

Anxiety and depression in adults with primary immunodeficiency: How much do these patients experience and how much do they attribute to their primary immunodeficiency?

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ABSTRACT

Introduction: Primary immunodeficiency (PID) is a rare group of disorders that manifest similarly with infection, neoplasms, allergic, and autoimmune diseases, and are treated with injectable medications. Often the burden of disease and cost of management is excessive, and premature death is not uncommon. In light of these features of PID, it was our objective to survey our cohort to assess for factors that can influence depression and anxiety.

Methods: We used an investigator-developed survey, in addition to the Hamilton Depression Rating Scale (HAM-D) and the Hamilton Anxiety Rating Scale, after institutional review board approval of our pilot study, to determine the extent of anxiety and depression that our patients with PID experienced and variables that may have affected the difference of expression. The differences among groups were tested by using Wilcoxon rank sum tests, Kruskal-Wallis tests, and chi-square tests.

Results: The patients with PID had similar depression compared with the U.S. population, as assessed by the HAM-D scale. Risk factors associated with elevated HAM-D scores included the following: not driving, intravenous immunoglobulin therapy (versus subcutaneous), nurse-administered therapy (versus self-administered), having unpleasant adverse effects from therapy, previously attempted suicide, and family members with reported anxiety and/or depression. Anxiety was not significantly increased in our cohort. Risk factors for significantly elevated Hamilton Anxiety Rating Scale scores included the following: having poor health, an unhealthy diet, lack of refreshing sleep, and family members with reported anxiety and/or depression.

Conclusion: Many factors influence depression and anxiety, and may add to the morbidity of PID. Patients should be assessed for our identified factors for depression and anxiety. Treatment or referrals should be initiated as it is hoped to improve our patients' quality of life and outcomes.

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Primary immunodeficiency (PID) represents a heterogeneous group of rare inherited disorders of the immune system. In the United States, the overall prevalence of diagnosed PIDs is estimated to be 1 in 1200 persons, and >200 different PIDs have been described.^{1,2} The resulting symptoms of PIDs can affect individuals in a variety of ways, which range from recurrent infections, autoimmune diseases, and allergic diseases, to increased propensity for malignancy.³

There has been great interest in assessing the health-related quality of life of individuals with PIDs.^{4–21} Several factors have already been linked to improved health-related quality-of-life outcomes, including administration of subcutaneous immunoglobulin G (IgG)

(SCIG) therapy at home and by one's self.^{7,18,22–24} Yet, there is evidence that an individual's mental health is still negatively impacted by PID diseases; in a recent study of children with PIDs, the results showed that these individuals are at increased risk of experiencing significant anxiety and depressive symptoms.³

There currently is a need for further investigation of the anxiety and depression experienced by individuals with PIDs.³ Particularly in adults, to our knowledge, neither the severity of these patients' anxiety and depressive symptoms nor the degree to which patients with PID attribute such symptoms to their PID diagnosis has been well-documented before. With the use of validated instruments,^{5,25} we hope to gain a deeper understanding of the aspects of adult patients' lifestyle, medical history, and immunoglobulin G replacement therapy that affect these two outcomes.

METHODS

Study Design

This pilot research study, conducted during a 2-month period, was designed to assess the efficacy of care delivered, as a means of quality assurance, in 2015

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to patients with PID at the division of pulmonary, allergy, and immunology at a university. The research was approved by the institutional review board at Penn State University before research was initiated. Each patient had a PID diagnosis that corresponded to The International Classification of Diseases, Ninth Revision codes 279.00–279.9 listed in their electronic medical record. Because all data were collected by a telephone survey, individuals were excluded if they (1) did not answer the telephone after two separate attempts, or (2) verbally declined participation in the study before or after hearing the study summary and relevant risks of participation. Thirty-three participants completed the entirety of the study. Participation was voluntary, and no compensation was provided. By participating in the survey, the participants provided implied consent.

Survey Instruments

Each participant responded to a 62-item questionnaire, designed by the study team, that gathered information about participants' lifestyle, PID diagnosis and treatment, comorbidities, and amounts of anxiety and depression that they experienced and attributed to their PID diagnosis. In addition, patients' depression and anxiety symptoms were evaluated by using the validated 17-item Hamilton Depression Rating Scale (HAM-D) and 14-item Hamilton Anxiety Rating Scale (HAM-A). The scales were applied to symptoms experienced within the week before participation. The study team member (J.S.) who administered these instruments to all participants was trained by a board certified psychiatrist (E.F.H.S.).

