

Drug-Induced Depression

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Modules of FDA Presentation

- Drug-induced Depression
 - Erick Turner
- Case Review
 - Marilyn Pitts
- Post Marketing Experience
 - Diane Wysowski
- Biologic Plausibility
- Options for Risk Management
 - Kathryn O'Connell

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Major Depressive Disorder (MDD): DSM-IV Diagnosis

- Duration of at least 2 weeks
- Present most of the day, nearly every day
- Clinically significant . . .
 - distress, or
 - impairment in social or occupational functioning

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Symptoms of Depression (at least 5 required to make the diagnosis)

- “Psychological” sx
 - Depressed mood
 - irritability in kids
 - Loss of interest/pleasure
 - Feeling of worthlessness/
guilt
 - Suicidality or thoughts of
death
- Neurovegetative sx
 - Appetite or weight ↑
or ↓
 - Sleep ↑ or ↓
 - Slowed down or
agitated
 - Energy ↓
 - Concentration ↓ or
indecisiveness

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Time Course of Depression

- Symptoms develop over days to weeks (DSM-IV requires > 2 weeks)
- If left untreated, full syndrome often lasts 6 months or more
- Residual symptoms can last months to years
- If treated, response becomes evident in 2 to 4 weeks

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Depression is Common

- Lifetime prevalence: ~15%
- Current prevalence: 3-6%
- Prevalence in adolescents: ~5%
- Epidemiological methods:
 - Random sample of population — systematic query of all symptoms
 - Rates would be much lower if based on spontaneous reporting

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Depression is Underrecognized

- Symptoms often not recognized as part of depressive syndrome
- Symptoms often not obvious and cannot be “proven” with an X-ray or lab test
- Symptoms often dismissed as . . .
 - “appropriate” reactions to stress
 - evidence that the person is not trying hard enough
 - conscious attempt to achieve secondary gain
- Only ~ 1/2 pts with MDD ever receive treatment

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Adolescent Depression may be Especially Underrecognized

- Adolescents often present atypically
- Less likely to display neurovegetative symptoms
- More likely: social withdrawal, irritability, behavioral problems

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Underrecognition of Adolescent Depression (cont'd)

- Use of drugs and alcohol may be seen as *the* reason for behavioral changes
- Signs of depression often seen as normal mood swings typical for age group
- Reluctance to label adolescents with a mental illness diagnosis (stigma)

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Depression and Suicide

- Suicide: ultimate adverse outcome of depression
- AERS can generate signals but is inadequate for establishing or ruling out a link between Accutane and suicide
- 15% of mood disorders subsequently end in suicide
- 45-70% of suicides have mood disorder
 - Other diagnoses: schizophrenia, alcohol dependence, other substance dependence, personality disorders

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Suicide: Epidemiology

- Overall rate
 - ~ 30,000 / year
 - #8 leading cause of death
- Adolescents
 - ~ 2,500 / year
 - #3 leading cause of death
- Gender
 - women and girls have more attempts
 - men and boys have more completed suicides

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Drug-induced Psychiatric Disorders

- Diagnosis rarely clear cut
- Clinical features vary with different drugs (different mechanisms)
- Clinical features can vary with *same* drug
 - Corticosteroids can cause mood changes (depression or mania), anxiety symptoms, or psychosis
- Lack of consensus – inconclusive and conflicting evidence

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Drug-induced Depression: Methodological Problems

- Confounding factors:
 - other meds, medical illness, background psychiatric illness
- Lack of rigorously collected data
 - Primarily case reports (from postmarketing clinical observation)
 - Any trials tend to be retrospective/observational rather than prospective, randomized, controlled
 - Rarely employ established observer-based depression rating scales

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Drugs Implicated in Depression (Partial list — various mechanisms)

- Corticosteroids, ACTH
- Sedative-hypnotics, alcohol
- L-DOPA
- Anticancer drugs
- Oral contraceptives
- Beta-blockers, clonidine, methyldopa
- Reserpine (led to implication of norepinephrine in depression)
- IFN alpha

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Drug-induced Depression: Summary

- Many drugs, with various mechanisms, have been implicated
- In theory, any drug that can cross the BBB can affect the brain
- Few rigorous studies of drug-induced depression
- Lack of consensus on causality and scope of problem

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Overall Summary

- Depression is common but underrecognized
- Depression may be especially underrecognized in adolescents
- Suicide is a leading cause of death, especially among adolescents
- The spontaneous reporting system underestimates the number of drug-induced adolescent depression

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