

SECTION 1:

DIAGNOSIS, EPIDEMIOLOGY, AND PATHOPHYSIOLOGY

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Part 1: Diagnosis

How should a “seasonal pattern” of depression be defined?

(1) Diagnostic Criteria

The first published criteria for seasonal affective disorder (SAD) were proposed by a group from the National Institutes of Health led by Rosenthal (Rosenthal et al., 1984a). Since then three additional sets of criteria for seasonal depression have been published. Both DSM-III-R and DSM-IV have included a “seasonal pattern” (SP) course specifier for affective/mood disorders, and ICD-10 includes the category of seasonal depressive disorder. A comparison of these diagnostic criteria is presented in Table 1. The four sets of diagnostic criteria are similar in their reliance on regular seasonal recurrences of depression with interepisode improvement as opposed to any specified symptomatic features. All of the diagnostic systems except ICD-10 exclude depressions that are apparently related to seasonally varying psychosocial stressors. Significant differences between the criteria include the specific definitions of the required seasonal pattern, the range of affective pathologies to which the criteria can be applied, and the inclusion versus exclusion of comorbid Axis I psychopathology.

(2) Onset and Duration

There has been some controversy in the psychiatric literature about the most appropriate criteria for defining a “seasonal pattern” (SP) (e.g., Bauer, 1992; Bauer and Dunner, 1993a; Blehar and Lewy, 1990). Despite the controversy, there are surprisingly few published studies that have systematically assessed the validity of the different sets of diagnostic criteria. The DSM-III-R criteria for SP attempted to be more precise and stringent in defining the temporal characteristics of seasonality

Table 1

Comparison of diagnostic criteria for SAD/seasonal pattern

Rosenthal criteria for winter depression	DSM-III-R criteria for seasonal pattern modifier	DSM-IV criteria for seasonal pattern specifier	ICD-10 criteria for seasonal depressive disorder
Recurrent fall/winter depressions	Regular onset within a 60-day period	Regular temporal relationship with a particular time of year	Regular onset of episodes within specific 90-day period
No seasonally varying psychosocial stressor	Excludes seasonal psychosocial stressors	Excludes seasonal psychosocial stressors	
Regularly occurring non-depressed periods in spring and summer	Full remission or switch to (hypo)mania within 60-day period	Full remission or switch to (hypo)mania at characteristic time of year	Remission within particular 90-day period
At least two of the depressions occurred during consecutive years	At least three episodes, two in consecutive years; ratio of 3:1 seasonal:nonseasonal episodes	Seasonal major depressive episodes occurred, and non-seasonal MDEs* did not occur, for the past two years; lifetime seasonal MDEs outnumber non-seasonal MDEs	Three or more consecutive episodes; seasonal episodes substantially outnumber any nonseasonal episodes
At least one of the depressions has met RDC** for major depression	May apply to bipolar disorders, recurrent major depression, depressive disorder not otherwise specified	Applies to bipolar disorder (type I or II) or major depressive disorder, recurrent	Applies to ICD-10 major depression
No other axis I pathology	Other diagnoses do not exclude application of the modifier	Other diagnoses do not exclude application of the specifier	Other mental and behavioural disorders do not exclude the diagnosis

*MDEs = major depressive episodes.

**RDC = research diagnostic criteria.

(i.e., 60-day onset and offset windows, 3:1 ratio of seasonal to non-seasonal episodes). Two studies using very different methods concluded that the 60-day window is unnecessarily restrictive (Dittman et al., 1994; Leonhardt et al., 1994). A longitudinal study using weekly self-reports of depressive symptoms in 26 SAD patients over an interval of at least two and a half years observed that the mean variability of onset and offset was 12 and 10 weeks respectively. None of the eight patients in this study who had experienced consistent winter seasonal depressions would have been diagnosed as SAD if the DSM-III-R 60-day window had been strictly applied (Leonhardt et al., 1994). A retrospective analysis of diagnostic stringency in relation to therapeutic response was carried out in a sample of 66 (Rosenthal defined) SAD patients (Dittman et al., 1994). The authors observed that a substantial number of patients (16 of 66) did not meet DSM-III-R criteria, principally because of the 60-day window criterion. However, the patients who did meet the more stringent DSM-III-R criteria did not differ significantly from the DSM-III-R (negative) group in terms of demographics, family history, prior antidepressant medication use, or response to a trial of light therapy. The authors also noted that a sizeable proportion of their SAD subjects was unable to retrospectively provide details of past depressive phases precisely. Dittman et al. thus concluded that the 60-day window criterion was invalid and that the DSM-III-R criteria were “unrealistic and impracticable.” Discussions of the validity of SAD diagnostic criteria led to the deletion of the 60-day window in the reformulated DSM-IV criteria (Bauer and Dunner, 1993a), whereas ICD-10 adopted a 90-day window for onset and offset of episodes.

(3) Remission

Another important difference between the Rosenthal SAD criteria and the other diagnostic criteria is the specification of “full remission” (or switch to hypomania or mania) in the DSM criteria versus “nondepressed periods” in the spring and summer in the Rosenthal criteria. Danilenko and Putilov (1996) conducted a comparison of two groups of patients with winter depression, characterized by complete (two months) or incomplete summer remissions ($n = 66$ and 32 respectively). Their incomplete remission group was characterized by an older age of onset, lower female predominance, fewer reverse vegetative symptoms, and less consistent seasonal episodes. The authors commented that patients with incomplete summer remissions were more heterogeneous and differed from the typical demographic and clinical profile of SAD. They

concluded that the DSM-IV criterion of “full remission” was valid but suggested that the minimum duration for “remission” could be reduced to two months.

The process of developing criteria for the diagnosis of SAD/SP has gone through a cycle of broad definition (Rosenthal) to more stringent definition (DSM-III-R, ICD-10) and back to a relatively broad definition (DSM-IV). For research purposes, when the identification of homogeneous study populations is critical, the application of a stringent/narrow definition of seasonality will often be appropriate. In routine clinical practice, however, the application of excessively stringent diagnostic criteria could result in failure to offer a helpful treatment (e.g., light therapy) to patients who may benefit from it. (It has been suggested that even subsyndromal forms of SAD may respond to light therapy [Kasper et al., 1988; Kasper et al., 1989a].) Blazer and colleagues (1998) demonstrated the effect of applying successive DSM-III-R diagnostic criteria to a community sample of patients with seasonal onset of major depression using data from the National Comorbidity Survey. The prevalence of major depression with seasonal onset was 3.1%, but only 0.3% of the sample fulfilled all of the DSM-III-R criteria for major depression with a seasonal pattern (see also Part 2, Epidemiology, Table 4). The less restrictive criteria in DSM-IV should be more appropriate for clinical populations (Table 2).

What are the usual symptoms of depression in SAD?

A specific symptom cluster consisting of so-called reverse vegetative symptoms of depression (hypersomnia, hyperphagia, and weight gain) has been associated with SAD. A large number of descriptive studies of SAD/SP have reported the prevalence of reverse vegetative features in winter depression. Rosenthal’s original report on 29 SAD patients indicated a prevalence of increased appetite of 66%, carbohydrate craving in 79%, weight gain in 76%, and hypersomnia in 97% (Rosenthal et al., 1984a). A larger sample ($n = 366$) described by Rosenthal’s group had similar proportions of reverse vegetative symptoms (increased appetite 67%, carbohydrate craving 71%, weight gain 75%, hypersomnia 79%) (Oren and Rosenthal, 1992). A large-sample Canadian study ($n = 454$) also found that reverse vegetative symptoms predominated in SAD (increased appetite 57%, carbohydrate craving 77%, weight gain 53%, hypersomnia 71%) (Lam, 1998). Several additional descriptive studies have reported a high frequency of reverse vegetative symptoms, although

Table 2

**DSM-IV criteria for major depressive disorder with a seasonal pattern
(equivalent to seasonal affective disorder)**

Major depressive episode

- A. Five (or more) of the following symptoms have been present during the same two-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure:
- (1) depressed mood most of the day, nearly every day;
 - (2) markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day;
 - (3) significant weight loss or weight gain, or decrease or increase in appetite nearly every day;
 - (4) insomnia or hypersomnia nearly every day;
 - (5) psychomotor agitation or retardation nearly every day;
 - (6) feelings of worthlessness or excessive or inappropriate guilt nearly every day;
 - (7) diminished ability to think or concentrate, or indecisiveness, nearly every day;
 - (8) recurrent thoughts of death, recurrent suicidal ideation, or a suicide attempt.
- B. The symptoms do not meet criteria for a mixed episode.
- C. The symptoms cause clinically significant distress or impairment in psychosocial functioning.
- D. The symptoms are not due to the direct physiological effects of a substance or a general medical condition.
- E. The symptoms are not better accounted for by bereavement.

