Stimulation — who dec?
Beasley

ACTIVATION AND SEDATION IN FLUOXETINE
CLINICAL TRIALS

Fluoxetine may produce both activation (nervousness, anxiety, agitation, insomnia) and sedation (somnolence, asthenia). Approximately 19% of patients might be expected to report activation during acute therapy with fluoxetine which was not present prior to therapy and which could be attributed to fluoxetine (in trials, 38% of fluoxetine-treated patients reported new activation but 19% of placebo-treated patients also reported new activation yielding a difference of 19% attributable to fluoxetine). Approximately 13% of patients might be expected to report sedation with fluoxetine which could be attributed to the drug (in trials, 28% with fluoxetine and 15% with placebo giving the 13%). Some patients report symptoms of activation and sedation during therapy and are included in both percentages above.

Tricyclics produce more sedation than activation but activation can occur. Approximately 4% of patients might be expected to report activation during acute therapy with tricyclics (2° amines) which was not present prior to therapy and which could be attributed to the tricyclic (in trials, 22% with tricyclics but 18% with placebo giving the 4%). Approximately 23% of patients might be expected to report sedation with tricyclics which could be attributed to the drug (in trials, 37% with tricyclics but 14% with placebo giving the 23%). Tricyclic patients also complain of both activation and sedation, as do fluoxetine patients, and are included in both percentages.

Fluoxetine is activating relative to tricyclics and tricyclics are sedating relative to fluoxetine. The difference in activation actually attributable to the drugs (19% vs. 4%) is greater than the difference in sedation (13% vs. 23%). Psychiatrists may focus more on absolute reports as opposed to the values with placebo rate subtracted: activation - 38% fluoxetine and 22% tricyclic; sedation - 28% fluoxetine and 37% tricyclic. A clinician is much less concerned with the "cause" than the impact of the event on his patient. The perception of the importance of these events will be relative to past experience. Any physician liking doxepin and/or amitriptyline with more sedating activity and perhaps less activating activity than the "average tricyclic" numbers above, will be especially likely to find the fluoxetine difference substantial.

Several suggestions may be helpful in presenting this information to physicians: 1) Emphasize that discontinuation rates are low and that the highest discontinuation rate is for the sedation associated with tricyclics. 2) Encourage physicians to understand the meaningfulness of subtracting the placebo rate from the drug associated rate (this suggests the maximum real drug effect) and point out that these values are relatively low. 3) Deal with the mixed group as a truly unique group.

11/8/88
cl

## KEY TO GROUPS

| | |
|---|---|
| ACTIVATION-1: | One or more of nervousness, anxiety, agitation, insomnia;<br>but neither somnolence, asthenia. |
| SEDATION: | One or both of somnolence, asthenia;<br>but not any of nervousness, anxiety, agitation, insomnia. |
| MIXED: | One or more of nervousness, anxiety, agitation, insomnia;<br>and one or both of somnolence, asthenia. |
| ACT-2: | One or more of nervousness, anxiety, agitation;<br>but not insomnia;<br>but neither somnolence, asthenia. |
| INS: | Insomnia;<br>but not any of nervousness, anxiety, agitation;<br>but neither somnolence, asthenia. |
| SED: | See SEDATION above. |
| ACT-2 SED: | One or more of nervousness, anxiety, agitation;<br>but not insomnia;<br>and one or both of somnolence, asthenia. |
| INS & SED: | Insomnia;<br>but not any of nervousness, anxiety, agitation;<br>and one or both of somnolence, asthenia. |
| ACT-2, INS & SED: | One or more of nervousness, anxiety, agitation;<br>and insomnia;<br>and one or both of somnolence, asthenia. |

system. I don't know if we are wrong or right, but we certainly haven't communicated well the rationale for what we are doing--so we'll fix that for sure.

