Published in final edited form as:
Am J Geriatr Psychiatry. 2010 May ; 18(5): 404–412.

EFFECT OF AGE ON THE FREQUENCY OF ANXIETY DISORDERS IN MAJOR DEPRESSION WITH PSYCHOTIC FEATURES

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Abstract

Objective—To compare the frequency of anxiety disorders in older and younger persons with major depressive disorder with psychotic features.

Design—Cross-sectional.

Setting—University medical centers.

Participants—Two hundred and fifty nine persons (n= 117 aged 18–59 years and n=142 aged ≥ 60 years) with major depressive disorder with psychotic features who were enrolled in the Study of the Pharmacotherapy of Psychotic Depression (STOP-PD).

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Financial disclosures:
Dr. Flint: research support or honoraria from Janssen-Ortho, Lundbeck Canada, Pfizer Canada.
Dr. Peasley-Miklus does not have financial disclosures to report.
Mr. Papademetriou does not have financial disclosures to report.
Dr. Meyers: research support or honoraria from Forest Laboratories, Pfizer Inc., and Eli Lilly
Dr. Mulsant: research support or honoraria from AstraZeneca, Corcept, Eisai, Eli Lilly, Lundbeck, Forest, GlaxoSmithKline, Janssen, Pfizer. Dr. Mulsant owns stock of less than $10,000 in value in Akzo-Nobel, Alkermes, AstraZeneca, Biogen Idec, Ceslsion, Elan, Eli Lilly, Forest, General Electric, Orchestra Therapeutics.
Dr. Rothschild: research support or honoraria from NIMH, Cyberonics, Eli Lilly, Pfizer, Takeda, and Wyeth. Dr. Rothschild has served as a consultant for Pfizer, GlaxoSmithKline, Forest Laboratories and Eli Lilly. Dr. Rothschild has received royalties for the Rothschild Scale for Antidepressant Tachyphylaxis (RSAT)™
Dr. Whyte: research support or honoraria from Pfizer, Forest, Ortho-McNeil and research support from NIMH and NICHD/NCMRR.

Measurements—DSM-IV-defined anxiety disorders were determined by SCID interview at baseline assessment. Younger and older participants were compared on the frequencies of any current anxiety disorder and any lifetime anxiety disorder, as well as the frequencies of individual anxiety disorders.

Results—Older persons had significantly lower frequencies of any current anxiety disorder and any lifetime anxiety disorder, even after controlling for relevant demographic and clinical variables. With respect to specific anxiety disorders, older persons had significantly lower frequencies of current and lifetime panic disorder, current and lifetime social anxiety disorder, and current and lifetime posttraumatic stress disorder.

Conclusion—The findings of this study are consistent with those of community-based epidemiologic surveys, that anxiety disorders are less prevalent in older than younger adults. Because of the rigorous assessment used in STOP-PD, our findings suggest that the age-related decline in the prevalence of anxiety disorders is not simply due to a failure to detect cases in older people, as has been previously suggested.

INTRODUCTION

Epidemiologic surveys of the general population have consistently found that current and lifetime anxiety disorders are less prevalent in older than younger adults.[1–5] Reasons for this finding are unknown, but several hypotheses have been proposed. These hypotheses include age-related changes in brain neurotransmitter function, age-related psychological and/or social changes, disorder-associated mortality, and a cohort effect.[6] Some people have challenged these findings, arguing that epidemiologic surveys may underestimate the prevalence of affective disorders in older persons.[7–9] Reasons that have been proposed for the possible underestimation of prevalence include reluctance on the part of older people to acknowledge emotional and psychological symptoms, reduced sensitivity of epidemiologic survey instruments in older persons, and recall bias. [7–9]