With seasonal pattern

(Can be applied to the pattern of major depressive episodes in bipolar I disorder, bipolar II disorder, or major depressive disorder, recurrent.)

- A. There has been a regular temporal relationship between the onset of major depressive episodes and a particular time of the year.
 - B. Full remissions (or a change from depression to mania or hypomania) also occur at a characteristic time of the year.
 - C. In the last two years, two major depressive episodes have occurred that demonstrate the temporal seasonal relationships defined in criteria A and B, and no nonseasonal major depressive episodes have occurred during the same period.
 - D. Seasonal major depressive episodes (as described above) substantially outnumber the nonseasonal major depressive episodes that may have occurred over the individual's lifetime.
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the proportions of patients have been more moderate in most of these reports (Krauchi et al., 1990; Lingjaerde and Reichborn-Kjennerud, 1993c; Takahashi et al., 1991; Thompson and Isaacs, 1988; Wirz-Justice et al., 1986). Two reports comparing winter depression with summer depression found higher frequencies of reverse vegetative symptoms in the winter SAD groups (Boyce and Parker, 1988; Wehr et al., 1991). Three studies comparing patients with winter depression and those with nonseasonal depression (Allen et al., 1993; Garvey et al., 1988; Thalen et al., 1995a) also found higher frequencies of reverse vegetative symptoms in the seasonal groups. A significant criticism of these studies has been that the majority of subjects for the studies were obtained by media recruitment or referrals. Because "typical" symptom patterns are commonly described for advertising purposes, the possibility exists that self-selected samples concurring with the publicized description are recruited (Bauer and Dunner, 1993a; Blehar and Lewy, 1990; Sakamoto et al., 1993a; Shapiro et al., 1994). One report based on nonrecruited patients found similarly elevated frequencies of reverse vegetative symptoms (Garvey et al., 1988), and a second such report found an unexpectedly low percentage of SAD patients with reverse symptoms (21-32%) except for hypersomnia (54%) (Sakamoto et al., 1993b). Furthermore, two studies that directly compared retrospectively reported vegetative symptoms with prospectively recorded data found more marked intensity and seasonal variability in reverse symptoms in the retrospective data (Nayyar and Cochrane, 1996; Shapiro et al., 1994). Other studies report classic melancholic symptoms (e.g., morning worsening of depressed mood) in some SAD patients (Graw et al., 1991).

Overall there is general support for a specific symptom cluster, including reverse symptoms and carbohydrate craving in SAD/SP, but it is difficult to be precise about these symptom patterns because of significant variability across samples and the possible role of patient self-selection. It has been debated whether clinical features of the SAD syndrome should be incorporated into the diagnostic criteria (Blehar and Lewy, 1990). While reverse vegetative symptoms may be common in SAD, these symptoms do not appear to be specific enough to warrant inclusion in diagnostic criteria.

Is the diagnosis of SAD stable over time?

If SAD is a valid diagnostic category for a lifelong disorder, then longitudinal follow-up of patients diagnosed with SAD should demonstrate stability of the diagnosis over time. Several medium-term and long-term

follow-up studies of SAD, using a variety of follow-up methods and variable definitions of patient outcomes, have been reported.

Sugishita and colleagues (1993) reported retrospectively collected follow-up data (one to four years) in 105 subjects diagnosed with SAD using the Rosenthal criteria. Seventy subjects continued to be called SAD, whereas the diagnosis for 27 subjects was “undecided” because of loss of seasonality or lack of information. The diagnosis of six subjects was “cancelled,” and two patients died in the follow-up period.

Leonhardt and colleagues (1994) reported a prospective follow-up study (2.5 to 8.25 years) of a select group of 26 SAD/SP patients who were able to comply with long-term weekly depression self-ratings using the Von Zerssen scale. They found that nine patients continued to experience seasonal depression (allowing for a broad window of onset and offset dates), whereas seven subjects showed a remitted pattern. Four patients evolved into chronic depression, and six patients had diffuse (i.e., not clearly seasonal) patterns of depressive symptoms. Note that this study did not rely on the application of diagnostic criteria; rather, it categorized outcomes according to the pattern of self-reported depression symptoms.

A British study using a narrower definition of SAD, and strictly applying the DSM-III-R 60-day onset and offset windows, was reported by Thompson and colleagues (1995). The study included 93 SAD subjects who had been diagnosed five to eight years previously with seasonal depression. Thirty-five subjects continued to have seasonal depression, 28 subjects had episodes that did not meet DSM-III-R criteria for seasonality, and 17 subjects had no further episodes.

A Japanese study of 41 retrospectively identified seasonally depressed patients, according to the Rosenthal criteria, was reported by Sakamoto and colleagues (1995). During the follow-up period (8.0 ± 5.4 years), nine patients showed a consistent fall/winter SAD pattern, 17 lost seasonality, and two were rediagnosed with schizoaffective disorder. Eleven patients who initially had nonseasonal depression changed to a seasonal pattern, and two patients with other nonaffective diagnoses were rediagnosed with SAD.

A follow-up study of the first 59 patients of the NIMH Seasonal Studies Program was reported by Schwartz and colleagues (1996). After a mean interval of 8.8 years, 25 of the 59 patients remained purely seasonal, 26 patients had varying degrees of nonseasonal depression, and eight patients had fully remitted.

Finally, a follow-up study (two to five years) of 39 Swiss SAD patients was reported by Graw and colleagues (1997). Ten subjects had ongoing SAD, and 17 had subsyndromal SAD (decreased severity or duration of episodes). In eight cases, the patients had recovered, and the diagnoses of four patients had been changed.

Collectively, the studies reviewed show evidence of both substantial change and relative stability of the diagnosis of SAD over time. These findings are in keeping with studies of other subtypes of major depression. For example, Nierenberg et al. (1996) report that 24% of subjects who present with an atypical major depression will not have atypical symptoms in the subsequent episode. With regard to the stability of SAD, most studies have found that approximately one-third of patients diagnosed with SAD still met criteria for the diagnosis at the time of follow-up (pooled data $88/258 = 34\%$) (Graw et al., 1997; Leonhardt et al., 1994; Sakamoto et al., 1995; Schwartz et al., 1996; Thompson et al., 1995). The exception was the study of Sugishita and colleagues (1993) that found the highest frequency of persistent SAD (67%). This study had the shortest follow-up period and used only questionnaires for follow-up. Several of these reports also indicated that the majority of study patients continued to suffer from fall and winter depressive symptomatology to a greater degree than at other times of the year (e.g., subsyndromal SAD, seasonal recurrent brief depression) (Graw et al., 1997; Leonhardt et al., 1994; Schwartz et al., 1996; Thompson et al., 1995). On the other hand, most studies indicated that a substantial proportion of SAD patients (approximately 20%) showed full remission of their conditions over the follow-up period (Graw et al., 1997; Leonhardt et al., 1994; Schwartz et al., 1996; Thompson et al., 1995). Arguably, some of these patients may not have had SAD at all (Thompson et al., 1995). Alternatively, a proportion of patients may have shown remissions because of ongoing treatment (light therapy or pharmacotherapy), as a sizeable proportion of patients used these treatments (naturalistically) in the years following diagnosis of SAD (Graw et al., 1997; Schwartz et al., 1996; Thompson et al., 1995). Furthermore, some patients may continue to have seasonal exacerbation of depressive symptoms (i.e., they continue to exhibit "seasonality") but remain depressed most of the year. Finally, it is possible that a seasonal pattern of depressive episodes is a phase of a depressive illness, much like rapid cycling may be a phase of bipolar illness. These suggestions are speculative and as yet untested.

