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 (3° 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.

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KEY TO GROUPS

ACTIVATION-1: One or more of nervousness, anxiety, agitation, insomnia;
but neither somnolence, asthenia.

SEDATION: One or both of somnolence, asthenia;
but not any of nervousness, anxiety, agitation, insomnia.

MIXED: One or more of nervousness, anxiety, agitation, insomnia;
and one or both of somnolence, asthenia.

ACT-2: One or more of nervousness, anxiety, agitation;
but not insomnia;
but neither somnolence, asthenia.

INS: Insomnia;
but not any of nervousness, anxiety, agitation;
but neither somnolence, asthenia.

SED: See SEDATION above.

ACT-2 SED: One or more of nervousness, anxiety, agitation;
but not insomnia;
and one or both of somnolence, asthenia.

INS & SED: Insomnia;
but not any of nervousness, anxiety, agitation;
and one or both of somnolence, asthenia.

ACT-2, INS & SED: One or more of nervousness, anxiety, agitation;
and insomnia;
and one or both of somnolence, asthenia.

PERCENT OF TOTAL REPORTS (ALL EVENTS) FOR EACH DRUG

DRUG	SUICIDE ATTEMPT	OVERDOSE	PSYCHOTIC DEPRESSION
FLUOXETINE (N = 14,198)	3.7	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	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

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