Throughout the adult lifespan, anxiety disorders frequently co-occur with depressive disorders.[10–12] It is not known, however, whether anxiety disorders are less frequent in older, compared with younger, persons with major depressive disorder. Although the National Comorbidity Survey-Replication (NCS-R)[3] included persons aged 18 years or older, there are no published data from that study pertaining to the effect of age on the prevalence of comorbid depressive and anxiety disorders. Husain et al.[13] found that increasing age was associated with fewer symptoms consistent with generalized anxiety disorder (GAD), panic disorder, agoraphobia, social phobia, and obsessive compulsive disorder (OCD) in outpatients with major depressive disorder enrolled in this STAR*D study. Although these data are informative, and are consistent with the aforementioned epidemiologic findings, they are limited by the fact that the dependent variable was the number of items on a self-report screening questionnaire, not clinician-rated psychiatric disorders.

In view of the absence of data on the relation between age and the frequency of anxiety disorders in persons with major depression, we examined this issue in patients enrolled in the Study of the Pharmacotherapy of Psychotic Depression (STOP-PD), a multi-center randomized controlled trial (RCT) of the treatment of major depressive disorder with psychotic features.[14] The assessment of anxiety disorders in STOP-PD differed from that used in epidemiologic surveys in several important ways. First, the assessment was conducted by clinical raters, under the supervision of study coordinators and research psychiatrists, who were trained and experienced in interviewing patients with psychiatric disorders, as opposed to lay interviewers who are traditionally used in population-based epidemiologic surveys. Moreover, three of the four sites of STOP-PD are geriatric

psychiatry research centers, with many years of experience in assessing affective disorders in older adults. Second, STOP-PD used the Structured Clinical Interview for DSM-IV-TR Axis 1 Disorders (SCID) [15] to assess psychiatric disorders. The SCID is a semi-structured interview that allows more flexibility in probing for and clarifying symptoms, compared with structured instruments frequently used in epidemiologic surveys. Moreover, the SCID can take into account information obtained from collateral sources, whereas epidemiologic surveys rely solely on information provided by the respondent. Thus, the STOP-PD assessment may have been more sensitive in determining anxiety disorders, compared with epidemiologic surveys. In support of this hypothesis, separate studies found that the Composite International Diagnostic Interview (a widely used epidemiologic instrument) had sensitivity of only 55% and 66%, respectively, for any lifetime anxiety disorder and any current anxiety disorder, compared with a semi-structured diagnostic interview administered by a clinically-trained interviewer.[3,16] The argument that older persons may be less willing than younger persons to acknowledge symptoms of anxiety is less compelling in STOP-PD, given that all participants had acknowledged other affective symptoms in order to be included in the study. Finally, we examined both current and lifetime anxiety disorders in STOP-PD. Whilst recall bias could contribute to a lower estimated prevalence of lifetime disorders in older adults, it is less likely to have an effect on the reporting of current symptoms in non-demented persons.

Based on previous research on the prevalence of anxiety disorders in older adults, we hypothesized that there would be a significantly lower frequency of ‘any current anxiety disorder’ and ‘any lifetime anxiety disorder’ in older than younger persons enrolled in STOP-PD. A secondary, exploratory aim of the study was to compare the frequencies of individual anxiety disorders in younger and older STOP-PD participants. The aims of our study have heuristic importance, in that finding a lower frequency of anxiety disorders in older compared to younger STOP-PD participants would support the validity of the aforementioned epidemiologic findings and suggest that these findings are not simply an artifact. In addition, our study would be the first to extend these findings to a clinical population.