Statistical Analysis

All variables were summarized with means, medians, and standard deviations, or with frequencies and percentages before any analysis. The distribution of continuous outcome variables was assessed before applying any statistical methods. Due to a lack of responses in some categories, Likert scale variables that measured the amount of anxiety or depression attributed to treatment were dichotomized as "yes" (some, quite a bit, an extreme amount, all) versus "no" (none). For these binary outcome variables, differences between groups of potential risk factors were tested by using a χ^2 test. For HAM-D and HAM-A scores, which were continuous but not normally distributed, a Wilcoxon rank sum test was used to compare groups of potential risk factors. For risk factors with more than two groups, a Kruskal-Wallis test was used with pairwise comparisons among groups made by using Wilcoxon rank sum tests adjusted for multiple comparisons by using the Bonferroni method to maintain the family-wise error rate. The level of statistical signifi-

Table 1 Basic clinical characteristics of participants (*n* = 33)

PID Subtype	ICD-9 Code	No. (%)
Common variable immunodeficiency	279.06	73
Hypogammaglobulinemia unspecified	279.00	21
Unspecified immunity deficiency	279.3	6

PID = Primary immunodeficiency; ICD-9 = International Classification of Diseases, Ninth Revision.

cance was set at $p < 0.05$. SAS 9.4 (SAS Institute, Cary, NC) was used to perform all analyses.

RESULTS

Of 211 patients solicited, 33 (8 men and 25 women) participated in our pilot study. We anticipated a 10–20% response rate, as expected for solicited surveys. In addition, because PID is a rare disease, a total of 33 patients was not inappropriate. The investigated group contained 24 patients with common variable immunodeficiency, 7 patients with unspecified hypogammaglobulinemia, and 2 patients with unspecified immunity deficiency (Table 1). All the patients were also currently receiving regular immunoglobulin replacement therapy; 54.55% of the patients received SCIG therapy, and 45.45% of the patients received intravenous immunoglobulin (IVIG) therapy. Although children were not directly excluded from our study, no child met all of the aforementioned criteria; the median age of the participants was 55 years, with upper and lower quartiles of 41 and 63.

Depressive Symptoms (HAM-D scores) and Risk Factors

On average, the patients with PID had a median score of 2, with upper and lower quartiles of 0 and 4, on the HAM-D scale, which corresponded to "normal" degrees of depressive symptoms for the general population. The maximum HAM-D score was 14, which corresponded to "moderate" depressive symptoms; the minimum HAM-D score was 0, which corresponded to "normal" degrees of depressive symptoms. Three of the 33 subjects (9%) had HAM-D scores higher than the clinical cutoff of 7, and this value reflected an abnormal degree of depression (Table 2, Figs. 1 and 2).

We found that patients who did not drive had significantly higher median HAM-D scores than those who did drive (5 versus 1.5, $p = 0.024$). The patients also scored significantly higher if they were receiving IVIG therapy (either at home or in an infusion room) as opposed to SCIG home therapy (3 versus 1, $p = 0.004$). In addition, the administrator of a patient's immunoglobulin replacement therapy (nurse, family mem-

Table 2 Significant prognostic factors found by using the Hamilton instruments (N = 33)

Variable	No. Patients	Median (Q1, Q3)	p Value*
Hamilton Depression Rating Scale score			
Do you drive?			0.024
Yes	30	1.5 (0.0, 3.0)	
No	3	5.0 (4.0,11.0)	
Type of IgG replacement			0.004
Subcutaneous	18	1.0 (0.0, 2.0)	
Intravenous	15	3.0 (5.0,14.0)	
Who gives treatment?			0.007
Self	18	1.0 (0.0, 3.0)	
Family member	2	0.0 (0.0, 0.0)	
Nurse	13	3.0 (2.0, 4.0)	
Unpleasant adverse effects of therapy?			0.018
Yes	21	3.0 (4.0, 11.0)	
No	12	0.0 (0.0, 2.0)	
Attempted suicide?			0.023
No	28	4.0 (4.0,11.0)	
Yes	5	1.5 (0.0, 3.0)	
Family member depression and/or anxiety?			0.004
Yes	11	3.0 (2.0, 6.0)	
No	22	1.0 (0.0, 3.0)	
Hamilton Anxiety Rating Scale score			
Good state of health?			0.032
Yes	21	1.0 (0.0, 4.0)	
No	12	4.0 (2.5, 6.0)	
Healthy diet?			0.016
Yes	25	1.0 (0.0, 3.0)	
No	8	5.0 (3.5, 6.0)	
Refreshing sleep?			0.012
Yes	20	1.0 (0.0, 4.0)	
No	13	3.0 (2.0, 7.0)	
Family member depression and/or anxiety?			0.035
Yes	11	4.0 (2.0, 7.0)	
No	22	1.0 (0.0, 3.0)	

Q1 = Quartile 1; Q3 = quartile 3; IgG = immunoglobulin G.