---------- Forwarded Message ----------

November 14, 1990 06:47

To: THOMPSON LEIGH RVAX
cc: MAYR GERHARD IVM1
TAUREL SIDNEY IVM1
WEBER HANS J IVM1
WEINSTEIN ALLAN J IVM1
ZERBE ROBERT L IVM1

November 14, 1990 05:58
RE:ADVERSE EVENT REPORTING-SUICIDE FLUOXETINE
Thank you very much for your prompt answer and your detailed explanations.Hans and I rediscussed the issue in depth.
Our point is the following:the physician has reported a suicide attempt.So we have a right to change it to some terminology which we may consider to be more specific,e.g. overdose.but which is not free from ambiguity and could be regarded as inaccurate or misleading?
The term overdose is not free from ambiguity because there are clearly forms of overdose which are not related to suicide attempts ,for instance wrong dose prescribed or dispensed,error on the part of the patient etc...In fact, and perhaps more importantly,the dictionaries we have looked at (medical dictionaries and non-medical)fail to associate (not to mention equal) the concept of overdose with suicide attempt.
In addition,it can be argued that the event term overdose is inaccurate or misleading because in this case the patient attempted suicide by taking an overdose of barbiturates and tricyclics and not,I repeat not,of fluoxetine.
Finally,on a very simple and non-scientific basis,I personnally wonder whether we are really helping the credibility of our excellent ADE system by calling overdose what a physician reports as suicide attempt and by calling depression what a physician is reporting as suicide ideation.We fully realize that there is no code in our DSN system for suicide ideation but it could be argued by people who have little sympathy for the company or by regulatory authorities that it is not a responsible way to deal with an issue which is getting so much attention in the scientific and in the general press.It could also be argued that the term depression is not specific in this case.
Of course,at the end of the day,we will do what we are told to do but Hans and I felt that we had to bring these points to your attention.
Regards.

Claude.

BOUCHY CLAUDE IVM1
---------- End of forwarded message(s) ----------

THOMPSON LEIGH RVAX

22 NOV '93 11:51 LILLY DEUTSCHLAND GMBH

This is message # 1 From: BOUCHY CLAUDE IVM1

November 13, 1990 10:49

To: THOMPSON LEIGH RVAX
WEINSTEIN ALLAN J IVM1
ZERBE ROBERT L IVM1
cc: MAYR GERHARD IVM1
TAUREL SIDNEY IVM1
WEBER HANS J IVM1

RE:ADVERSE DRUG EVENT REPORTING-SUICIDE FLUOXETINE
Hans Weber and I have problems with the directions our safety people are getting from the corporate group(Drug Epidemiology Unit) and requesting that we change the identification of events as they are reported by the physicians.

-GEB-FLM039(DEN #GE90100350A).On this one,our safety staff is requested to change the event term "suicide attempt"(as reported by the physician) to "overdose".

-GEB-FLM025(DEN #GE90090437A).On this one,it is requested that we change from "suicidal ideation" to "depression".

Press ENTER for more, PF3 to end display, or PF7 to page back

Hans has medical problems with these directions and I have great concerns about it.I do not think I could explain to the FDA,to a judge,to a reporter or even to my family why we would do this especially on the sensitive issue of suicide and suicide ideation.At least not with the explanations that have been given to our staff so far... I am quoting"When an overdose is taken in a suicide attempt,our Research Physicians prefer to list the event term overdose"even if "when tracking suicides,we always look at all overdose and suicide attempts reports".
This issue has been argued back and forth for about a month between Bad Homburg and Indy ,therefore I am bringing it to your attention and await your directions.
Regards,

Claude.

BOUCHY CLAUDE IVM1
---------- End of message # 1 ----------

Type a command (e.g. View, Print, Forward, Reply, Delete, ?, etc.)
or press ENTER to display the mailbox
==>

# COSTART Terms

SUICIDE ATTEMPT (JANUARY 1989)

PSYCHOTIC DEPRESSION

OVERDOSE

HOSTILITY

INTENTIONAL INJURY (JULY 1989)

Pz1548 1903

# SPONTANEOUS DOMESTIC REPORTS RECEIVED JANUARY 1982-JULY 1991

| DRUG | SUICIDE ATTEMPT | OVERDOSE | PSYCHOTIC DEPRESSION | |
|---|---|---|---|---|
| FLUOXETINE | 519 | 468 | 321 | 1308 |
| TRAZODONE | 4 | 90 | 5 | 99 |
| AMITRIPTYLINE | 9 | 82 | 5 | 96 |
| DESIPRAMINE | 4 | 83 | 14 | 101 |
| MAPROTILINE | 0 | 84 | 1 | 85 |