METHODS

Participants

STOP-PD is a double-blind RCT that compared the efficacy, tolerability, and safety of combined olanzapine and sertraline with combined olanzapine and placebo in younger and older persons with psychotic depression.[14] Participants were randomized to treatment at 4 sites: Cornell University, the University of Massachusetts, the University of Pittsburgh, and the University of Toronto. Participants were enrolled from psychiatry inpatient and outpatient services. Inclusion criteria were: aged 18 years or older, ability to speak English fluently, a DSM-IV diagnosis of major depressive disorder with psychotic features (delusions +/− hallucinations), a score of 21 or higher on the 17-item version of the Hamilton Depression Rating Scale (HAM-D),[17] the presence of one or more delusions as indicated by a score of 3 or higher on the delusion item of the Schedule for Affective Disorders and Schizophrenia (SADS),[18] and a score of 2 or higher on one or more of the conviction items of the Delusion Assessment Scale (DAS).[19] We excluded patients with any of the following: meeting DSM-IV criteria for current or lifetime bipolar disorder, schizoaffective disorder, schizophrenia, or other psychotic disorders; meeting DSM-IV criteria for current body dysmorphic disorder or obsessive compulsive disorder; a history of substance abuse or dependence, including alcohol, within the last 3 months; a diagnosis of dementia or history of ongoing significant cognitive impairment (from informant report) prior to the index episode of depression; unstable medical illness; medical conditions (such as hypothyroidism), metabolic abnormalities (such as folate or B12 deficiency), or

medication (such as carbidopa) that could contribute to psychopathology, confound response to pharmacotherapy, or render participants unable to tolerate or complete the study; being pregnant, planning to get pregnant, or breastfeeding a child; a documented history of being unable to tolerate either sertraline or olanzapine; failure to respond to olanzapine taken at a dose of 15 mg per day or greater for at least 4 weeks during the current depressive episode; or being sufficiently ill to require immediate open pharmacotherapy or ECT (e.g., due to imminent risk of suicide or refusal to eat). Randomization to treatment was stratified by age (18–59 years and 60 years or older), to allow for comparison between younger and older adults on outcomes of interest and clinical phenomena. Written informed consent was obtained from participants, using procedures approved by local institutional review boards, prior to the initiation of any research assessments.

Measures and Reliability

Upon enrollment, each participant was assessed with the SCID and a number of rating scales, including the 17-item HAM-D, the Mini-Mental State Examination (MMSE),[20] and the Cumulative Illness Rating Scale for Geriatrics (CIRS-G).[21] In addition, data on gender, race, marital status, years of education, and number of lifetime episodes of major depression were recorded.

The dependent variable in this current report is SCID-defined current and lifetime anxiety disorders. The SCID was administered by trained bachelor's or master's level research associates (RAs) who were experienced in assessing younger and older patients with major depressive disorder. Before RAs were allowed to assess patients for this study, they were required to view the eight SCID training tapes produced by the Biometrics Research Department of the New York State Psychiatric Institute, observe administration of the SCID by the site's study coordinator, and demonstrate competence in administering the SCID based on the observation and judgment of the site's study coordinator and principal investigator. Inter-rater reliability has been previously established for SCID anxiety disorder diagnoses, including those in older individuals.[22] Inter-rater reliability pertaining to the SCID was not specifically assessed for STOP-PD. Inter-rater reliability was, however, established on an annual basis for STOP-PD's primary outcomes of depression severity and delusional conviction; it was found to be consistently high, with intra-class correlation coefficients (ICCs) of 0.93–0.98 for the HAM-D total score and 0.69–0.84 for the conviction domain of the DAS. In addition, annually-determined ICCs for the total score of the Brief Psychiatric Rating Scale,[23] a general measure of psychopathology, were 0.84–0.93. These data suggest that raters in STOP-PD had a high level of reliability in assessing psychopathology.

Data Analyses

The primary dependent variables in these analyses were 'any current anxiety disorder' and 'any lifetime anxiety disorder'. 'Any anxiety disorder' included one or more of the following DSM-IV anxiety disorders: panic disorder with or without agoraphobia, agoraphobia without a history of panic disorder, specific phobia, social phobia, posttraumatic stress disorder (PTSD), acute stress disorder, GAD, anxiety disorder due to a general medical condition, and substance-induced anxiety disorder. The DSM-IV residual category of Anxiety Disorder Not Otherwise Specified (NOS) was not included in these analyses, because this residual category includes persons who simply have anxiety symptoms as a manifestation of the depressive episode, as opposed to a separate anxiety disorder. The exclusion of Anxiety NOS also facilitated comparison of our findings with those of epidemiologic surveys, which do not include Anxiety NOS. Given that current OCD was an exclusion for participation in STOP-PD, OCD was not included in our analyses. The SCID allows for a diagnosis of GAD only if it is currently present. In our

analyses, cases of GAD were included in estimates of both any current anxiety disorder and any lifetime anxiety disorder, since, by definition, a current disorder counts towards a lifetime disorder.