*The Wilcoxon rank sum test or Kruskal-Wallis test with Wilcoxon rank sum tests for pairwise comparisons adjusted for multiple comparisons with the Bonferroni correction.

ber, or self) had an effect on median HAM-D scores ($p = 0.007$). The patients who had nurse-administered therapy had a significantly higher median HAM-D score than those patients whose therapy was self-administered (3 versus 1, $p = 0.030$). Higher HAM-D scores were associated with having experienced unpleasant or harmful adverse effects from current immunoglobulin replacement therapy (3 versus 0, $p = 0.018$).

Risk factors and severity markers of psychiatric illness were also associated with more depressive symptoms. Those who had family members who were depressed or had anxiety also scored significantly higher than those who did not have family

members who were depressed or had anxiety (3 versus 1, $p = 0.004$). Those patients who had attempted suicide scored significantly higher on the HAM-D scale than those who did not (4 versus 1.5, $p = 0.023$).

Anxiety (HAM-A scores) and Risk Factors

The patients scored an overall median of 2 with upper and lower quartiles of 1 and 5 on the HAM-A score, which corresponded to "none to mild" degrees of anxiety. The maximum HAM-A score was 16, which corresponded to "none to mild" anxiety; the minimum HAM-A score was 0, which corresponded to a "none"

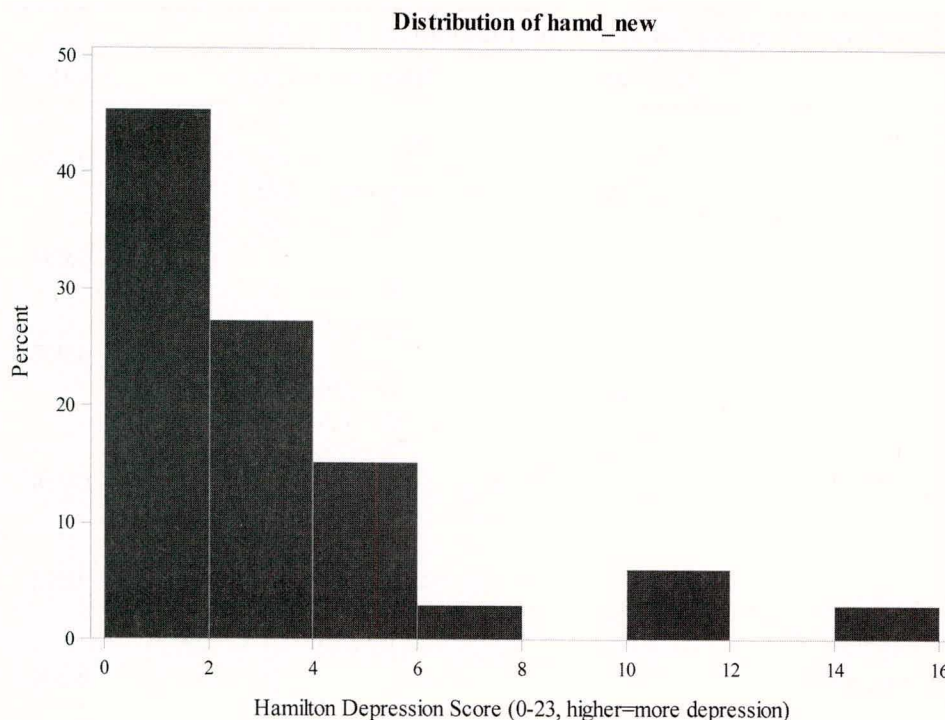


Figure 1. Hamilton Depression Rating Scale (HAM-D) scores from our cohort. Median of our cohort, 2.00 (0.00, 4.00). Scoring: 0–7, normal; 8–16, mild depression; 17–23, moderate depression; ≥ 24 , severe depression.

