SECTION 3:
MEDICATION TREATMENT

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Are antidepressants effective in the treatment of SAD?
The best evidence for efficacy of antidepressants in SAD involves the selective serotonin reuptake inhibitors (SSRIs). Two multicentre, double-blind, randomized, placebo-controlled studies of sertraline (187 patients) and fluoxetine (68 patients) confirm that these medications are effective in the treatment of SAD. The first placebo-controlled study of antidepressants in SAD that had sufficient numbers of subjects and that involved an appropriate design was published by Lam and coworkers (1995). In this study, the season of recruitment was tightly defined and taken into account in the data analysis. In addition, there was a week-long placebo washout/run-in period. In this study, 86 subjects were recruited over two seasons in five Canadian centres. Only 68 remained depressed following single-blind placebo treatment. Thirty-six subjects were randomly assigned to 20 mg of fluoxetine for five weeks, and 32 were randomized to placebo. Mean change in HAM-D over the five weeks was not significantly different between the two treatment groups, but response rates, defined as greater than 50% improvement in SIGH-SAD scores, were significantly different (fluoxetine 59%, placebo 34%). Two major methodological issues limited this study. First, sample size, although larger than that of any previous SAD antidepressant study, was still somewhat small for an RCT. However, the effect size of the difference in improvement in depression between fluoxetine and placebo was 0.5, an effect size consistent with an effective antidepressant. Second, the trial lasted only five weeks. If the data are extrapolated to the sixth week, then fluoxetine would have appeared significantly superior to placebo using mean severity scores. In addition, this was a fixed-dose study, and it is not known whether a higher or lower dose may have

been more effective. Therefore, this study can be considered strongly suggestive that fluoxetine is effective in the treatment of SAD.

Moscovitch et al. (1995) completed the largest of the antidepressant studies in SAD. Nineteen centres in Canada and Europe participated to recruit 187 patients. Again, care was taken to recruit subjects during the appropriate season, and there was both a washout and a one-week placebo run-in period. Ninety-three subjects were randomized to sertraline and 94 to placebo. Treatment spanned eight weeks, and the dose of sertraline could be titrated up to 200 mg. The mean final dose for sertraline was 111 mg, and the most common dose was 100 mg. The response rate, defined as a rating of "improved" or "much improved" on the Clinical Global Impression scale, to sertraline (63%) was significantly superior to that of placebo (46%). Furthermore, the improvement in depression score was also significantly greater for sertraline by the end of the study. Although sertraline was superior to placebo for all outcome measures, the effect size was approximately 0.4, in the same range as that for antidepressant trials in nonseasonal depression.

Ruhrmann et al. (1998) conducted another controlled study with fluoxetine. Forty SAD patients were randomized to five weeks of treatment with either fluoxetine, 20 mg per day, plus a dim-light box (placebo light condition), or placebo drug plus a bright-light box (3,000 lux for two hours per day). Thus, the study compared active drug versus active light therapy conditions. The overall response rate, as defined by greater than 50% reduction in SIGH-SAD scores, was similar for both conditions (fluoxetine 65%, light therapy 70%). Note that this study did not have a true placebo condition.

Other antidepressant studies have been conducted but included too few subjects, selected subjects in an idiosyncratic fashion, were not placebo-controlled, or were not controlled for season of treatment. Partonen and Lonnqvist (1996a) examined 581 consecutive depressed subjects from outpatient clinics and health centres in Europe. Of these subjects, 183 patients were eligible (nonpsychotic, not on medications, not medically ill, not acutely suicidal), and only 32 subjects had DSM-III-R seasonal mood disorder. Subjects were randomly assigned to treatment with either moclobemide or fluoxetine in a double-blind fashion. Of 11 subjects with SAD treated with 300-450 mg of moclobemide over six weeks, 7 (64%) responded, and of 18 treated with 20-40 mg of fluoxetine over six weeks, 8 (44%) responded. There were no significant differences in response rate. However, the sample size was small,

and the response rate to fluoxetine was poor overall and hard to explain. Unfortunately, the absence of a placebo group makes conclusions from this study limited.

Lingjaerde et al. (1993b) published a study with few subjects and with a very complicated design. In short, it involved a three-week placebo-controlled trial of moclobemide in doses of 200 mg bid. Response rate in the moclobemide group was 44% (7 of 16), as it was in the placebo group (8 of 18). However, few antidepressant studies demonstrate a difference between active medication and placebo at the third week. No conclusions regarding the potential benefit of moclobemide may be drawn from this small study.

Dilsaver et al. (1990b) studied 11 consecutive outpatients with DSM-III-R seasonal depression treated with the monoamine oxidase inhibitor tranylcypromine. The endpoint of treatment was considered the maximum improvement achieved within five weeks of treatment. This means that early or placebo responders may be overrepresented in the subjects considered to be responders. All 11 subjects had a favourable response at some time within the first five weeks of treatment with 30-40 mg of tranylcypromine. All seven subjects with chronic pain and SAD also had remission of pain. The same group (Dilsaver et al., 1992b) published another open study of 15 consecutive subjects who agreed to take bupropion in an open trial for up to five weeks in an unspecified dose (the manuscript abstract suggests 200-400 mg per day). Again virtually all subjects responded, and again the design favoured early or placebo responders. Bupropion and tranylcypromine may be effective in SAD; however, these studies are small, and treatment was not placebo controlled, so the results are only suggestive.