Chi-square analysis was used to compare older subjects (age 60 years or older) with younger subjects (aged 18–59 years) on the frequency of any current anxiety disorder and any lifetime anxiety disorder, respectively, as well as the frequencies of individual anxiety disorders. Odds ratios and their 95% confidence intervals were calculated.

In the general population, anxiety disorders are associated with being female, being unmarried or separated/divorced/widowed, and having a lower level of education.[3–5,24] Some, but not all, surveys have found a lower prevalence of anxiety disorders in African Americans and Hispanics, compared with whites.[2,3,25,26] In addition, cognitive function and physical status are potentially relevant to the ascertainment and interpretation, respectively, of symptoms of anxiety. Logistic regression analysis was therefore used to compare older and younger groups on the frequency of any current anxiety disorder and any lifetime anxiety disorder, after controlling for statistically significant between-group differences in these baseline variables.

All analyses were performed with two-tailed alpha set at 0.05. With respect to the analyses pertaining to individual anxiety disorders, alpha was not adjusted for multiple comparisons.

RESULTS

Three hundred and seventy five persons consented to participate in the study. Of these individuals, 65 were found not to meet criteria for unipolar major depression with psychotic features, 25 were excluded for other reasons, and 26 withdrew consent prior to randomization. Thus, 259 persons (n=117 aged 18 – 59 years and n=142 aged 60 years or older) were randomized to treatment in STOP-PD. Baseline data on the frequency of anxiety disorders were available on all randomized participants. Table 1 presents a comparison of younger and older groups on relevant demographic and clinical variables. As noted in Table 1, there were statistically significant differences between the two age groups on race, marital status, MMSE total score, and CIRS-G total score. The groups did not significantly differ on baseline HAM-D total score, baseline SADS delusion severity score, or the number of lifetime episodes of major depression. Table 2 presents a comparison of younger and older groups on any current anxiety disorder and any lifetime anxiety disorder, as well as individual current and lifetime anxiety disorders. Consistent with our hypothesis, older subjects had a significantly lower frequency than younger subjects of any current anxiety disorder and any lifetime anxiety disorder. Older subjects had a significantly lower frequency than younger subjects of current and lifetime panic disorder, current and lifetime social phobia, and current and lifetime PTSD. The two groups did not significantly differ in the frequency of current or lifetime agoraphobia without panic, specific phobia, or GAD. There were no cases of acute stress disorder, anxiety disorder due to a general medical condition, or substance-induced anxiety disorder in either age group.

Separate logistic regression analyses were performed to determine the effect of age on the frequency of any current anxiety disorder and any lifetime anxiety disorder, respectively, independent of other relevant variables that differed between the two groups. Race, marital status, MMSE total score, and CIRS-G total score were first entered into the model, followed by age group. In the first logistic regression analysis, any current anxiety disorder was significantly less frequent in the older compared with younger group (wald x^2=18.36, df=1, p<0.0001), and in the second analysis, any lifetime anxiety disorder was significantly less frequent in the older compared with younger group (wald x^2=20.92, df=1, p<0.0001),

independent of the other variables in the model. Race, marital status, MMSE total score, and CIRS-G total score were not significantly associated with any current anxiety disorder or any lifetime anxiety disorder in the final models.

