Positive Rechallenge Cases of Accutane®-Associated Depressive Symptoms

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Introduction

- **Objective**:
  - To describe the dechallenge/rechallenge cases of Accutane-associated depression, depressive symptoms and mood disorders
- **Rationale**:
  - Best evidence to support a link between a drug and an observed adverse event

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Outline of Presentation

- Describe FDA principal data source for detecting rare adverse drug events
- Reasons for suspecting a drug-adverse event relationship
- Describe cases included in the 1998 Analysis
- Describe cases included in the 2000 Analysis
- Present Case Reports from the 1998 and 2000 Case Series

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FDA Adverse Event Reporting System for Drug Products

- Adverse Event Reporting System (AERS)
  - Computerized database of Adverse Event reports
  - Searchable via drug names & keywords
- Established in 1969 (SRS)
  - Updated system and coding 1997
- Individual records based on MedWatch Forms (Adverse Drug Event Reports)

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Sources of Adverse Event Reports

- MedWatch forms are ***voluntarily*** submitted:
  - Pharmacists, physicians, consumers, and other health professionals
    - To manufacturers (~94%)
    - Directly to FDA (~6%)
- Manufacturers must report to FDA
  - Expedited for "serious" unlabeled events
  - Periodically for other events

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Strengths of FDA Adverse Event Reporting System

- Simple
- Sensitive:
  - Small numbers of cases can signal a problem
- Good for detecting rare and unusual events associated with drug exposure:
  - Hepatic failure, Aplastic anemia
- Relatively inexpensive compared to alternative surveillance strategies

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Limitations of Spontaneous Adverse Event Reporting

- **Incomplete Data:**
  - Missing Fields
    - Race not encoded, reported only in narrative
    - Even encoded information can be missing
  - Narrative information
    - Variable quality and documentation

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Limitations of Spontaneous Adverse Event Reporting

- **Under-Reporting:**
  - FDA receives only a fraction of events that occur
  - Underreporting of suspected events has been estimated to be as low as 1%
  - Possible Reasons May Include:
    - Limitations in recognition of adverse events
    - Limitations in associating events with drug exposure
    - Burdens of reporting

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Limitations of Spontaneous Adverse Event Reporting

- Variability in Reporting:
  - Reporting may increase or decrease with:
    - Serious or notable event
    - Publication of Dear Doctor letters
    - Scientific and lay publications
  - Year of reporting
  - Length of time product has been on the market

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Summary of AERS Features

- Limitations:
  - ***Voluntary*** System
  - Incomplete data
  - ***Substantial*** Under-reporting
  - Reporting variability
- Strengths:
  - Sensitive to rare events
  - Excellent source of case material
  - Useful for hypothesis generation

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Reasons to Suspect a Drug-Adverse Event Relationship

- Temporal Relationship
- Dose Response
- Mechanism of Action/Biological Plausibility
- Class Effect
- Absence of Alternative Explanations
  - For example other drugs, disease states or previous medical history
- Dechallenge
- Rechallenge

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Background - 1998 Case Series

- Spontaneous Adverse Drug Reaction Reports:
  - Positive Dechallenge/Rechallenge Cases
    - Depression
    - Mania
    - Psychosis
    - Suicide Attempt
- 1998 Labeling Change:
  - **Warnings: *Psychiatric Disorders:* Accutane may cause depression, psychosis and, rarely, suicidal ideation, suicide attempts and suicide . . .**

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Findings - 1998 Case Series

- Twenty Cases - USA (19), Foreign (1)
  - Depression (14)
  - Psychosis/Psychotic Depression (5)
  - Mood Disorder (1)
- Sex Distribution:
  - Female (9), Male (9), Not Reported (2)
- Median Age: 20 years old
- Psychiatric History (5)
- Required Hospitalization (5)

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Comparison Between 1st and 2nd Treatment Courses: 1998 Case Series (20 Cases)

	1st Course	2nd Course - Rechallenge
Total Daily Dose Median (Range) n	 50 mg (20 - 80 mg) 13	 40 mg (20 – 80 mg) 13
Time to Onset Median (Range) n	 31 Days (9 – 100) 13	 35.5 Days (1 – 426) 12
Time to Recovery Median (Range) n	 3 Days (8 hours – 8) 6	 3 Days (12 hours – 7) 4
Outcome	Recovered/Improved (19) Persisted (0) Not Reported (1)	Recovered/Improved (11) Persisted (4) Not Reported (5)