GRAPH

Pz1548 1904

# SPONTANEOUS DOMESTIC REPORTS RECEIVED JANUARY 1982-JULY 1991

| DRUG | HOSTILITY | INTENTIONAL INJURY |
|---|---|---|
| FLUOXETINE | 234 | 115 |
| TRAZODONE | 10 | 2 |
| AMITRIPTYLINE | 6 | 1 |
| DESIPRAMINE | 9 | 0 |
| MAPROTILINE | 5 | 0 |



# PERCENT OF TOTAL REPORTS (ALL EVENTS) FOR EACH DRUG



| DRUG | SUICIDE ATTEMPT | OVERDOSE | PSYCHOTIC DEPRESSION |
|---|---|---|---|
| FLUOXETINE (N = 14,198) | 3.1 | 3.3 | 2.3 |
| TRAZODONE (N = 2648) | 0.2 | 3.4 | 0.2 |
| AMITRIPTYLINE (N = 1064) | 0.8 | 4.7 | 0.5 |
| DESIPRAMINE (N = 1434) | 0.3 | 5.8 | 1.0 |
| MAPROTILINE (N = 1173) | 0.0 | 7.2 | 0.1 |

# PERCENT OF TOTAL REPORTS (ALL EVENTS) FOR EACH DRUG

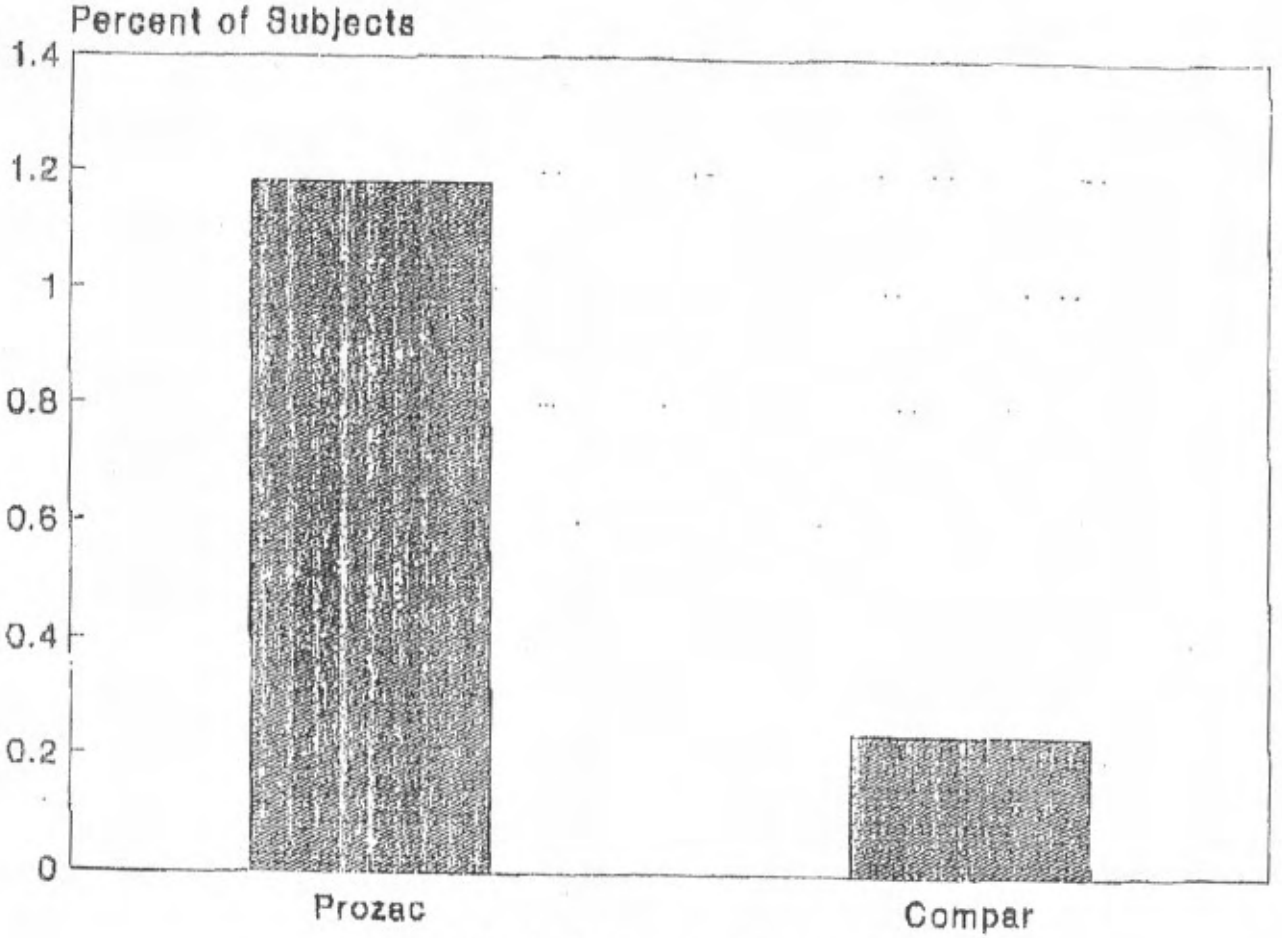


| DRUG | HOSTILITY | INTENTIONAL INJURY |
|---|---|---|
| FLUOXETINE (N = 14,198) | 1.6 | 0.8 |
| TRAZODONE (N = 2648) | 0.4 | 0.1 |
| AMITRIPTYLINE (N = 1064) | 0.6 | 0.1 |
| DESIPRAMINE (N = 1434) | 0.6 | 0.0 |
| MAPROTILINE (N = 1173) | 0.4 | 0.0 |

