more than expected. None of those conditions exist in the relationship under investigation.

If caseness was defined rigorously in 100 clean incident cases of diagnosed major depression, certain comparisons would have been interesting and valuable. Unfortunately, there are only 38 of 1276 reports with any form of mood disorder diagnosis. Comparing the age/sex distribution of these (either the 38 or the 1276) reports vs. Accutane usage would be misleading because of the extensive heterogeneity both across and within these cases. Therefore, direct epidemiological analysis of these cases is of very diminished value and plays little role in this assessment.

The only epidemiological study conducted to look for any association between Accutane and depression is the recently completed, Roche-commissioned study by Dr. Jick of the Boston Collaborative Drug Surveillance Program (BCDSP) and Dr. Maradit-Kremers. This is the first population-based study looking at the risks of psychiatric disorders and suicides in Accutane-exposed patients. This was an epidemiological analysis of a set of record-linked databases to determine the rates and relative risks of suicides, suicide attempts, psychotic and neurotic disorders among users of oral Accutane compared to nonusers who had antibiotic-treated acne. The results of the analyses of 9000 Accutane users compared to matched cohorts gave relative risk estimates all around unity regardless of the data source used. They concluded that there was no association between any psychiatric disorder and Accutane, but rather an association with the underlying disease.

Though the epidemiological evaluation of these case reports is very limited in this case, the epidemiologic approach can still play a primary role in determining the likelihood of a drug-depression relationship.

5.1 Assessment of Mood Disorders

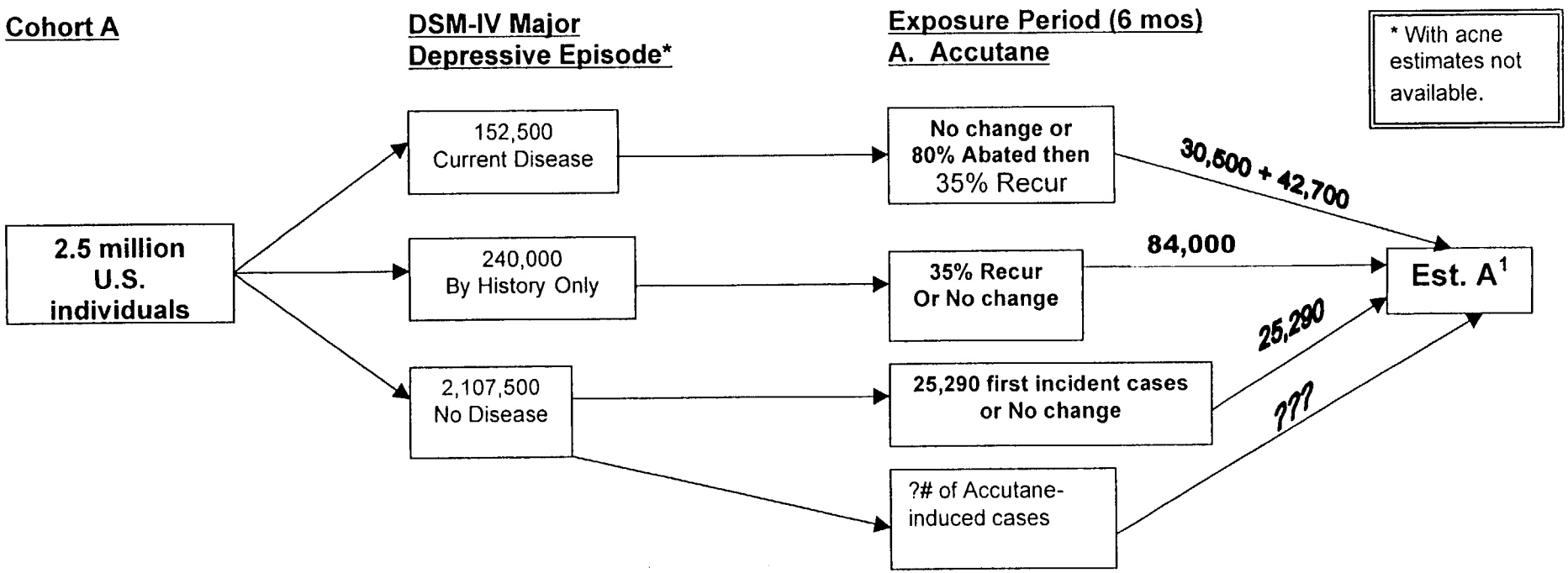
The Model of the Relationship (refer back to Figure 1) displayed the complex relationships surrounding this issue. An overview of the epidemiology of mood disorders is contained in Appendix D.