In order to appreciate the significance of these observations, it is also useful to compare the observed temporal stability of the diagnosis of SAD/SP with the temporal stability of nonseasonal depressive disorders. Studies of patients with major depression have indicated a stability of 44% to 76% during follow-up periods ranging from five to seven years (Clayton et al., 1992; Lenz et al., 1991; Rice et al., 1992), with lower rates of stability (perhaps as low as 15%) in samples of depressed outpatients (Angst & Preisig, cited in Graw et al., 1997). The stability of SAD (approx. one-third) is therefore consistent with the general level of stability seen in outpatients with major depression. If both full SAD and subsyndromal SAD are considered as “stable” outcomes, then approximately two-thirds of SAD subjects are stable over follow-up – a figure consistent with depressed inpatients (Clayton et al., 1992; Lenz et al., 1991; Rice et al., 1992).

What instruments are useful for the diagnosis and measurement of SAD?

Some of the unique features of SAD/SP present measurement challenges that have necessitated the development of specific instruments for use in SAD/SP. The diagnosis of SAD depends not only on the identification of a characteristic depressive syndrome but also on the regular recurrences of the syndrome at a characteristic time of year. Also, though a wide range of instruments is available for the measurement of depression, most of them do not assess some of the most common symptomatic manifestations of SAD/SP. For example, commonly used measures of depression such as the Hamilton Rating Scale for Depression (HRSD, an observer rating [Hamilton, 1967]) and the Beck Depression Inventory (BDI, a self-report instrument [Beck and Steer, 1987]) do not contain items reflecting increased appetite/weight gain, carbohydrate craving, or hypersomnia. Following is a review of the instruments used for assessment in SAD/SP.

The Seasonal Pattern Assessment Questionnaire (SPAQ) (Rosenthal et al., 1987d) is a self-report questionnaire that retrospectively assesses the magnitude of seasonal change in sleep, socialization, mood, weight, appetite, and energy. A score reflecting global seasonality (GSS) is obtained by summing up the scores on these six items, yielding a number between 0 and 24 (Table 3). The SPAQ also asks respondents to rate impairment due to seasonal changes from “no problem” to “disabling.” The pattern of seasonal change is assessed by having the subjects note

the months during which they feel best/worst, socialize most/least, and gain/lose the most weight.

The SPAQ has been the primary instrument used in the majority of epidemiological studies of SAD (e.g., Eagles et al., 1996; Kasper et al., 1989b; Magnusson and Stefansson, 1993; Terman, 1988; Terman et al.,

Table 3

Seasonal Pattern Assessment Questionnaire

The purpose of this questionnaire is to find out how your mood and behaviour change from season to season. We are interested in *your* experience, *not that of others* you may have observed.

1. To what degree do the following change with the seasons?

	<i>No change</i>	<i>Slight change</i>	<i>Moderate change</i>	<i>Marked change</i>	<i>Extremely marked change</i>
Sleep length	0	1	2	3	4
Social activity	0	1	2	3	4
Mood (overall feeling of well-being)	0	1	2	3	4
Weight	0	1	2	3	4
Appetite	0	1	2	3	4
Energy level	0	1	2	3	4

Global Seasonality Score (GSS) = total score summed from the six items.

2. If you experience changes with the season, do you feel that these are a problem for you?

- No Yes – If yes, is this problem:
- | | |
|-----------|---|
| mild | 1 |
| moderate | 2 |
| marked | 3 |
| severe | 4 |
| disabling | 5 |

A GSS of 11 or more on the first question, and a seasonal problem score of moderate (2) or greater on the second question, indicate a positive screen for seasonal affective disorder.

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1989c). Cases of SAD and S-SAD have been identified in these studies by using a combination of GSS cut-off scores and the rating of the individual's problem with seasonal changes. Cut-off scores were originally developed by Rosenthal's research group based on SPAQ data and personal experience with the instrument in 168 patients with SAD (Kasper et al., 1989b). The proposed SPAQ criteria to "diagnose" SAD were a GSS of 11 or higher and a response to the degree of seasonal impairment question of moderate or greater. These criteria were used to estimate the prevalence of SAD in Montgomery County (near Washington, DC) as 5.3% (Kasper et al., 1989b). A cluster analytic study of SPAQ results from 416 subjects identified clusters of patients with demographic characteristics, symptomatic patterns, and GSS closely corresponding to groupings of SAD and S-SAD subjects and thus provided some evidence of the validity of the suggested cut-off scores (Bartko and Kasper, 1989).

Several studies examining the reliability, validity, and internal consistency of the SPAQ have been reported. Thompson and colleagues (1988) reported one-year test-retest reliabilities for the SPAQ in a group of 20 SAD patients. The median reliability for the six severity of clinical change scales was $r = 0.51$ (range 0.37 to 0.72), indicating only modest test-retest reliability. The global impairment rating showed good reliability at 0.79. Hardin and colleagues (1991) reported eight-month test-retest reliabilities for 50 SAD patients. Their results were somewhat more favourable with a median reliability of $r = 0.72$ for the six severity of seasonal change items (range 0.67 to 0.80), and the reliability of the global impairment rating was 0.80.

A clinical evaluation study of 81 people who had participated in a community study of SAD reported that the SPAQ had an estimated sensitivity of 94%, specificity of 73%, and positive predictive value of 45% for detecting "winter problems" (i.e., a combined group of SAD and S-SAD) (Magnusson, 1996). The SPAQ showed poor discrimination between SAD and S-SAD, and as a result the authors concluded that it had a poor "case-finding" ability for winter depression. A follow-up study (five to eight years) of 47 patients reported fair test-retest reliability for the GSS of the SPAQ ($r = 0.62$) (Raheja et al., 1996). More detailed analyses of the study results suggested that higher seasonality scores were more likely to indicate persistent seasonality (i.e., high scores are traitlike), whereas subsyndromal seasonality scores were particularly unreliable and tended to fall during follow-up. These results require cautious interpretation in view of the lengthy follow-up duration of

the study; long-term outcome studies of SAD/SP have found that a substantial proportion of patients diagnosed with SAD do not show persistence of SAD over a period of three to eight years (see earlier review). The internal consistency of the six severity of seasonal change items of the SPAQ was evaluated in a group of 587 subjects (a random sample of the general population) (Magnusson et al., 1997). A high degree of internal consistency ($\alpha = 0.82$) was observed.

The SPAQ has also been criticized because of the highly skewed distribution of SPAQ GSS in the general population (Spoont et al., 1991). The possible range of GSS on the SPAQ is between 0 and 24, but the observed range of scores in the general population is narrower (between 0 and 18), with 80% of the population scoring between 0 and 8 (Kasper et al., 1989b). These features of the SPAQ are not particularly problematic when it is used for screening purposes (i.e., higher sensitivity for the upper 20% of the population). However, Spoont and colleagues (1991) have noted that dimensional measurement of seasonality for other research purposes (e.g., examining the relationship of seasonality to other continuous variables) requires more evenly balanced psychometric properties. For such purposes, these authors developed the Inventory of Seasonal Variation (ISV), and their initial report provided evidence of the internal consistency, external validity, and sensitivity of the measure. Unfortunately, searches of Medline and PsycLit databases did not yield any subsequent publications assessing the validity of this instrument.

In summary, the SPAQ has been a very popular screening tool in SAD research, particularly epidemiological studies. Reports on the reliability of the instrument have been mixed, and there have been criticisms of the psychometric properties of the instrument. However, it remains popular because of its early development and dissemination, a high degree of face validity, and the absence of better-validated alternative measures.