Ave

Graph

Graph

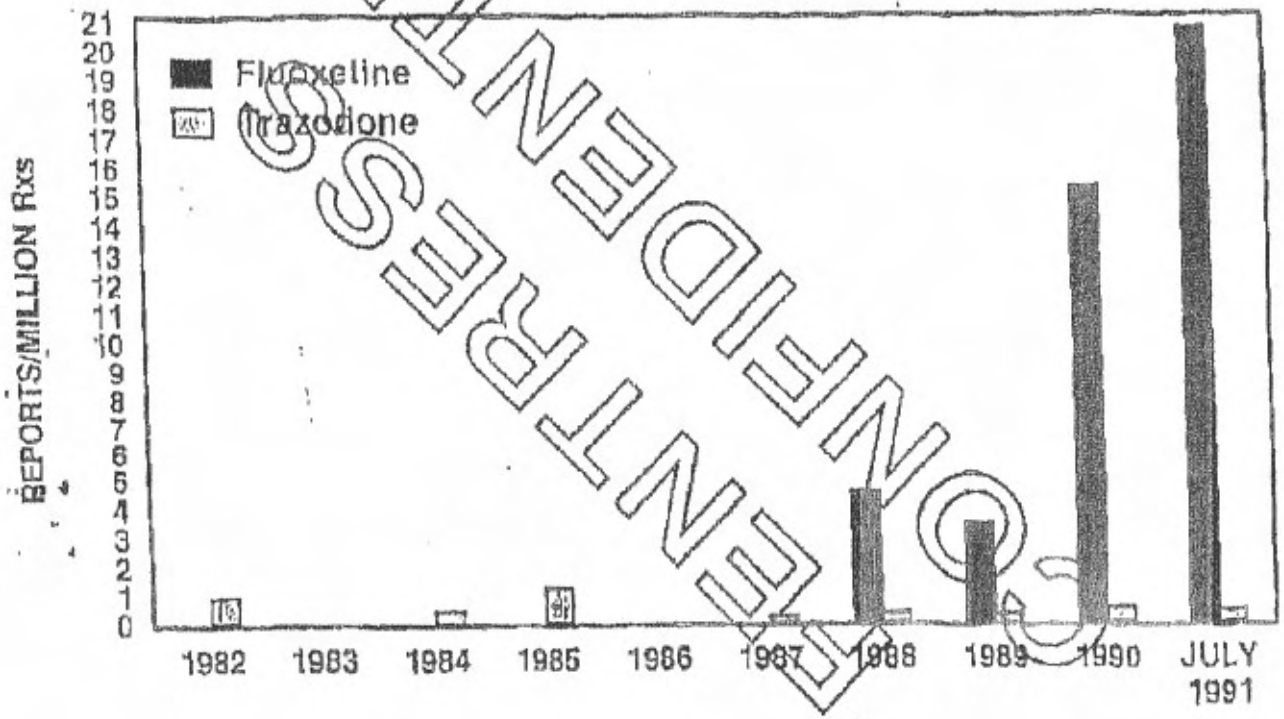



Suicide Reports

6 / 12

# HOSTILITY AND INTENTIONAL INJURY