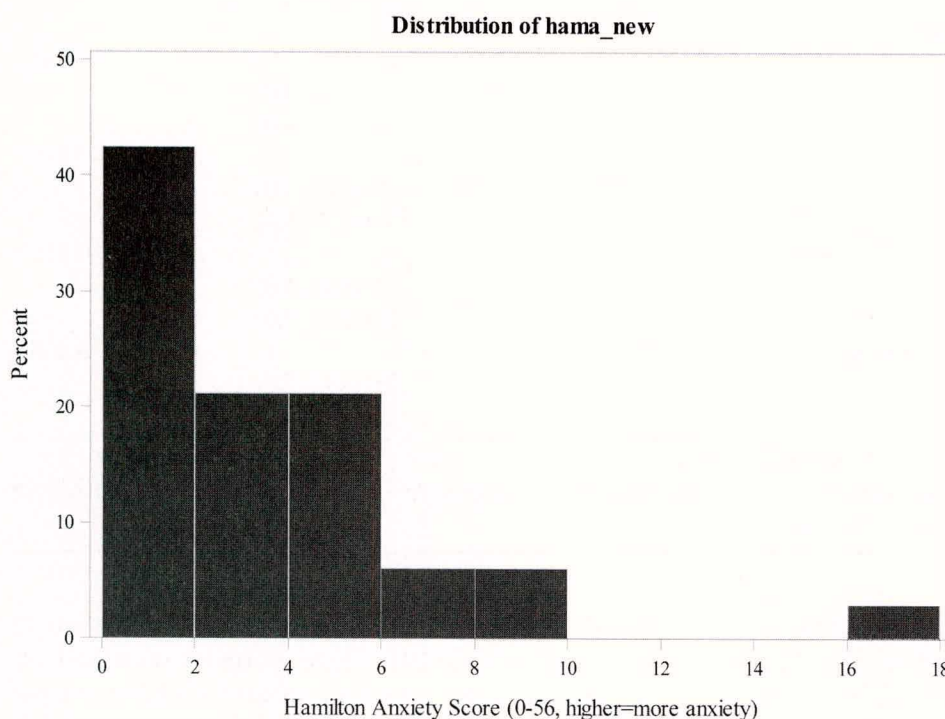


Figure 2. Hamilton Anxiety Rating scale (HAM-A) scores from our cohort. Median, 2.00 (1.00, 5.00) of our cohort. Scoring: 0–16, normal-to-mild anxiety; 17–24, mild-to-moderate anxiety; 25–30, moderate-to-severe anxiety.

amount of anxiety. Factors associated with greater anxiety included not perceiving their current health as being “good” (4 versus 1, $p = 0.032$), unhealthy eating (5 versus 1, $p = 0.016$), and not describing an average night’s sleep as “refreshing” (3 versus 1, $p = 0.012$). The patients also had significantly higher HAM-A scores if they had family members who were depressed or had anxiety (4 versus 1, $p = 0.035$).

Attributing Anxiety or Depressive Symptoms to a PID diagnosis

The patients who had been hospitalized in the past year attributed significantly higher percentages of their anxiety (50% versus 6%, $p = 0.015$) and depressive symptoms (60% versus 6%, $p = 0.004$) as resulting from their diagnosed PID compared with those who had not been hospitalized. The patients who received IVIG re-

Risk Factors for Depression

Risk Factors for Anxiety

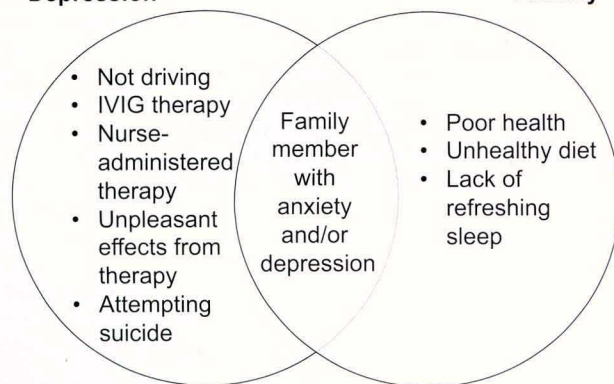


Figure 3. Risk factors for anxiety and depression in patients with primary immunodeficiency (PID).

placement therapy also attributed higher amounts of their anxiety to their diagnosed PID compared with those who received SCIG therapy (40% versus 6%, $p = 0.030$). In addition, the patients who had attempted suicide attributed higher amounts of their depressive symptoms to their diagnosed PID compared with those who had not attempted suicide (80% versus 25%, $p = 0.033$).

DISCUSSION

The results from our pilot study confirmed previous reports that indicated that individuals who receive SCIG home therapy have lower depression scores than those who receive intravenous therapy; individuals who receive self-administered therapy, as opposed to therapy by a nurse, also had lower depression scores.^{4,11,17,18} Cause and effect cannot be proven, that is, the process of self-infusion and home infusion may not in itself improve mental health but may instead select those with less depressive symptoms to choose this route of therapy. In addition, similar to previous studies, we did not find other comorbidities, including bronchiectasis, to have a significant effect on depression and anxiety.¹⁶

Because our survey included open-ended questions, we were able to ask participants who received IVIG therapy in an infusion room, the population expected to have the worst quality of life, their reasons for not being on home and/or SCIG therapy. The most common responses included personal discomfort with using needles or difficulty getting insurance to cover home therapy to the same degree as infusion-room therapy. Some patients who received infusion-room therapy said that they did not have the option of SCIG because of previous immediate and harmful effects that they had experienced during previous infusions. A small percentage of patients reported preferring IVIG therapy because of previously experiencing worse adverse effects from SCIG therapy than from

IVIG therapy. These may be very practical concerns for patients and their physicians to discuss when selecting among different types of immunoglobulin therapy.