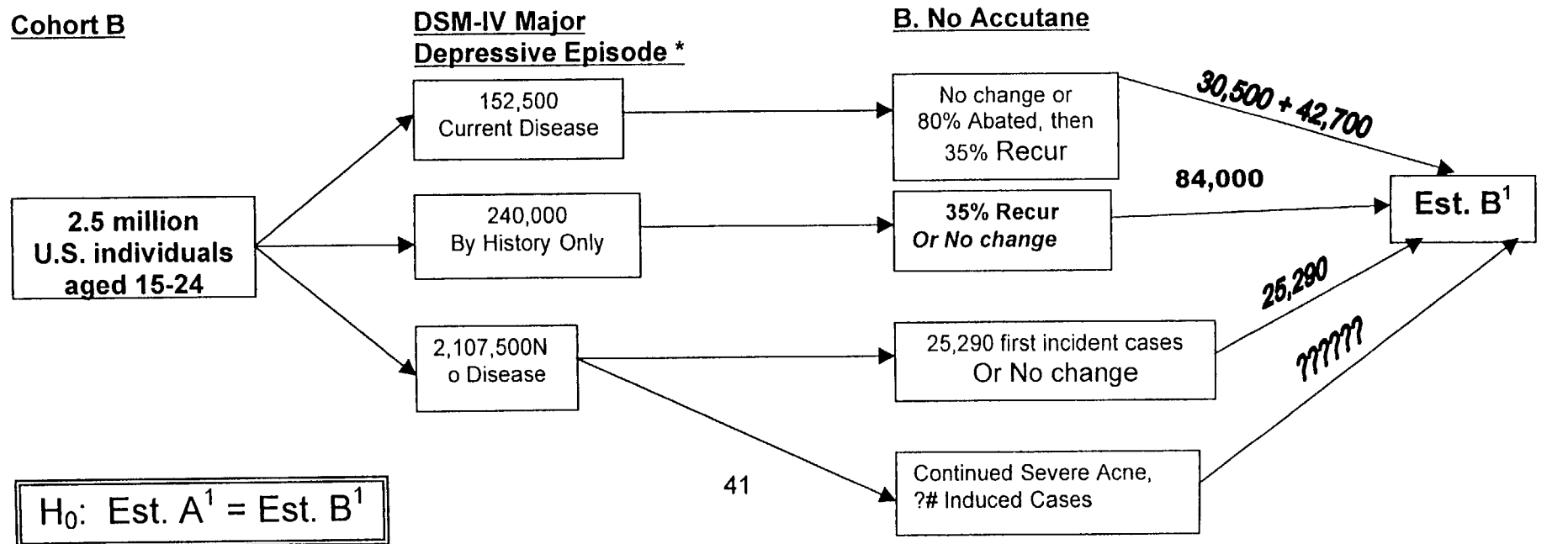
Even in modern times using standardized instruments there remains disagreement regarding the total morbidity resulting from medically significant mood disorders. The range can be from 4.8-8.6% for MDD/MDE to 15.3 – 22% if dysthymic, minor and intermittent/brief are added.