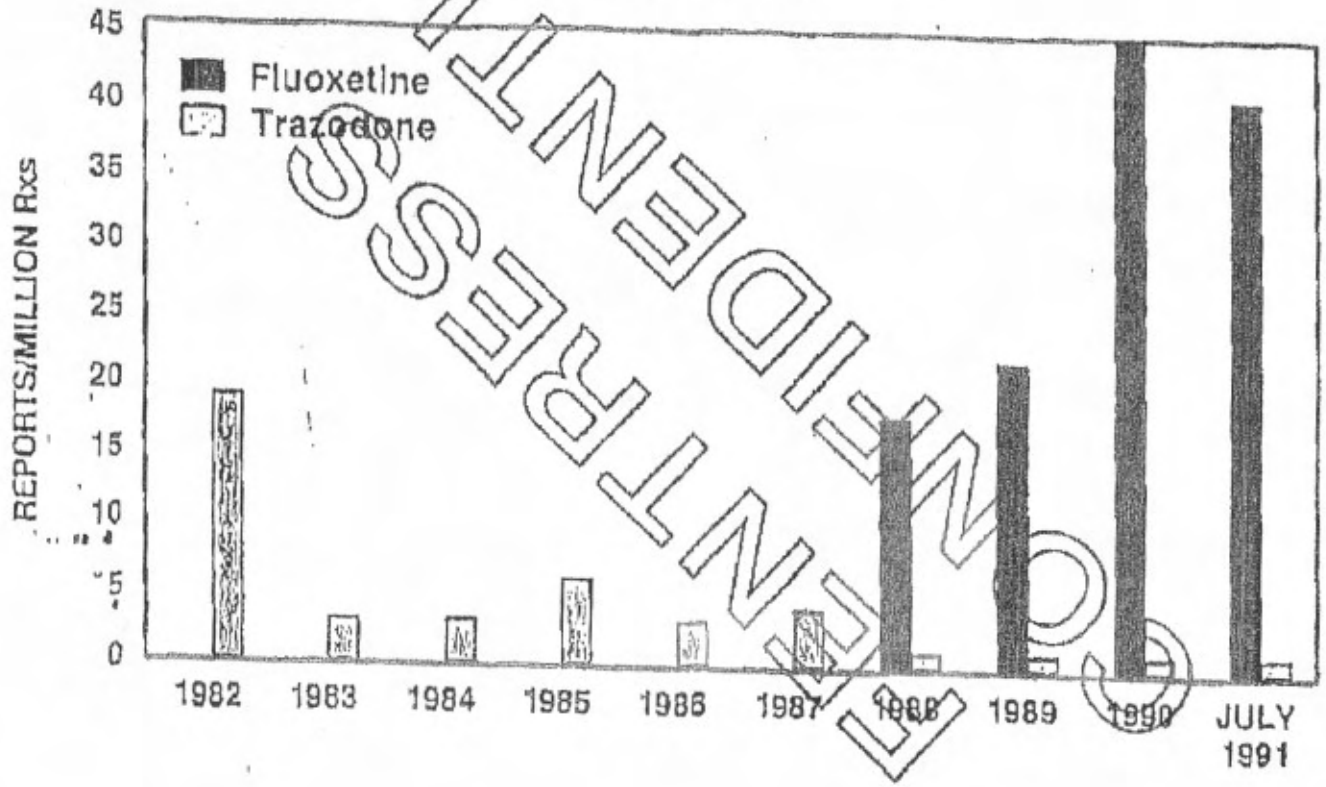
## Reports per Million Rxs

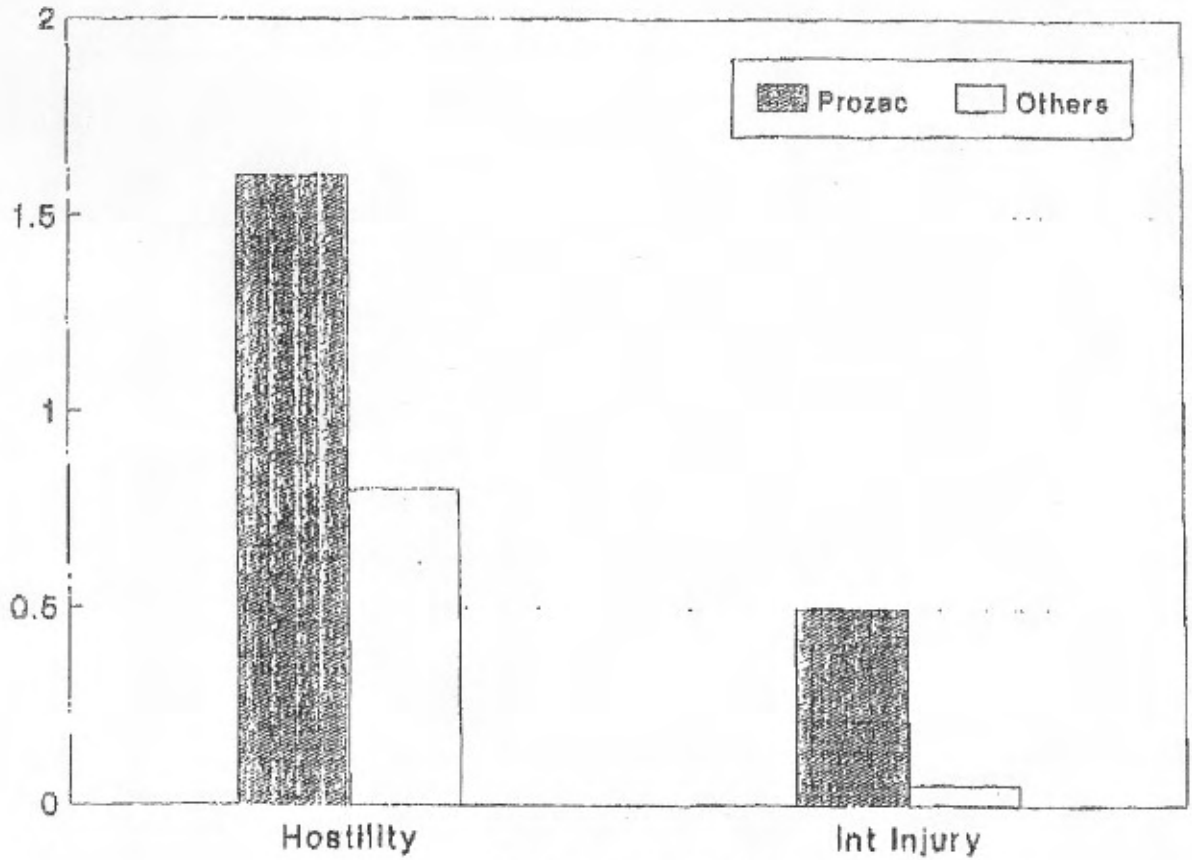


Pz1548 1911

# SUICIDE ATTEMPT, OVERDOSE, AND PSYCHOTIC DEPRESSION

Reports per Million Rxs






Percent of Total Reports

Ex 11

# Rxs FOR SELECTED ANTIDEPRESSANTS

(IN MILLIONS)