The Hamilton Rating Scale for Depression (HRSD) (Hamilton, 1967) has been the dominant observer-rated instrument for the measurement of depressive disorders in clinical trials. In their preliminary report on SAD and light therapy, Rosenthal and colleagues (1984a) noted that "the HRSD does not fully reflect the severity of depression in SAD. Hypersomnia, overeating, weight gain and carbohydrate craving, which are commonly found in SAD, are not represented at all on the HRSD, and fatigability is given little weight." Nevertheless, early reports on the outcome of light therapy were able to demonstrate treatment efficacy

using the standard HRSD (e.g., Rosenthal et al., 1984a; Wirz-Justice et al., 1986). Supplementary items were subsequently developed for the HRSD to provide a more representative and valid measurement tool (Rosenthal et al., 1987a). A structured interview to elicit the symptoms measured by the HRSD for SAD more reliably was then developed (Structured Interview Guide for the Hamilton Depression Rating Scale, SAD version; SIGH-SAD [Williams et al., 1988]). The SIGH-SAD combines the 21 Hamilton Scale questions with an additional eight items for the “atypical” symptoms. The new scale thus benefits from the established validity, reliability, and wide acceptance of the Hamilton scale and has excellent face validity and reliability (Terman et al., 1998). Evidence of the validity of the SIGH-SAD is also indirectly provided by a substantial number of treatment studies. Studies using a wide range of treatment modalities have demonstrated that the SIGH-SAD is a sensitive instrument for detecting clinical change in patients with SAD (e.g., Lam et al., 1995; Schlager, 1994; Teicher et al., 1995; Terman et al., 1996). Furthermore, scores on the supplementary items of the instrument may be associated with light therapy treatment outcome – thus providing evidence of predictive validity (e.g., Nagayama et al., 1991; Terman et al., 1996). There also exists a self-report version of the SIGH-SAD (Terman et al., 1994). However, there are few data regarding reliability and validity of this version of the scale.

One of the most widely used self-rating instruments for depression is the Beck Depression Inventory (Beck and Steer, 1987). Although most psychiatric investigators have relied more heavily on observer-rated measures of depression, there may be significant advantages in using self-rating instruments in some contexts (e.g., time savings, ease of obtaining frequent assessments in long-term studies, ease of comparing results between study centres). The original BDI does not contain items reflecting atypical symptoms of depression. One group of investigators developed an “addendum” to the BDI (BDI-add) consisting of five items reflecting the atypical symptoms of SAD (Meesters and Jansen, 1993). Their report indicated a high correlation ($r = 0.67$) between BDI-add scores and the atypical items from the SIGH-SAD in a group of 76 SAD patients. No follow-up reports on this instrument were identified. However, Beck and colleagues (1996) developed a newer version of the BDI (BDI-II), which also includes items measuring reverse symptoms. Several reports have indicated that the new version is both reliable and valid (Steer and Clark, 1997; Steer et al., 1997).

Is SAD distinct from other mood/affective disorders?

A number of conditions need to be considered in the differential diagnosis of SAD. Much of this differential diagnosis is similar to that of major depressive disorder in general. SAD shares features with other mood/affective disorders. In particular, it has been observed that the reverse vegetative features seen in SAD resemble atypical depression and that SAD patients are slightly more likely to have bipolar illnesses as compared with nonseasonal depressed patients. These two issues will be considered in more detail below.

(1) Is SAD distinct from depression with “atypical features”?

The symptom pattern in depression with “atypical features” as described in DSM-IV includes mood reactivity plus at least two of the following four symptoms: weight gain/increased appetite, hypersomnia, leaden paralysis, and long-standing rejection sensitivity. DSM-IV also notes that reverse vegetative symptoms are more common in major depression occurring in a seasonal pattern (see prior section for review). Given the overlapping symptom picture of SAD/SP and atypical depression, the ability to distinguish between depression with atypical features and seasonal depression is important in establishing the validity of SAD.

Three papers addressing the distinction between these two forms of major depression were identified. First, Stewart and colleagues (1990) conducted a comparison of light therapy responsiveness in SAD patients versus patients with nonseasonal atypical depression. They found that bright artificial light was significantly less effective in treating eight patients with atypical depression than 25 SAD patients. However, significant weaknesses of the trial included the smaller group of atypicals, the exclusion of “seasonal” atypicals, and the use of raters who were not blind to patient diagnosis. Second, Pande and colleagues (1992) examined whether patients with atypical depression demonstrated a seasonal pattern in their mood-related symptoms and went on to compare those patients with and those without seasonal features. They observed that over half of their atypical depression patients had high seasonality scores (19 of 30 patients had SPAQ scores > 10). However, seasonal atypical depression patients did not differ from nonseasonal patients on a variety of demographic and symptom measures. A significant weakness of the study was the failure to include a control or comparison group in the design. Nevertheless, the findings of the report did not support a clear distinction between atypical and seasonal

depression. And third, a study examining the prevalence of a wide range of atypical symptoms in patients with SAD and nonseasonal major depressive disorder was reported by a group of Canadian investigators (Tam et al., 1997). As expected, increased appetite and hypersomnia were significantly more frequent in the seasonal group. Mood reactivity and leaden paralysis did not differ between groups, whereas rejection sensitivity was significantly more frequent in the nonseasonal depression group. Only 26% of the 53 SAD patients also met criteria for DSM-IV atypical depression. These results suggested that the overlapping features of SAD and atypical depression are limited to reverse vegetative symptoms and do not include the entire set of criteria for atypical depression. Other investigators, however, have reported that up to 93% of patients with SAD meet criteria for atypical depression (Terman and Stewart, 1993).

(2) Do SAD patients frequently have bipolar illnesses?

One of the most variable features of patients with seasonal depression in the published literature has been the reported frequency of bipolar mood disorders. Three groups of investigators in particular reported a high frequency of bipolar II disorder (i.e., spring/summer hypomania) in their case series, ranging from 51% to 83% (Rosenthal et al., 1984a; Rosenthal and Wehr, 1987; Thompson and Isaacs, 1988; Wirz-Justice et al., 1986). These reports also indicated a high frequency of bipolar I disorder (spring/summer mania), ranging from 6% (Rosenthal et al., 1987) to 20% (Thompson and Isaacs, 1988). In contrast, the majority of published studies indicates a substantial predominance of unipolar disorders (Allen et al., 1993; Lam et al., 1989; Lam et al., 1997b; Lingjaerde and Reichborn-Kjennerud, 1993c; Sakamoto et al., 1995; Takahashi et al., 1991; Thalen, et al., 1995; Wehr et al., 1991; White et al., 1990; Yerevanian et al., 1986); moreover, estimates of the frequency of bipolar disorders (bipolar I and II combined) have been as low as 8% (White et al., 1990). Comparisons of winter SAD patients with nonseasonal depressed groups (Garvey et al., 1988; Thalen et al., 1995a) and summer seasonal depressed groups (Wehr et al., 1991) have failed to demonstrate an elevated frequency of bipolarity in winter SAD.

Studies reporting a high frequency of bipolar disorders have generally applied the Research Diagnostic Criteria (RDC). The RDC are consid-

ered rather lenient in the diagnosis of hypomania (i.e., allowing the diagnosis during a period of improved social or professional functioning) (Blehar and Lewy, 1990). Investigators who previously reported high rates of bipolarity now recognize lower rates using the more stringent DSM criteria (Rosenthal NE, Wirz-Justice A, personal communications, 1998). Better instruments are also now available to diagnose hypomania and hyperthymic states, such as the Hypomania Interview Guide (including Hyperthymia) for Seasonal Affective Disorder (HIGH-SAD) (Goel et al., 1999).

What is the differential diagnosis for SAD?

Clinicians need to consider a variety of conditions in the differential diagnosis of SAD. As with other affective illnesses, primary medical conditions (e.g., hypothyroidism) need to be ruled out. Nonseasonal mood disorders, of course, may also present with depression in the fall or winter; in fact, some patients with chronic depression (dysthymia or chronic major depression) experience winter worsening of their symptoms (Danilenko and Putilov, 1996). A significant number of patients with winter depression experience elated mood phases in the spring or summer. A longitudinal history is therefore necessary to identify those SAD patients with bipolar I or II disorders (the presence of a bipolar diagnosis has important treatment implications – e.g., the role of mood-stabilizer medications; see section on treatment). Seasonally recurrent psychosocial stressors (e.g., fall/winter unemployment, anniversary grief reactions during the fall or winter) may produce symptoms that mimic SAD. Some people experience marked changes in sleep, appetite, weight, and energy during the winter but do not meet criteria for a major depressive episode – such patients are generally considered to have “subsyndromal” SAD. Preliminary reports suggest that such patients may also have a good response to light therapy (Kasper et al., 1988, 1989a). Finally, a number of reports have indicated that conditions other than major mood disorders may be subject to significant seasonal influences. These conditions include eating disorders (Brewerton et al., 1994; Lam et al., 1996a; Levitan et al., 1996), premenstrual syndrome (Maskall et al., 1997), anxiety-panic disorders (Marriott et al., 1994), obsessive compulsive disorder (Yoney et al., 1991), and posttraumatic stress disorder (Solt et al., 1996).