Figure 5 is an attempt to clarify a specific, fairly rigorous sub-pathway. It also explicitly demonstrates the difficulties that exist in addressing the question of attributable risk due to the alleged association between Accutane and Major Depressive Disorder. Two identical cohorts are described: one the aggregated cohort that received Accutane therapy anytime between 1982 and present, and an age-matched cohort with acne that did not. A U.S. cohort is used because the available disorder rate data used are from U.S. surveys. *The hypothesis would be - Is the Total Incidence in Cohort A' greater than the Total Incidence in Cohort B'?* One can immediately realize the enormous numbers involved even when the most conservative figures, those for diagnosed Major Depressive Disorder, are used. For a cohort of persons the size of that which has been treated with Accutane, that is 3.6 million in the U.S., 2.5 million of which were under 25 years, there were an estimated 152,500 persons with active disease (some percentage diagnosed and on medication, some not) at the point when Accutane therapy was begun. In addition, there were another estimated 240,000 persons with a history of the major clinical disorder (currently inactive or subclinical) at the initiation of therapy. Of the actively morbid cohort, about 80% are expected to have their disease abate in a 6-12 month period, with 35% of those recurring within that same window. Of those with a lifetime history, an estimated 25-35% will recur in that 6-month window [Note: six months was chosen to include a full 120 day treatment with Accutane and a period following discontinuation of that therapy]. Importantly, during that 6-month window, over 25,000 new incident cases are expected. The only difference between the cohorts in Figure 5 is Accutane exposure. If one accepts the reasoning that severe acne itself is a life stressor and therefore a proximal risk factor, then there could be some unknown number of disease-induced depression cases in cohort B. Likewise **if** Accutane is causally associated then there will be an unknown number of substance-induced depression cases. The total incidence (new plus recurred) without the acne or hypothetical Accutane contribution to these figures, is approximately 152,000. That is the expected number of cases that would have arisen to the clinical or diagnostic level in this group of patients while on Accutane therapy, by background risk factors alone.

That means that during the course of 2.5 million Accutane treatments in 15-24 year old patients, *151,900* total incident cases of Major Depression would have occurred even in the absence of any effect, direct or indirect, of either severe acne or Accutane. If the time of onset of each of these *151,900* episodes was known, and could be plotted within the 6-month reference window, the resulting scatterplot would be markedly dense and would cover every possible onset value many thousands of times. Similarly, if the resolution of symptom (offset) time were known for all 151,900 cases that abated in this 6-month window and plotted, that resultant scatterplot would also be extremely dense,

with all possible values covered many thousands of times. Given this extreme density of occurrence, it is even difficult to value the most rigorous individual spontaneous case report; those with either a positive-dechallenge or even a positive dechallenge/positive rechallenge scenario. Each could have easily been due to normal expected background.





H_0: Est. A^1 = Est. B^1

Figure 5 Part 2: Calculations and Citations

2.5 million:	National Prescription Audit	(IMS, 1998)
152,500:	6.1% of 2.5 million **	(NCS, Blazer, 1994)
240,000:	9.6% of 2.5 million (15.7% minus 6.1%)	(NCS, Blazer, 1994)
30,500:	20% of current disease with duration of 6 months to 1 year	(Katon, 1992)
42,700:	35% recurrence of the 80% that abated within 6 months	(Katon, 1992)
84,000:	35% recurrence within a 6-month period for those with a history of Major Depressive Episode	(Katon, 1992)
25,290:	1.2 % of persons with no disease who are expected to develop new disease in a 6-month time period (Annual incident rate: 2.3% halved)	(Murphy, 1989)

** Range is 4.8 to 8.6%. If dysthymic disorder, 2.1 to 3.7%; if minor depression, 3.4 to 4.7%; and if intermittent depression, 5%. Resulting range is 15.3 to 22 percent.

TOTAL INCIDENCE

42,700
84,000
25,290
151,900 or 6.1%

For Mood Disorders category there were 102 new diagnoses and 234 patients (from Table 1) with a psychiatric history reported from a expected populations of 25,000 and 392,500, respectively.

The 102 new reported cases were analyzed in an attempt to identify characteristics, if any, that distinguished them from the estimated 25,000 new incident cases that were expected to occurr amongst the Accutane-exposed but were not reported?

What symptoms or time-course characteristics did these 336 symptomatic patients that were reported have that were different from the estimated 152,000 total incident cases that were expected to arise to clinical or diagnosable levels during therapy?