It is important to note that any treatment's adverse effects, including those that are most common, can increase an individual's risk for developing depressive symptoms; the most commonly reported effects matched those of a previous study, including chills, fever, muscle pains, nausea, and headaches.⁹ Therefore, it may be especially important for patients to try more than one type of therapy if they experience any adverse effects from their initial therapy selection. In addition, there may be a need for future research to investigate the most-effective methods for coping with adverse effects to minimize the depression experienced by these patients. Patients are at higher risk of depressive symptoms in particular if they do not currently drive, if they have ever attempted suicide, or if they have family members who they believe to have depression or anxiety. Physicians may be better equipped to identify patients at greater risk for developing depressive symptoms if they note these pieces of patients' mental health and social history.

A healthy diet, a norm of refreshing sleep, and the perception of having good health were all associated with lesser degrees of anxiety. To minimize the anxiety symptoms experienced by patients, physicians may consider inquiring about these areas of a patient's lifestyle and recommending nutritional counseling or sleep aids to patients with these lifestyle factors. Because individuals with family members who are believed to have depression or anxiety are at increased risk for experiencing anxious symptoms, collecting this portion of a patient's family history may help physicians identify and more closely monitor these patients at higher risk.

It has already been hypothesized that diseases, *e.g.*, common variable immunodeficiency, may cause depression or anxiety.¹⁶ Therefore, it is not surprising that certain participants attributed a significant amount of their experienced anxiety and/or depressive symptoms to their PID disease. We found that patients hospitalized in the past year were also more likely to think of their PID as the cause of any anxiety or depressive symptoms that they experienced. This indicated that how recently a patient has been hospitalized was directly related to how significantly his or her PID was currently affecting his or her quality of life, especially his or her mental health. Individuals who received IVIG therapy were most likely to attribute any anxiety that they experienced to their PID. Although none of the participants reported anxiety as an experienced adverse effect of therapy, previous findings indicate that these participants' anxiety directly results from their IVIG therapy and, therefore, indirectly results from their diagnosed PID.⁹

In the survey's last open-ended question, the participants were asked about what they thought would most improve their quality of life with respect to their PID disease. Responses ranged from wishing for better insurance coverage of treatments and better prevention of infections (*e.g.*, decreased fear of being around people because of the increased risk for infection), to wishing for physicians to better customize care to the particular needs of patients with PIDs by weighing these patients' subjective infection-related experiences more heavily than they would those of patients a typical immune system (*e.g.*, prescribing antibiotics at earlier signs of infection to shorten the length of recovery time that these patients will need). Because the results of our study found that recent hospitalization, within the past year, increased the risk for both anxiety and depressive symptoms, further consideration of these infection-related concerns may keep these individuals out of the hospital and, therefore, make noticeable improvements in their mental health and overall quality of life.

Study Limitations

Because this was a retrospective study, results were subject to recall bias. We were also limited by a small sample size and participation that was <20%; however, because PID is a rare disease, a small sample size was expected. Nonetheless, a larger sample size may have made more of the results from our survey statistically significant.

CONCLUSION

This study provided evidence that even normal-to-mild degrees of anxiety and depression, as found in our study, may be associated with certain aspects of a patient's lifestyle, immunoglobulin replacement therapy characteristics, mental health history, and even a family history of mental health disorders, as evident in Fig. 3. Patients at highest risk for anxiety reported an unhealthy diet, nonrefreshing sleep, a perception that their current health was not good, and a family history of anxiety or depression. The patients at highest risk for depressive symptoms were those who did not drive, had previously attempted suicide, received IVIG therapy, had a nurse administer their therapy, experienced adverse effects from their immunoglobulin G replacement therapy, and had a family history of anxiety or depression. The patients were more likely to associate their PID with their anxiety and/or depression if they had been hospitalized in the past year, received IVIG therapy, or had previously attempted suicide. If physicians keep these risk factors in mind, they may be more effectively able to identify patients at higher risk for anxiety or depression, and help patients make positive lifestyle changes to minimize their risks of PID disease that negatively impact an individual's mental health.

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