Conclusions: Diagnosis of Seasonal Affective Disorder (SAD)

- (1) The DSM-IV criteria for recurrent major depressive disorder, seasonal pattern (equivalent to SAD), are appropriate for use in clinical settings.
 - (2) The DSM-IV criteria specifying that seasonal major depressive episodes occurred in the past two (consecutive) years and that nonseasonal major depressive episodes did not occur in the past two years should be used with discretion. For example, a patient who has had winter depressions for five of the preceding six years – but not the past year – could reasonably be considered to have a seasonal pattern.
 - (3) A time period of two months is sufficient to define a “full remission” for the diagnosis of seasonal pattern.
 - (4) The atypical or reverse vegetative symptoms of depression are commonly found in SAD. However, the diagnostic criteria for SAD are based on identifying a specific pattern of depressive episodes and not on specific symptomatic features of the depressive episodes.
 - (5) At least one-third of patients with SAD continue to have seasonal episodes of depression and are therefore likely to require ongoing intervention.
 - (6) The Seasonal Pattern Assessment Questionnaire is an appropriate *screening* instrument for SAD but is not adequate for the diagnosis of SAD.
 - (7) Most patients with SAD have a unipolar depressive disorder, but seasonal patterns can also occur in bipolar disorder.
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Part 2: Epidemiology**What is the prevalence of SAD?**

There have been more than 25 community-based investigations of the epidemiology of seasonal depression or SAD. These studies have significant differences in the method of sampling and diagnostic approach. Most of these studies have focused specifically on seasonal change in symptoms of SAD, without necessarily making a clear diagnosis of major depression. Almost all these studies have employed the Seasonal Pattern Assessment Questionnaire (SPAQ; Rosenthal et al., 1987d) to

estimate the prevalence of SAD. Most studies have been completed in North America (Blazer et al., 1998; Booker et al., 1992; Carskadon and Acebo, 1993; Dam et al., 1998; Hegde and Woodson, 1996; Kasper et al., 1989b; Magnusson and Axelsson 1993; Potkin et al., 1986; Rosen et al., 1990; Schlager et al., 1993; Swedo et al., 1995; Terman, 1988; Williams and Schmidt, 1993). A smaller number have been undertaken in Europe (Blacker et al., 1997; Haggag et al., 1990; Lingjaerde and Reichborn-Kjennerud, 1993; Magnusson and Stefansson, 1993; Mersch et al., 1995; Murase et al., 1995; Partonen et al., 1993b; Wicki et al., 1992) and Asia/Australia (Ito et al., 1992; Morrissey et al., 1996; Okawa et al., 1996; Ozaki et al., 1995a; Partonen et al., 1993b; Suhail and Cochrane, 1997).

Community-based surveys in North America have reported the prevalence of SAD between 0.7% and 9.7%, with some evidence that prevalence increases with higher latitude (i.e., more northern in the northern hemisphere). European community-based studies that have used the SPAQ estimate prevalence at 1.3% to 3% of the population, and studies in Asia report rates of 0% to 0.9%. The discrepancies in these findings may be attributable to different designs, methods of distribution, sociocultural issues, and possibly latitude. In addition, the time of year that the survey is conducted influences estimates of lifetime prevalence of SAD using the SPAQ; in one study, mean depression ratings were 46% higher in those respondents interviewed in December as compared with respondents interviewed in July (Mersch, 1995). Most importantly, most studies report crude prevalence rates without standardization for the gender or age distribution of the population sample.

The most serious limitation of many of the studies to date, however, is probably the use of the SPAQ as a diagnostic instrument. The SPAQ was developed as a screening questionnaire designed to detect SAD in clinical populations (Kasper et al., 1989b). The positive predictive capacity of the SPAQ has been reported as less than 50% in both a clinical sample (Raheja et al., 1996) and a community sample (Magnusson, 1996; Mersch et al., 1995). The reduced ability to detect the presence of the disorder may be due to several factors:

- (1) The SPAQ includes only four symptoms (appetite/weight, mood, sleep, energy) of the nine symptoms required to make a DSM-III-R or DSM-IV diagnosis of major depressive disorder.

- (2) The SPAQ does not directly assess impaired function that may result from each of these symptoms.
- (3) The SPAQ does not distinguish symptoms that might result from medical or physical conditions or drugs.
- (4) The SPAQ does not determine the number of major depressive episodes that the individual may have experienced in the past, nor their relationship to one another or to the seasons. For a diagnosis of SAD, DSM-III-R requires that three such episodes have occurred, two in consecutive years, and the DSM-IV requires two episodes in the past two years.
- (5) The SPAQ does not determine whether episodes were followed by complete remissions.
- (6) The month(s) in which mood is “best” or “worst” is(are) reported, but not when mood may be “depressed” or “high” or “normal.” Therefore, hypomanic or manic episodes cannot be detected, and bipolar disorders cannot be diagnosed.

Overall, the SPAQ gives insufficient data for diagnosis and for adequate epidemiological conclusions. A more appropriate estimate of prevalence would result from determining both the presence of major depression and the seasonality of such a disorder, with sampling equally across the seasons. Three such studies have been completed to date, and they are reviewed below.

Levitt et al. (1995, 1997) and Blazer et al. (1998) have studied the prevalence of the seasonal subtype of major depression in the community using structured diagnostic instruments, with added sections to determine the seasonality of the major depression episodes. Levitt et al. (1995), using a validated and structured telephone interview based on the Composite International Diagnostic Interview (CIDI), found that the lifetime prevalence of SAD (DSM-III-R defined) in the city of Toronto, Canada, was 2.2%. In a subsequent study, they used the same instrument to sample across the province of Ontario, Canada, and found that the prevalence of SAD was 1.7% (Levitt et al., 1997).

Blazer et al. (1998) used data from the CIDI collected during the US National Comorbidity Survey to derive a diagnosis of SAD. Table 4 demonstrates how prevalence estimates from that study change according to the use of successively more stringent diagnostic criteria. Note that this study used the DSM-III-R criterion that requires a 60-day “window”

for onset and remission of the seasonal depressive episodes. This criterion was widely thought to be overly restrictive and was dropped from the DSM-IV criteria for seasonal pattern.

What is the female-to-male ratio in people with SAD?

Virtually all studies to date have demonstrated a female preponderance in this condition. Only one study (Blazer et al., 1998) reports that men are more likely than women to suffer from SAD. In some clinical samples, the ratio of females to males is close to 4 to 1; however, when all community studies are taken together, the female-to-male ratio is about 1.6 to 1.

What is the prevalence of SAD with respect to age?

Most studies to date report increasing prevalence of SAD from teen years through the mid-50s and then a decline in rates in the elderly. Blazer et al. (1998), in contrast, is the only study to find that prevalence continued to increase with increasing age. This observation may be related to the fact that the investigators only included subjects between 15 and 54

Table 4

Lifetime prevalence estimates of DSM-III-R major depression with a seasonal pattern, using successively more strict criteria

Successive criteria	Number with criteria	% of total sample (8,098)
Onset of depressive symptoms occur at same time of year	248	3.1
Remission of depressive symptoms occur at same time of year	145	1.8
≥ three episodes start within same three-month period	105	1.3
≥ three episodes end within same three-month period	64	0.8
≥ 66% of episodes show seasonal pattern	22	0.3

Source: Blazer DG, Kessler RC, Swartz MS. Epidemiology of recurrent major and minor depression with a seasonal pattern: the National Comorbidity Survey. *Br J Psychiatry* 1998; 172:164-7.

years of age. Other studies found that prevalence declines sharply in older subjects. For example, Levitt et al. (1995, 1997) reported a significant decline in prevalence after age 60. Since Blazer and colleagues did not include anyone over 54, they may not have observed the expected decline in rates.