Answer to both: Nothing that could not be explained by the biased manner in which these cases were detected

5.2 Assessment of Psychotic Disorders

As stated earlier, psychotic disorders arise gradually as an underlying factor in the age group most likely to be treated with Accutane. Strong family history is a risk factor. The male-to-female ratio is balanced. Prognosis is chronic and poor.

These case reports occurred mostly in the young while reports in older individuals would more likely have a causal explanation. The male-to-female ratio of the 29 most rigorous cases gave an excess of males that would indicate another covariate, most likely alcohol/drug abuse.

The are no epidemiological studies of sufficient power to shed light on this research question.

5.3 Assessment of Alcohol and Drug Abuse on Mental Disorders and Suicide

Young individuals as a group use alcohol. Most drink socially, but for many it is a drug of abuse . In section 3.11, the prevalence of alcohol/substance abuse and the co-morbidity with psychiatric disorders are presented and discussed.

Table P3 in Appendix P, shows that persons with high problem scores are more likely to use and/or abuse illicit substances than persons with normal scores. However, substance abuse does also occur in that latter group.

Extracting data from Table P2 in Appendix P, using 2.7 % for the 12-17 age group and 11.6% for the 18-25 and taking a non-adjusted average, yields an estimate of 7.2% heavy alcohol users. Also, on crude average, 70% (55% females and 85% males) of Accutane users are between 12-25 years of age. This yields 2.5 million (70% of 3.6 million) U.S. exposed since 1982. Therefore approximately, 180,000 (2.5 million X 7.2%) Accutane users between 12-25 years of age were also heavy alcohol users. Based on population information, most of the remainder are likely to be more casual users, although some occasional 'binge' use can be expected in a minority.

As indicated in the literature reviews in Appendices D and F, heavy alcohol use is usually comorbid with many mood and personality disorders, especially in males, and is both a strong covariate and an independent risk factor for suicide.

A similar number could be calculated (from data on Table P3) for illicit drug use, but these two abusing populations have high overlap, so the number of distinct individuals could not be readily determined.

How many of those 180,000 heavy alcohol-consuming Accutane-treated young adults had mood swings, depressive symptoms, or psychotic-like symptoms during their dual exposure period is unknown. However, that number could be assumed to be substantial.

How many of those 180,000 illicit drug-abusing Accutane-treated young adults had mood swings, depressive symptoms or psychotic-like symptoms during their dual exposure period is unknown. However, that number could also be assumed to be substantial.

Combined alcohol and drug abuse may have included over 250,000 young Accutane patients (an estimate adding the 180,000 alcohol and 180,000 drug abusers and allowing for an extensive, though unknown, degree of comorbidity). This equates to 10% of the adolescent and young adult Accutane users.

What the combined attributable risk of these two variables is cannot be calculated, but it is logical to assume that it plays a substantial role in the variant and deviant behavior patterns of young adults.

It is very interesting to note that very, very few (exact number not obtained) of the 2111 reviewed reports contained any mention of alcohol and/or drug abuse. The omission of this important risk factor is a major handicap in the evaluation of these spontaneous reports. This error of omission also highlights an important source of information bias. If a youth were asked if his/her recent unusual behavior is due to the prescription drug he/she is taking or the substance he/she is abusing illegally, the answer would surprise few.

The co-existence of major depressive disorder with alcohol/drug abuse complicates prevalence data.

Summary: Nearly one-quarter million alcohol/substance abusers are expected amongst the 2.5 million Accutane exposed cohort. Many of these abusers were also comorbid with the 151,900 incident Mood Disorder cases or with the many more individuals with either only depressive symptoms or different disease. Therefore, the total numbers in the cohort with some form a DSM-IV disorder cannot be determined by adding these figures. However, the total number is very substantial, and may be up to 16-20% of the total Accutane exposed cohort.

