Clinical Question: Does isotretoin use cause depression and/or suicide in treated patients with acne?

Reference:

Methods

Design: Prospective case series from post-marketing voluntary FDA reports of adverse drug events, dating from 1982 to May 2000.

Setting: United States, post-marketing FDA Adverse Event Reporting System Database.

Patient Population: US patients (presumably with severe acne) treated with isotretoin, compared with all other licensed drugs in the US with voluntary drug reports during the same years.

Description of exposures being considered: Isotretoin, at variable doses and duration of treatment compared with other drugs licensed in the US.

Analysis: No statistical analysis was performed. Numbers of reports of depression and suicide attempts were compared between all drugs in the FDA Adverse Event Reporting System database.

Outcomes: Number of reports of depression and suicide attempt.

Follow-up: None.

Validity

Were the comparison groups clearly delineated and treated similarly outside of the putative exposure?
This is unknown. In this prospective series comparing patients treated with different classes of drugs (presumably with different disease states) one would assume they were not treated similarly. No data related to this were presented.

Did the groups have similar exposures to other possible determinants of outcome?
This is also unknown. Since the FDA database contains patients treated with all drugs approved for marketing in the US, for different indications and diseases – presumably they were not treated similarly.

Were outcomes and exposures measured similarly in each comparison group?
Yes. All reports were voluntary post-marketing adverse event reports with diagnostic codes of suicide or suicide attempt, and depression and related disorders.

Was follow-up of sufficient duration?
Yes, all years of available data since approval of isotretoin were included in the analysis.

Were all patients accounted for and analyzed?
Probably not. Voluntary reporting likely missed a significant number of cases. Data for isotretoin may be significantly biased as 49% of cases were reported in 1998 – after suicide and depression were added to the product labeling in February 1998!

Is there a reasonable temporal relationship between exposure and outcome?
Yes. All patients were treated with isotretoin prior to the diagnosis of depression and/or suicide (or attempt). Some patients had medication discontinued prior to diagnosis.

Is there a dose-response gradient?
This could not be addressed with this study design. Only patients with events (depression or suicide) were documented with the analyzed reports. Without a denominator (number of patients treated) and doses received, dose response could not be determined.
Do the study population characteristics describe your patient?
Yes.

Results
What is the strength of the association between exposure and outcome?
This study did not permit a quantification of the risk. Questions of reporting bias (with the significant number of cases reported after labeling of the drug changes in 1998) severely limit the conclusions we can draw about the number of reports associated with isotretinoin. There were a relatively large number of reports of events for isotretinoin (only nonpsychiatric drug in the top 10 drugs ranked for suicide attempts), and case reports of positive re-challenges with drug.

How precise are the risk estimates for the exposure?
Cannot be determined from this study, as the design did not allow statistical analysis of this sort.

What is the absolute level of risk from this exposure?
This remains unknown for the same reasons as above. See the limitations below.

Comments
Strengths and Weaknesses of Study (internal and external validity)
This study provides the largest available series of patients reported with psychiatric complications that may be related to isotretinoin. Certainly this relatively systematic approach for monitoring reports of drug adverse events is superior to expert opinion or a simple case series, but it is limited by methodology, lack of an appropriate comparison group and reporting bias.

Should the study results cause avoidance of the exposure?
For a number of reasons, isotretinoin should be used with caution and close follow-up (teratogenicity, lipid abnormalities...), and should be reserved for patients with significant and/or refractory acne. These data in the context of previous literature suggest that close monitoring and follow-up of patients is clinically appropriate – but they do not necessarily suggest the drug should not be used.

Next steps for further study of this problem:
To better answer this question, a study with an appropriate, matched control group (such as a case control study) or prospective cohort study with comparison to non-treated, matched controls could be conducted. Given the low frequency of significant events (suicide attempts, and diagnoses of depressive disorders) a large prospective study would be necessary and thus is unlikely to be undertaken. Careful follow-up and continued post-marketing reporting of events may yield further evidence of the risk – though it is likely we will not have a certain answer.

Returning to the Clinical Scenario:
In the mean time, despite the flaws in this study design, this represents the strongest piece of evidence available to date on this question. Therefore, we will have to consider this information (in the context of the design flaws) and still make a clinical decision. After consideration of the evidence, you do not feel that the strength of the evidence should stop you from a monitored trial of isotretinoin in the 15 year old patient you saw in the morning and you do not change your recommendation. You do, however reiterate your commitment for close follow up.

Teaching points to highlight for this paper:
This paper highlights the unfortunate reality that we frequently face when searching real life questions in the course of caring for our patients. It is not uncommon that the level of evidence that we seek simply does not exist. Therefore, like it or not, we must make clinical decisions with the best information that is available to us. Discussion of this paper might lead to a perfect opportunity to discuss the meaning of ‘the hierarchy of evidence’. In addition, this paper can be a jumping point for discussion of the methodologic stumbling blocks that face researchers when they are attempting to address issues of harm. One might take the opportunity to review different methodologies in the context of how a researcher might design different kinds of studies to answer this very question and the pros and cons of each method.