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Case Presentation: 1998 Case Series

- 19 year old male, described as cheerful, with an "uneventful medical history", and receiving no concomitant medications
- Three courses of Accutane® to treat cystic acne

	1st Course	2nd Course - Rechallenge 1	3rd Course - Rechallenge 2
Symptoms	Depression, Mood Swings, Personality Changes	Depression, Mood Swings, Personality Changes	Depression, Mood Swings, Personality Changes
Intervention	Course Completed, No intervention	Course Completed, No intervention	Course Completed, Counseling
Outcome	Symptoms Cleared After Course Completed	Symptoms Cleared After Course Completed	Symptoms Persisted After Course Completed

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Year 2000 Case Series

- Spontaneous Adverse Drug Event Reports
  - Positive Dechallenge/Rechallenge
- 41 Dechallenge/Rechallenge Cases:
  - 20 cases included in the 1998 analysis
  - 21 new dechallenge/rechallenge cases
    - Depression
    - Suicide Attempt

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Findings - 2000 Case Series

- Twenty-One Cases: USA (17), Foreign (4)
  - Depression (14)
  - Depression with Suicidal Ideation (3)
  - Mood Changes (4)
- Sex Distribution:
  - Female (16), Male (5)
- Median Age: 23 years old
- Psychiatric History (5)
- Required Hospitalization (1)

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Comparison Between 1st and 2nd Treatment Courses: 2000 Case Series (21 Cases)

	1st Course	2nd Course - Rechallenge
Total Daily Dose Median (Range) n	50 mg (20 – 80 mg) 16	30 mg (10 – 40 mg) 9
Time to Onset Median (Range) n	30 Days (4 – 90 days) 14	9 Days (5 – 50 days) 8
Time to Recovery Median (Range) n	8 Days (2 – 34 days) 6	7 Days (7 – 30 Days) 5
Outcome	Recovered/Improved (21) Persisted (0)	Recovered/Improved (13) Persisted (5) Not Reported (3)

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Case Presentation: 2000 Case Series

- 18 year old male receiving Accutane® to treat cystic acne
- No concomitant medications
- Relevant medical history not stated

	1st Course	2nd Course - Rechallenge
Total Daily Dose	80 mg	40 mg
Time to Onset	29 Days	5 Days
Symptoms	Depression, Poor School Performance	Depression, Poor School Performance
Time to Recovery	8 Days	7 Days
Outcome	Symptoms Cleared w/discontinuation	Symptoms Cleared w/discontinuation. Therapy later restarted with *40 mg every week* w/o recurrence of symptoms.

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Combined 1998 + 2000 Case Series (41 Cases)

	1st Course	2nd Course - Rechallenge
Total Daily Dose Median (Range) n	 40 mg (10 – 80 mg) 29	 35 mg (10 – 80 mg) 22
Time to Onset Median (Range) n	 30 Days (1 – 365 Days) 27	 10 Days (1 – 60 Days) 20
Time to Recovery Median (Range) n	 4.5 Days (8 hours – 34 Days) 12	 7 Days (1 – 30 Days) 9
Outcome	Recovered/Improved (40) Persisted (0) Not Reported (1)	Recovered/Improved (24) Persisted (10) Not Reported (8)

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Summary

- 41 cases of positive dechallenge/rechallenge
- 76% without reported psychiatric history
- Onset Time of Symptoms:
  - 1st Course: median 30 days, recovery in 4.5 days
  - 2nd Course - shorter onset time in the cases that provided information
- During the 2nd course of Accutane®, depression persisted in some patients after discontinuation, and/or medical intervention
- Possible Dose Response:
  - Observed in 6 patients

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Conclusion

- Dechallenge/Rechallenge cases provide strong evidence to support a link between a drug and an observed adverse event
- We have presented 41 cases of positive dechallenge/rechallenge which provide further evidence to support a relationship between Accutane® and depressive symptoms

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