5.4 Assessment of Suicide

Based on National Center for Health Statistics data for 1997, there were 30,535 (24,492 or 80.2% males, 6043 or 19.8% females) suicides that year in the U.S. – 4,186 in the 15-24 age group (3357 males; 829 females). Suicide is the third leading cause of death in persons in the 15-24 year age group, after unintentional accidents (usually automobiles) and homicide. These rankings are different if race is factored in, with suicide being second amongst whites. A consistent 80% of suicides are in males (4:1 M: F), most of them white. The incidence and point prevalence rate is 11.4 per 100.000 per year (18.7 for males; 4.4 for females), or 0.01%. Suicide in the young is rare but important and tragic.

The almost 4,200 (of the 30,500 annual U.S. suicides) suicides in this age group are drawn from a population composed of 36.6 million individuals (of 267.6 million U.S., overall). If extrapolated to the 17 years of Accutane marketing, there were approximately 68,000 completed suicides amongst this age group in the U.S. The 4:1 male:female ratio provides estimates of 3357 male and 829 female suicides in this age group in the calendar year 1997 (approximately 18.7 and 4.4 per 100,000, M:F, respectively).

In 1998 there were 454,000 individuals (378,000 new and 20% multi-course patients) who were treated with Accutane in the U.S. or about 256,500 males (454,000 X 56.5%) and 197,500 females (454,000 X 43.5%). An estimated 85% of males are under 25 years or a total of 218,000. An estimated 55% of females (or 109,000) are under 25 years.

Therefore, 40.8 males (218,000 X 18.7 per 100,000) and 4.8 females (109,000 X 4.4 per 100,000) who were Accutane users in the under 25 age group, would have been expected to have a completed suicide in 1998 alone (U.S. only).

Cumulatively, (in the 15-24 age group) that yields for males, 1.4 million Accutane exposed and 262 expected (1.4M X 18.7 per 100,000 – U.S. rate) suicides. The calculations for females in the 15-24 age group yields 1.1 million exposed and 48 expected (1.1M X 4.4 per 100,000 - U.S. rate) suicides. Therefore, an estimated 310 young U.S. adults who took Accutane were expected to attempt suicide in their therapy year.

The worldwide figure can be estimated to be double (as presented in Appendix E, the suicide rate per country varies considerably, therefore this double estimate allows many assumptions), or 620 (524 males, 96 females) expected.

These estimates also attribute no increased risk for suicide for the acne itself, therefore they may be underestimate the true numbers by some unknown amount.

From Appendix F the data indicating that there are 53 completed suicide reports for males and 11 for females is extracted. These data are divided into two age groups and inserted into Table 2, as the observed values. The results of the above calculations are similarly divided and inserted as the expected values.

Table 2: Observed vs. Expected Suicides in 15-24 Year-Old Accutane-Exposed Cohort. (United States Data and Estimates)

Observed Suicide by Gender & Age						
Male (33)			*Female* (5)			
Under 25	Over 25	Unk.	Under 25	Over 25	Unk	Total
27	4	2	5	0	0	38
Expected Suicide by Gender & Age						
Male			**Female**			
Under 25	Over 25		Under 25	Over 25		Total
262	57		48	31		398

In the U.S. the suicides that were reported represent 9.55% (38 of 398) of those that were expected in the Accutane exposed population.

(Non-U.S. suicides were: for males under 25, 14; over 25, 3, with 3 unknown age. For females under 25, 3; over 25, 1 with 2 of unknown age. Worldwide figures would be 64 reported (53 males and 11 females), with 796 expected (638 males, 158 females) and an 8% reporting rate.

The M:F ratio in the U.S. is greater than 6.6. The non-U.S. ratio is 3.34 vs. the only slight excess of males in Accutane users. These ratios are consistent with background and not Accutane exposure.

The important questions are:

- ***Are there any characteristics that discriminate the reported 64 from the estimated 732 that would have been expected while exposed but not reported?***
- ***Why were those 64 suspected and the other 732 not suspected?***
- ***Was there a reason behind the reporting or was it random?***
- ***If there was a reason, what was it?***
- ***If there was a reason why wasn't it stated and the case reported in more detail?***
- ***Are there common covariates?***

A similar set of questions could be assembled regarding suicide attempts. The literature indicates an attempts/completions ratio of 50-100 in these young individuals. Even with the acknowledgement that only 10-25% come to the attention of the medical system, many more than the 104 reports should have been received, perhaps a hundred times more.