What is the effect of time of year of interview on prevalence?

The season of interview affects prevalence estimates for a lifetime diagnosis of seasonal depression. In the Levitt et al. (1995) study, lifetime estimates for SPAQ-defined SAD were significantly higher for subjects interviewed in the winter as compared with subjects interviewed in the summer. Other investigators have also found an increase in prevalence estimates for subjects interviewed in the autumn as compared with subjects interviewed in the summer.

Does latitude influence the prevalence estimate of SAD?

One US study examined the prevalence of SAD, based on SPAQ criteria, in middle-aged subjects in four cities from Florida to New Hampshire and found that the rate of SAD increased with more northern latitude (Rosen et al., 1990). In a Canadian study, a population in the province of Ontario was sampled, using a telephone interview, equally across eight degrees of latitude (Levitt et al., 1997). In contrast to the US study, there was no significant effect of latitude on prevalence of SAD using SPAQ or DSM-III-R diagnostic criteria. In fact, there was a significant negative correlation between overall seasonality of depressive symptoms and latitude: that is, as latitude increased, the seasonality of depressive symptoms among the general population decreased. Blazer et al. (1998) also failed to show an impact of latitude on prevalence of SAD.

What is the impact of other demographic variables on prevalence of SAD?

There is controversy regarding the roles of various “risk factors” for SAD. Blazer et al. (1998) reported that SAD subjects tend to be more educated and that subsyndromal SAD subjects tend to have higher incomes than subjects without the condition. They also found a higher risk of SAD in rural compared to urban settings. These findings remain to be confirmed in other surveys and in other regions of the world.

Conclusions: Epidemiology of Seasonal Affective Disorder (SAD)

- (1) The prevalence of SAD by DSM-III-R or DSM-IV criteria is between 1.7% and 2.2% in Canada and between 0.8% and 2.2% in North America.
 - (2) In the most comparable studies in Asia, the prevalence may be less than 1%, and in Europe the prevalence may be 1% to 3%.
 - (3) Women outnumber men with the disorder 1.6 to 1.
 - (4) The prevalence of SAD increases with age until the mid-50s and is uncommon in older age groups.
 - (5) Subjects are more likely to recall lifetime winter difficulties when they are interviewed in the winter.
 - (6) The prevalence of SAD may increase with higher latitude, but this effect needs further study to confirm results.
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Part 3: Etiology and Pathophysiology

Is SAD simply due to decreased light?

The superficial similarity of the SAD syndrome to the process of hibernation in animals has led to the speculation that SAD may reflect an exaggerated response to seasonal changes in the day-and-night cycle. Early work with animals demonstrated that seasonal rhythms are cued to length of day or photoperiod (Aschoff, 1984). Pittendrigh (1989) suggested that animals use length of day as a cue to season via innate pace-making systems entrained to the external cycle, which in the daily case is the cycle of light and dark. According to this model, animals use the duration of nighttime darkness as a signal of seasonally appropriate behaviours. For example, hibernation is initiated by the photoperiod signal of longer nights that mark the approach of winter.

Consistent with a photoperiod hypothesis, several studies have found a relationship between prevalence rates of SAD and latitude (see section on epidemiology). In England, Suhail and Cochrane (1997) used the SPAQ to compare seasonality in indigenous white and nonindigenous Asian populations and found that, among the environmental and psychosocial factors examined, hours of daylight was the best predictor of seasonal variations in mood. Oren et al. (1994c) used light monitors

worn by SAD patients and controls to examine the relationship between ambient light and depression. Among patients, severity of depression was inversely related to photoperiod, and a trend indicated a correlation between severity of depression and a later onset of morning light exposure.

To further explore the possible role of photoperiod in SAD, Young et al. (1997) examined the relative contribution of photoperiod, mean daily temperature, and hours of daily sunshine to the onset of SAD. Based on a pooled sample of 387 subjects, they report a relationship between decreased photoperiod and risk of onset, regardless of whether the decreased photoperiod is determined by latitude or calendar date. In a second study of 190 subjects, none of the climatic factors accounted for the onset of SAD, but photoperiod again correlated highly with risk of onset. The use of interviews rather than self-report surveys, the large numbers of subjects, and the study design make these findings more valid than many past studies. These results offer strong support in favour of the photoperiod hypothesis.

Other authors have reported findings that do not support a photoperiod model of SAD. For example, prevalence studies have not always shown an increase with higher latitude (see section on epidemiology). Also, the effectiveness of bright-light exposure is not limited to “extending” the photoperiod. Finally, studies that monitor light exposure have not found any differences between SAD patients and normal subjects in winter (Eastman, 1990a; Graw et al., in press), although SAD patients spend more time outdoors in the summer (Graw et al., in press). Similarly, no differences in total light exposure were found in people with and without subsyndromal SAD (Guillemette et al., 1998).

What is the role of melatonin in SAD?

Given the importance of melatonin in the entrainment of biological rhythms in animals, researchers have examined the possible role of abnormal melatonin secretion in SAD. This work has been based on the observation that exposure to bright light suppresses nocturnal pineal melatonin secretion (Lewy et al., 1980; Terman et al., 1987, 1988). Studies in SAD have focused on melatonin levels and on the pattern of melatonin secretion as an indicator of circadian phase.

Partonen et al. (1996, 1997) found no differences in melatonin levels between SAD patients and controls, both before and after light treatment.

They also noted that response to light was not associated with changes in melatonin levels. The antidepressant effects of light treatment are also not dependent on nocturnal melatonin suppression (Rosenthal et al., 1986b). Conversely, Danilenko et al. (1994) reported differences in melatonin levels in untreated depressed SAD patients compared with controls. They also found that light treatment resulted in a phase advance of melatonin rhythms in SAD, a finding that has been observed by other researchers (Dahl et al., 1993). However, Checkley et al. (1993) examined 24-hour melatonin rhythms in SAD patients and controls and found no significant differences between the two groups. A phase advance in the timing of nocturnal melatonin secretion in SAD has not been shown to differentiate between responders and nonresponders to light treatment (Rice et al., 1995). The timing of melatonin secretion also does not predict whether SAD patients respond to morning or evening light (Wirz-Justice et al., 1993).

Several investigators have examined the role of melatonin in the treatment of SAD. Rosenthal et al. (1988a) compared the effects of a placebo and atenolol, a beta-adrenergic blocker that inhibits melatonin secretion, in a double-blind crossover study. They found no therapeutic difference between atenolol and placebo, a finding that goes against a melatonin hypothesis. However, Schlager (1994) attempted to truncate the morning melatonin secretion curve (in a manner similar to bright light) by giving a short-acting beta blocker, propranolol. He successfully treated patients using open-label propranolol; during a double-blind placebo-substitution phase, only the patients switched to placebo relapsed. In another approach using melatonin as potential treatment, neither nighttime administration (to increase amplitude and thus zeitgeber strength) nor morning administration (to elongate the melatonin duration of secretion and/or to phase delay) had any effect on SAD symptoms (Wirz-Justice et al., 1990). In contrast, Lewy et al. (1998a) reported a study showing beneficial effects of low-dose melatonin timed during the afternoon to provide a corrective circadian phase advance. These findings suggest that any abnormalities of melatonin in SAD reflect changes in circadian phase – that is, a circadian phase shift hypothesis – rather than directly implicating melatonin levels.

What is the role of circadian rhythm disturbance in SAD?

An internal pacemaker that matches internal rhythms to the 24-hour

day drives circadian (daily) rhythms. “Phase shifting” (Aschoff, 1984) refers to advancing rhythms (the internal cycle shifts to an earlier clock time) or delaying rhythms (the internal cycle shifts to a later clock time) and can be done reliably with exposure to bright light. The direction and magnitude of phase shifting depends on when the bright light occurs within the circadian cycle.