DISCUSSION

The main findings of this study are that current and lifetime anxiety disorders were less frequent in older than younger persons with major depression with psychotic features. These findings were independent of age-related differences in race, marital status, cognitive function, and medical comorbidity. To our knowledge, this is the first clinical study to directly compare the frequencies of concomitant anxiety disorders in older and younger persons with major depressive disorder.

The findings of this study are consistent with the findings of community-based epidemiologic surveys, showing an age-related decline in the prevalence of both current and lifetime anxiety disorders. Our study extends these community-based findings to a clinical group of depressed adults. As noted in the introduction of this article, the assessment used in STOP-PD was potentially more sensitive in detecting anxiety disorders than the assessment typically used in surveys of the general population. We hypothesize, therefore, that the lower prevalence of DSM-IV anxiety disorders in later life is not simply explained by failure to detect these disorders.

While this study has implications for understanding age-related differences in the frequency of DSM-IV-defined anxiety disorders, it does not address the issue of the validity of DSM-IV criteria in older persons. It is possible that some manifestations of anxiety in later life are qualitatively different from the criteria used in DSM-IV.[27–29] For example, fear of falling is a common fear in older adults that can be disabling and frequently leads to avoidance of activities. Yet, in a clinical study of fear of falling, fewer than 10% of elderly people with moderate-severe fear of falling met criteria for a DSM-IV phobic disorder, even though more than 80% of these individuals curtailed activities because of the fear.[28] By way of another example, a fairly common manifestation of anxiety in late life is a cluster of symptoms characterized by anxious mood, feelings of tension, and diffuse somatic complaints. Many older persons with these symptoms, however, do not endorse chronic, multiple, uncontrollable worries, which is the core feature of DSM-IV GAD.[27] Thus, the possibility remains that older persons are as anxious as younger persons, but that anxiety is expressed in ways that are qualitatively different from the current criteria used in DSM-IV. Our study was also not able to address the related question of whether clinically significant anxiety in older persons is more likely to be expressed as subsyndromal symptoms compared with younger adults. Although the SCID allows for a subthreshold rating of individual symptoms, its diagnostic algorithm does not allow for a rating of subthreshold *disorder*. This reflects the fact that the DSM-IV classification describes disorders dichotomously, as either present or absent.

In addition to having a lower frequency of any current anxiety disorder, older participants in STOP-PD had a lower frequency of any lifetime anxiety disorder compared with younger participants. With the exception of dementia, the lifetime prevalence of psychiatric disorders in general has consistently been found to be lower in older than younger persons.[3] Recall bias is the most likely explanation for this seemingly counterintuitive finding, although a cohort effect and/or disorder-associated mortality have also been proposed as possible contributing factors. In older STOP-PD participants, the frequency of any lifetime anxiety disorder was exactly the same as that of any current anxiety disorder. In the absence of treatment, anxiety disorders tend to be persistent or recurrent conditions.[30] Thus, persistent non-remission of disorders may have contributed to the same frequency of current and

lifetime anxiety disorders in older persons. However, it is improbable that non-remission is the sole explanation for this finding, in that it is highly unlikely that not a single case of anxiety disorder resolved during an older person's lifetime. Thus, recall bias probably also contributed. It is also interesting to note, however, that there was little difference in the frequency of current and lifetime anxiety disorders in the younger group (a finding that is consistent with other studies of mid-life patients with major depression[31,32]), suggesting that similar factors (that is, non-remission of disorders and/or recall bias) were also in play in younger participants.

A secondary aim of this study was to compare the frequencies of individual anxiety disorders in younger and older participants. Older participants had significantly lower frequencies of panic disorder, social phobia, and PTSD than younger participants, which is consistent with the findings of community-based studies.[3,5,33] Community-based epidemiologic surveys have also consistently found a lower prevalence of GAD in older than younger persons, with odds ratios in the order of 0.3–0.5.[34] In our study the odds of an older person having GAD was approximately two-thirds that of a younger person, which was not statistically significant. Throughout the adult lifespan, there is frequent association between major depression and generalized anxiety disorder.[34] Epidemiologic surveys and clinical studies of older depressed persons have usually found GAD to be the most frequent concomitant anxiety disorder,[34] as was the case in STOP-PD. On the other hand, there is greater variability in the frequency of GAD, relative to other anxiety disorders, in younger depressed persons.[35] Thus, the strength of the association between GAD and major depression in later life may be one explanation for why we did not find a statistically significant difference in the frequency of GAD between younger and older persons enrolled in STOP-PD.