What is the usual effective dose of antidepressants in SAD?

There are no "dose finding" antidepressant studies in patients with SAD. Clinical experience suggests that the starting dose of the antidepressant in SAD depends on several factors. The clinician should start at a lower dose and increase the dose cautiously in (1) patients with previous sensitivities to antidepressants, (2) adolescent or elderly patients, (3) patients with a concurrent medical illness, or (4) patients who are taking other medications that interact with and increase the blood levels of the antidepressant.

From the data that do exist, some inferences may be drawn. The sertraline study (Moscovitch et al., 1995) was a flexible-dosing study

using doses of 50 mg to 200 mg per day. Most patients took 50 mg or 100 mg per day, and the average dose of sertraline was 111 mg per day. The fluoxetine study (Lam et al., 1995) used a fixed dose of 20 mg per day. The response rates and doses in these two studies are similar to those found in antidepressant studies of nonseasonal depression, using similar methodologies. Most clinicians agree that the antidepressant doses required for treatment of SAD are probably the same as those required for nonseasonal major depression.

What are the side effects of antidepressants?

The only studies to have systematically reported on side effects with antidepressants are the two double-blind studies involving serotonin reuptake inhibitors. Lam et al. (1995) reported that 97% of fluoxetine-treated and 91% of placebo-treated subjects reported one or more side effects. The most frequently reported side effects in fluoxetine-treated subjects were headache, flulike syndrome, rhinitis, and pharingitis. The most frequent side effects in the placebo group were headache, insomnia, and dyspepsia. Two patients (5.5%) treated with fluoxetine terminated that study as a result of side effects; one became hypomanic, and one had abdominal pain and flu symptoms. The one subject (3.1%) in the placebo group who terminated the study as a result of side effects had severe flu, fever, and nausea.

In the Moscovitch et al. (1995) study, 82% of sertraline-treated and 50% of placebo-treated subjects had at least one adverse event. Withdrawal from the study occurred in 7.5% of sertraline-treated and 4.3% of placebo-treated subjects. The most common side effects in the sertraline group were nausea, insomnia, and diarrhea. The most common side effects in the placebo group (similar to those in the fluoxetine study) were headache, insomnia, and nausea.

There are no data available regarding whether side effects to antidepressants are specifically different in SAD as compared with nonseasonal depression. The side effects reported in the two studies above seem to suggest that side effects are similar in SAD patients as compared to patients with nonseasonal depression.

How long should an acute trial of antidepressant last?

Patients in the fluoxetine study were treated for five weeks, but not all

the outcome measures favoured fluoxetine. If the study is extrapolated to the sixth week, then all outcome measures would have been significant. The sertraline study treated patients for eight weeks and showed superiority of sertraline over placebo in all outcome measures. Therefore, an adequate trial of antidepressants should last six to eight weeks, similar to that recommended for nonseasonal depression.

Have other medications been studied in the treatment of SAD?
Several studies have looked at nonantidepressant medications in the treatment of SAD. Studies with negative results, although small sample sizes could not definitively rule out Type II errors, include B12 and levodopa. Melatonin has been investigated for SAD, given the relationship between melatonin and many seasonal animal behaviours. One study of open-label melatonin, given in the morning or the evening, was negative (Wirz-Justice et al., 1990). Preliminary results of a placebo-controlled study using a lower dose of melatonin and an afternoon dosing schedule were reported as positive (Lewy et al., 1998a). Beta adrenergic antagonists suppress nocturnal melatonin secretion in a manner similar to light, so several studies have examined beta blocker medications for SAD. One study with atenolol, a long-acting beta blocker, was negative (Rosenthal et al., 1988a). However, another study using propranolol given in the early morning (theoretically to truncate a phase-delayed melatonin-secretion curve, similar to morning light therapy) was positive (Schlager, 1994). However, efficacy cannot be definitively established with the placebo-substitution design used in that study.

Other positive studies with small sample sizes include two studies of d-fenfluramine (O'Rourke et al., 1987, 1989). Unfortunately, because of severe adverse side effects, d-fenfluramine was voluntarily withdrawn from the North American market. One study of l-tryptophan found it superior to pill placebo, and similar in response to evening light therapy, but the sample size was very small (McGrath et al., 1990). Another study found that l-tryptophan had similar response rates to bright-light therapy, but response took four weeks for l-tryptophan, compared to two weeks for light therapy (Ghadirian et al., 1998). Finally, a small study showed beneficial effects of hypericum (St. John's Wort) plus a dim-light box, compared to a pill placebo plus a bright-light box (Martinez et al., 1994).

Recommendations: Medication Treatment

(1) Sertraline and fluoxetine are effective first-line treatments for seasonal affective disorder (SAD). [Level 1 evidence]
(2) The effective doses of these antidepressants are similar to those used in the treatment of nonseasonal depression. [Level 2 evidence]
(3) These two antidepressants are well tolerated by SAD patients. [Level 1 evidence]
(4) Other antidepressants may also be effective in the treatment of SAD, using doses similar to those recommended for nonseasonal depression. [Level 5 evidence]
(5) An adequate trial of antidepressants involves at least six weeks of treatment. [Level 2 evidence]
(6) Other medications (propranolol, l-tryptophan, hypericum, melatonin) require further study before they can be recommended for treatment of SAD. [Level 2 evidence]

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