The science of epidemiology is predicated on the fundamental assumption that diseases do not distribute randomly in populations, but rather distribute in relation to their determinants.

Given the content, nature and the quantity of spontaneous reports of suicide while exposed to Accutane therapy, there is no evidence that argues against a random occurrence independent of the exposure under study.

6. CONCLUSIONS

6.1 Mood Disorders

6.1.1 Evidence Suggestive of an Association

- More than 1500 reports (1544, including 1247 from Mood, 174 from Cognitive, 41 from Personality, and 82 from Sleep Disorders) with some level of mood symptomatology information.
- 425 reports contained information on positive dechallenge, 25 of which also contained information on positive rechallenge
- There were also a few reports were symptoms were reported to be perceived with dosing or dose increases and resolved with lowered doses
- Scheinman and Peck (1990) collected information on 7 of 700 study patients with depressive symptoms, one case with a positive rechallenge.

6.1.2 Evidence Suggestive of No Association

- Paucity of well documented, diagnostically confirmed cases. Surprisingly few reports contained information concerning alcohol/drug abuse history or long term follow-up.

- The high prevalence of major depression (4.8%- 8.6%), an even higher prevalence of diagnosed background mood disorders (15.3% - 22%) and rates of subclinical depression and depressive symptoms that are much higher in adolescents and young adults.

- Alcohol and drug abuse are prevalent (10%) in the predominant age group (adolescents and young adults) of potential Accutane users.

- Mental disorders of GAD and MDD have mixed symptomatology in the predominant age group (adolescents and young adults) of potential Accutane users.

6.1.3 Conclusion

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 these kinds of data do not allow any potential risk factor to be completely ruled out, no matter how unlikely it may appear.

6.2 Psychotic Disorders

6.2.1 Evidence Suggestive of an Association

- 29 documented individual reports with a positive dechallenge, five of which also had a positive rechallenge; 14 of the 29 had a formal diagnosis, and there were three reports that strongly supported an association.

6.2.2 Evidence Suggestive of No Association

- Only 120 total individual reports, almost all of which lacked good quality information.
- Alcohol/drug abuse is seldom mentioned but is most likely to be the determinant in many of these cases.

- The etiology of psychotic disorders characteristically involves a strong likelihood of a family history, a gradual onset usually with a precipitating external event

- The epidemiology of psychotic disorders indicates a balanced male to female ratio, a gradual onset in adolescence into young adulthood, and a chronic course with a poor prognosis.

- Lack of any experimental or epidemiological confirmation of these spontaneous reports in the literature.

- The reports lack the confirmation of a diagnosis of a psychotic disorder, which requires specific symptomatology and a duration of at least six months.

6.2.3 Conclusion

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 these kinds of data do not allow any potential risk factor to be completely ruled out, no matter how unlikely it may appear.

6.3 Suicidal Behavior

As stated throughout this review, suicidal behavior includes both attempts and completions. Accutane as a risk factor was examined for a possible direct suicidal effect, an indirect cause through Mood or Depressive Disorders.

6.2.2 Evidence Suggestive of an Association

- 64 spontaneous reports for completed suicides and 104 attempted suicides

6.3.2 Evidence Suggestive of No Association

- The 64 reports are poorly documented, none with psychological autopsy
- A proportion of these reports contain information about known risk factors for suicide (firearms, family history, previous suicidal behavior, personality disorders, and life stresses)
- Background incidence of suicide is more than 10 times greater than reported
- No reported characteristics of the 64 reported suicide cases differentiated them from the expected 796 completed suicides that were not reported amongst the Accutane exposed.
- Given the content, nature and the quantity of spontaneous reports of suicide while exposed to Accutane therapy, there is no evidence that argues against a random occurrence independent of the exposure under study.
- There is no plausible direct pharmacological link between Accutane use and suicidal behavior

6.2.3 Conclusion

There are no reports amongst the 168 reviewed that would imply causality between suicidal behavior and Accutane. 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.