The frequency of any current anxiety disorder in this study is 3- to 4-fold higher in younger participants and 2- to 5-fold higher in older participants than in the general population.[4,5,11,24,36] This finding is consistent with previous research, in both younger and older adults, showing that anxiety disorders are more prevalent in depressed than non-depressed individuals, especially those seen in clinical settings.[10–12] Interestingly, the frequencies of any current anxiety disorder in younger and older STOP-PD participants were comparable to those reported in clinical studies of non-psychotic depression,[31,32,37,38] suggesting that the frequency of concurrent anxiety disorders in major depression is not influenced by the presence or absence of psychotic features. Despite the age-related decline in the frequency of anxiety disorders in this study, more than 20% of older participants met DSM-IV criteria for a current anxiety disorder. Anxiety symptoms and some anxiety disorders can adversely affect the short-term and long-term outcome of major depression.[6,34] We suggest, therefore, that clinicians carefully evaluate patients with psychotic depression for concurrent anxiety disorders, regardless of the patient's age.

This study has a number of strengths, including the direct comparison of younger and older participants, the relatively large sample size for a clinical study, and the in-depth assessment of subjects performed by well-trained and experienced clinical raters. However, there are also limitations. Given that this was a study of the treatment of delusional depression, the results cannot necessarily be generalized to non-delusional major depression. However, as previously noted, the frequencies of 'any current anxiety disorder' in both younger and older STOP-PD participants were consistent with the frequencies reported in clinical studies of non-psychotic depressed patients. Second, the findings are based on a group of patients who agreed to participate in a treatment study. Given that participants had to consent to the study before they could undergo baseline research assessments, we do not have SCID data on individuals who were screened but did not consent. Thus, it is possible that non-response bias contributed to the findings, whereby older persons with anxiety disorders were less

likely to participate in STOP-PD than their younger counterparts. The same argument can be made regarding data from random-sample community-based surveys; this is, unfortunately, an unanswerable question, since the assessment of psychopathology in these surveys obviously depends on individuals agreeing to be interviewed. However, it should be noted that the epidemiologic findings have been consistent across a number of countries and a number of decades, so non-response bias would need to be pervasive in order to adequately explain the findings. Third, given that persons with current OCD were excluded from the study, we did not examine all anxiety disorders. However, the prevalence of OCD is very low in late life,[12] including late-life depression,[37] and it is unlikely that the exclusion of this disorder had a significant impact on the results. Persons with recent alcohol abuse or dependence and/or any history of bipolar affective disorder were also excluded from the study. Some anxiety disorders have an association with alcohol use disorders and bipolar disorder.[10,24] In addition, the prevalence of alcohol abuse/dependence and bipolar disorder is higher in younger than older persons.[1,3,5] Thus, if individuals with these disorders had been included in STOP-PD, we may possibly have found an even greater difference in the frequency of anxiety disorders between younger and older participants. Finally, as previously noted, although acceptable inter-rater reliability has been previously established for SCID anxiety disorder diagnoses, inter-rater reliability of SCID diagnoses was not examined specifically for STOP-PD. Nevertheless, inter-rater reliability on other measures of psychopathology was assessed on an annual basis and was found to be consistently good.

To conclude, the findings of this clinical study are consistent with those of community-based epidemiologic surveys, that anxiety disorders are less prevalent in older than younger adults. Factors contributing to this lower prevalence require further investigation.