Given some of the melatonin results in SAD, and that bright light clearly has effects on the circadian system, there has been much interest in a circadian rhythm hypothesis for SAD. The phase shift hypothesis (Lewy et al., 1986) postulates that the therapeutic effect of light in SAD is due to a corrective phase shifting of delayed endogenous circadian rhythms. In a phase shift hypothesis, exposure to bright light must be timed appropriately within the circadian cycle to correct a specific phase shift. For example, morning exposure to bright light should correct a phase-delayed circadian rhythm, whereas evening light exposure should worsen those rhythms.

Several studies, including Lewy et al. (1987a), Sack et al. (1990), Dahl et al. (1993), Endo et al. (1993), and Avery et al. (1997), have found that SAD patients have a phase delay in circadian rhythms correctable by morning bright-light treatment. Teicher et al. (1997) demonstrated that circadian rhythms are not only phase delayed in SAD but also poorly entrained (synchronized) to the 24-hour day. Thompson et al. (1997) speculated that the instability of circadian rhythms in SAD is due not to a fixed phase abnormality but to a high-amplitude phase-response curve. Glod et al. (1997) examined children with SAD and found evidence of dysregulated circadian rhythms in this population. Interestingly, children with SAD were found to have blunted circadian rhythms, whereas adults have been shown to demonstrate delayed and poorly entrained rhythms. The circadian time of morning light exposure has been shown to have a significant effect on the magnitude of the antidepressant response to light therapy (Terman, 1998). Finally, three recent large-sample studies found that morning light exposure was superior to evening light exposure (Eastman et al., 1998; Lewy et al., 1998b; Terman et al., 1998) and that the morning light caused phase advances in circadian rhythms whereas the evening light caused phase delays (Lewy et al., 1998b).

While these observations have lent strong support to the phase shift hypothesis, contrary evidence has also been reported. The effectiveness of light therapy may not depend solely on morning timing (e.g., Lee et

al., 1997a; Wehr et al., 1986; Wirz-Justice et al., 1993) or on the initial circadian phase of a patient (Wirz-Justice et al., 1993). Several studies have not found abnormalities of phase or circadian rhythms in SAD (Eastman et al., 1993; Oren et al., 1996; Rosenthal et al., 1990). In the studies reporting phase-delayed circadian rhythms, not all SAD patients had phase delays, and there were no clear relationships between individual improvement and the circadian effects induced by light. These findings argue against a circadian phase delay hypothesis as the sole factor in the etiology of SAD and against the necessity of a phase advance by morning light for treatment efficacy.

Is the eye involved in the etiology of SAD?

Research on the role of the visual system in SAD was stimulated by the finding that the antidepressant effects of light are greater with exposure to the eyes than to the skin (Wehr et al., 1987b). Additionally, there is a direct neural pathway, the retinohypothalamic tract, that leads from the retina to the suprachiasmatic nucleus (SCN) of the hypothalamus. The SCN functions as the circadian pacemaker in humans, and the circadian effects of light appear mediated via the retinohypothalamic tract. Therefore, it is possible that the light signal may be attenuated at the level of the eye or retina.

In a study using electrooculography (EOG) to measure retinal light responses, Lam et al. (1991a) found significantly lower EOG ratios in SAD patients than in normal controls. These results were replicated by Ozaki et al. (1993), who found low EOG ratios in SAD patients both before and after light treatment and during the summer. Lam et al. (1992a) also described lower b-wave amplitude on another measure of retinal light sensitivity, flash electroretinography, in female SAD patients, with normalization of results after light therapy (Tam et al., 1998). These findings point to a possible abnormality in SAD at the level of the retina. Stojek (1991) tested intraocular pressure (IOP) in depressed SAD patients, finding significantly lower IOP in female SAD subjects than in controls. Other retinal mechanisms have been explored in SAD (Ozaki et al., 1995b), but large intersubject variability and low subject numbers limit the validity of such findings. Another negative study was reported by Oren et al. (1993), who found no ophthalmic changes in SAD patients on measures of retinal dark adaptation, intraocular pupillary size, colour vision, and pattern electroretinography.

Which neurotransmitters contribute to SAD?

(1) Serotonin

Many researchers have examined a possible role for the neurotransmitter serotonin (5-hydroxytryptamine, or 5-HT) in the etiology/pathophysiology of SAD. Animal studies and human postmortem studies have demonstrated clear seasonal changes in serotonin metabolism (Brewerton et al., 1988; Carlsson et al., 1980; Lacoste and Wirz-Justice, 1989), with the overall evidence pointing to decreased serotonergic metabolism in the winter period. Serotonergic agents working via different mechanisms to enhance serotonin neurotransmission, including d-fenfluramine (O'Rourke et al., 1987), l-tryptophan (Ghadirian et al., 1998; Lam et al., 1997a; McGrath et al., 1990), and selective serotonin reuptake inhibitors (Lam et al., 1995; Moscovitch et al., 1995), have been found to be effective in the treatment of SAD. Additionally, rapid depletion of the serotonin precursor, tryptophan, can reverse the antidepressant effect of light therapy in SAD (Lam et al., 1996b; Neumeister et al., 1997a, 1998a). Patients with SAD report increased activation following high carbohydrate meals, whereas normal controls feel more sedated (Rosenthal et al., 1989b). This finding may be consistent with altered tryptophan and serotonin metabolism in the SAD population, since dietary carbohydrates are believed to enhance serotonin synthesis and transmission via increased tryptophan uptake into the brain (Wurtman and Fernstrom, 1976; Wurtman et al., 1989).

There is significant evidence for abnormal neuroendocrine responses to a variety of serotonergic agents in SAD. Abnormal responses to the nonselective serotonergic agonists 5-hydroxytryptophan (Jacobsen et al., 1987a) and d,l-fenfluramine (Coiro et al., 1993) have been reported, although one study with d,l-fenfluramine was negative (Yatham and Michalon, 1995). The postsynaptic 5-HT_{1C} agonist m-chlorophenylpiperazine (m-CPP) has been found to produce abnormal hormonal and mood responses in SAD patients compared to controls (Garcia-Borreguero et al., 1995; Jacobsen et al., 1994; Joseph-Vanderpool et al., 1993; Levitan et al., 1998a; Schwartz et al., 1997b). Blunted growth hormone responses to the 5-HT_{1D} receptor agonist sumatriptan have also been reported (Yatham et al., 1997).

Taken as a whole, these various lines of evidence point to a significant role for serotonin in the pathophysiology of SAD, with both presynaptic and postsynaptic mechanisms likely involved.

(2) Dopamine and Noradrenaline

Dopamine and noradrenaline dysregulation has also been postulated to play a role in SAD. The evidence for noradrenaline is less robust. Rosenthal et al. (1987c) found blunted plasma noradrenaline responses to an orthostatic challenge, and Anderson et al. (1992) found decreased levels of urinary noradrenaline and metabolites after light therapy. Other studies, however, have not found noradrenaline abnormalities in cerebrospinal fluid or plasma (Rudorfer et al., 1993).

As for dopamine, measures of prolactin have typically been used as a measure of dopaminergic function, and authors have interpreted observed prolactin abnormalities as evidence of dopamine deficiency (Jimerson, 1984). Several studies have found that plasma prolactin is decreased in SAD patients (Depue et al., 1989, 1990; Oren et al., 1996). This decrease is evident across seasons and is unaffected by light therapy, suggesting that it may be a trait marker for the disorder. Additional evidence in favour of dopamine dysfunction has been supplied by studies that examine thermoregulatory heat loss. Arbisi et al. (1989, 1994) found that thermoregulatory heat loss in SAD patients was blunted in the winter, compared to controls, and similar to controls after light therapy and in the euthymic state. They postulate that light and summer may facilitate central dopamine functioning and normalize thermoregulatory heat loss in depressed SAD patients. Neumeister et al. (1998b) reported on a study in which SAD patients in remission with light therapy underwent both catecholamine depletion and tryptophan depletion. Both techniques reversed the antidepressant effect of light therapy, suggesting that light acts through effects on both serotonin and catecholamines (dopamine and/or noradrenaline). A dopaminergic mechanism has also been suggested to explain the reduced eye-blink findings in SAD (Barbato et al., 1993; Depue et al., 1989) and the alterations in the b-wave on electroretinography (Lam et al., 1992a). Contrary to the dopamine hypothesis, Oren et al. (1994b) did not find any therapeutic effect of l-dopa+carbidopa over placebo. There is also some evidence, however, that dopaminergic abnormalities (and response to dopaminergic drugs) may be limited to premenopausal women (Tam et al., 1998).

Are there genetic vulnerability or protective factors in SAD?

There is emerging evidence that one or more genetic factors establish

vulnerability to or protection from seasonality and SAD. Magnusson and Axelsson (1993) and Magnusson and Stefansson (1993) found that the prevalence of SAD was significantly lower among Icelanders and their descendants living in North America than among Americans living on the east coast of the United States. They suggest that a genetic adaptation in Icelandic populations may establish increased tolerance to winter darkness. Madden et al. (1996) surveyed 4,639 Australian twins to examine the relative contributions of genetic and environmental factors to the development of seasonal symptoms. Genetic effects were found to account for at least 29% of the variance in seasonality based on the Seasonal Pattern Assessment Questionnaire (SPAQ). Jang et al. (1997a) used the SPAQ in 339 Canadian twin pairs and found that genetics accounted for 69% of the variance in Global Seasonality Score (GSS) in males and 45% in females.

Genetic association studies of SAD have begun to emerge. Rosenthal et al. (1998) reported an association between the short allele of the serotonin transporter gene and the trait of seasonality. Levitan et al. (1998c) found a preliminary association between tryptophan hydroxylase polymorphism, increased eating behaviour, and SAD in a small sample with family-based controls. Ozaki et al. (1996) reported a lack of association between two naturally occurring amino acid polymorphisms of the serotonin 5-HT_{2A} gene and the expression of SAD.

What are the hormonal and metabolic changes in SAD?

Overactivity of the hypothalamic-pituitary-adrenal (HPA) axis has been well documented in nonseasonal unipolar depression (Chrousos and Gold, 1992), but few studies of HPA-axis activity in SAD have been conducted. James et al. (1986) found that, unlike patients with melancholia, SAD patients have robust cortisol suppression following oral dexamethasone. Joseph-Vanderpool et al. (1991) found significantly delayed and reduced ACTH and cortisol responses to corticotrophin-releasing hormone (CRH) in SAD patients compared to controls, despite normal baseline plasma cortisol levels. These findings returned to control values after treatment with light therapy. The symptoms of fatigue were interpreted as indicating deficient activity of the arousal-producing CRH system in SAD. Schwartz et al. (1997a) examined pituitary volume to determine whether changes in size would be found as in nonseasonal depression. Using magnetic resonance imaging of the pituitary gland,

they found that neither SAD nor a change in the seasons is associated with pituitary size.

Bauer et al. (1993b) found no difference in thyroid function between SAD patients and controls. Lingjaerde et al. (1995) examined T3, Free T4, and TSH and found no correlation between the severity of winter depression and levels of these hormones. Furthermore, most patients were found to have hormonal levels well within the normal reference ranges. On the other hand, when Coiro et al. (1994) examined the nocturnal TSH surge and TSH response to thyroid releasing hormone (TRH), they found that euthymic and depressed SAD patients did not show the normal nocturnal surge compared to controls. In addition, the mean peak response of TSH to TRH was lower in patients, regardless of season. Raitiere (1992) also reported low TSH responses and lack of nocturnal surge, providing further evidence of thyroid dysfunction in SAD.

Since many of the winter symptoms of SAD could be construed as having an energy-conserving function, Rosenthal et al. (1987b) hypothesized that resting metabolic rate (RMR) might be reduced in SAD. Interestingly, Gaist et al. (1990) found significantly higher RMRs in SAD patients than in controls, which were normalized after light treatment. This finding was replicated in another report, and SAD patients were found to have accelerated postglucose glycemia (Krauchi et al., 1999). These findings go against a simple hibernating model of SAD.

Other authors have postulated that vitamin abnormalities may contribute to SAD. Oren et al. (1994a) assessed vitamin D3 levels in SAD patients and found no differences versus controls. They also examined the efficacy of vitamin B₁₂ in a randomized controlled trial and found that it was not effective in the short-term treatment of depression in SAD (Oren et al., 1994b).

Are there psychological and/or personality factors associated with SAD?

While it is generally thought that biological changes triggered by decreased environmental light underlie the symptoms of SAD, research to date has not conclusively ruled out a role for psychological mechanisms in the onset and treatment of this disorder (Eastman, 1990b). By exposing subjects to symbolic light, Bouhuys et al. (1994) found altered cognitive sensitivity to light in patients with SAD and suggested that the

observed sensitivity was a key factor in the onset of depressive episodes. O'Brien et al. (1993), using tests of attention, memory, and learning, found slow response rates in SAD subjects that reflected not only simple sensory or motor slowing but also slowed information processing. Levitan et al. (1998b) found that negative attributional style predicted poor response to pharmacotherapy in non-seasonal depression but failed to predict response to light therapy in SAD patients. Although highly preliminary, these various studies suggest that SAD patients might in fact have a unique cognitive vulnerability profile that is distinct from other subtypes of depression.

In terms of personality variables, Reichborn-Kjennerud et al. (1994) found that 23% of SAD patients met DSM diagnostic criteria for personality disorders. Although further analyses revealed that the two disorders are distinct, with independent causes, the high rate of personality disorders in SAD lends credence to a possible link between personality and seasonality. Later, Reichborn-Kjennerud and Lingjaerde (1996) examined factors that affect treatment outcome and found that temperament accounts for 25% of the variance in response rates, whereas personality disorders are generally associated with poor treatment outcome. They also demonstrated a significant association between personality disorders and the depressed and nondepressed states in SAD (Reichborn-Kjennerud and Lingjaerde, 1997).

Dimensional aspects of personality, as opposed to discrete personality disorder diagnoses, have also been described in relation to SAD and seasonality. One study compared 24 SAD patients to 17 patients with nonseasonal major depression (Schuller et al., 1993). The SAD group had lower scores on the self-criticism and dependency dimensions of the Depressive Experiences Questionnaire and significantly higher scores on three personality trait scales (schizotypal, narcissistic, and avoidant) of the Millon Clinical Multi-Axial Inventory. These findings suggest that personality characteristics of SAD patients might differentiate them from nonseasonal depressive patients. Several studies have shown that neuroticism is significantly correlated with seasonality (Murray et al., 1995), but these personality factors accounted for only 15% of the total variance in seasonality scores (Jang et al., 1997a). In contrast, using the Freiburg Personality Inventory and Giessen Test in 240 diagnosed SAD patients (tested in summer when free of symptoms), no abnormal personality variables or any correlation between personality dimensions and seasonality could be documented (Schule, 1995).

Conclusions: Etiology and Pathophysiology of Seasonal Affective Disorder (SAD)

- (1) The etiology and pathophysiology of seasonal affective disorder remains unknown. However, SAD is likely a heterogeneous condition because no one factor has accounted for the onset and course of SAD.
 - (2) The major hypotheses for SAD include phase-delayed circadian rhythms that are corrected by exposure to bright early morning light and serotonergic dysregulation that is corrected by serotonergic medications and light therapy. These hypotheses may not be mutually exclusive.
 - (3) Genetic research suggests that there are significant heritable factors for SAD and seasonality, with preliminary studies implicating serotonin candidate genes.
 - (4) Photoperiod may be involved in the onset of SAD, but it remains unclear what influence that photoperiod plays in the pathophysiology of SAD.
 - (5) Less consistent evidence has suggested abnormalities relating to reduced retinal light sensitivity, melatonin, other neurotransmitters (dopamine, noradrenaline), and other hormones (thyroid, corticotrophin-releasing hormone).
 - (6) SAD may be a psychologically distinct subtype of depression, with preliminary evidence that psychological mechanisms and/or personality factors may be important in the expression of SAD and in response to treatment.
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