Acknowledgments

Supported by USPHS grants MH 62446, MH 62518, MH 62565, and MH 62624 from the National Institute of Mental Health.

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Table 1

Baseline Characteristics of Older Participants

	Young (n=117)		Old (n=142)		Analysis		
	n	**%**	**n**	**%**	**x^2**	**df**	**p**
Gender					0.0	1	1.0
Male	42	35.9	51	35.9			
Female	75	64.1	91	64.1			
Race					10.82	2	0.005
White	89	76.1	129	90.9			
Black	19	16.2	10	7.0			
Asian	9	7.7	3	2.1			
Marital					43.24	4	<0.0001
Single	46	39.3	21	14.8			
Married	42	35.9	64	45.1			
Separated	9	7.7	4	2.8			
Divorced	18	15.4	18	12.7			
Widowed	2	1.7	35	24.7			
Number of lifetime depressive episodes					0.40	3	0.94
1	36	30.8	42	29.6			
2–3	40	34.2	51	35.9			
>3	36	30.8	41	28.9			
Undetermined	5	4.3	8	5.6			
	Mean	**SD**	**Mean**	**SD**	**t**	**df**	**p**
Age	41.3	10.8	71.7	7.8	−25.48	205[a]	<0.0001
Years of education	12.9	3.2	12.2	3.6	1.66	254	0.10
HAM-D total score	29.3	5.0	30.2	5.4	−1.31	257	0.19
SADS delusion severity score	5.7	0.9	5.9	0.9	−1.79	257	0.08
CIRS-G total score	2.8	3.2	6.8	3.8	−8.91	255	<0.0001
MMSE total score	27.7	2.4	26.3	3.4	3.74	246[a]	0.0002

HAM-D: 17-item Hamilton Depression Rating Scale; SADS: Schedule for Affective Disorders and Schizophrenia; CIRS-G: Cumulative Illness Rating Scale for Geriatrics; MMSE: Mini-Mental State Examination

[a] Reflects unequal variances

Table 2

Comparison of Younger and Older Age Groups on the Frequency of Individual Anxiety Disorders and Any Anxiety Disorder [a]

	Young (n=117)		Old (n=142)		Analyses		
	n	**%**	**n**	**%**	**x^2 [df=1]**	**p**	**OR (95% CI)**
Panic Disorder							
Current	22	18.8	4	2.8	18.15	<0.0001	0.13 (0.04–0.37)
Lifetime	23	19.7	7	4.9	13.59	0.0002	0.21 (0.09–0.51)
Agoraphobia without Panic Disorder							
Current	4	3.4	4	2.8	0.08	0.78	0.82 (0.20–3.35)
Lifetime	4	3.4	4	2.8	0.08	0.78	0.82 (0.20–3.35)
Social Phobia							
Current	18	15.4	5	3.5	11.16	0.001	0.20 (0.07–0.56)
Lifetime	19	16.2	5	3.5	12.34	0.0004	0.19 (0.07–0.52)
Specific Phobia							
Current	12	10.3	8	5.6	1.92	0.17	0.52 (0.21–1.33)
Lifetime	12	10.3	8	5.6	1.92	0.17	0.52 (0.21–1.33)
Posttraumatic Stress Disorder							
Current	24	20.5	3	2.1	23.58	<0.0001	0.08 (0.02–0.28)
Lifetime	28	23.9	3	2.1	29.07	<0.0001	0.06 (0.02–0.23)
Generalized Anxiety Disorder							
Current	21	18.0	18	12.7	1.39	0.24	0.66 (0.34–1.31)
Any Anxiety Disorder							
Current	62	53.0	31	21.8	27.06	<0.0001	0.25 (0.15–0.43)
Lifetime	65	55.6	31	21.8	31.28	<0.0001	0.22 (0.13–0.38)

[a] There were no cases of Acute Stress Disorder, Anxiety Disorder Due to a General Medical Condition, or Substance-Induced Anxiety Disorder in either age group.