Title: Gout characteristics associate with depression, but not anxiety, in primary care: baseline findings from a prospective cohort study

James A Prior, Christian D Mallen, Priyanka Chandratre, Sara Muller, Jane Richardson & Edward Roddy

Authors:

JA Prior, Research Associate, PhD*[1]

CD Mallen, NIHR Research Professor in General Practice, PhD[1]

P Chandratre, Clinical research training fellow and Rheumatology Specialist Registrar, PhD[1]

S Muller, Research Fellow, PhD[1]

J Richardson, Senior Lecturer in Health Services Research, PhD[1]

E Roddy, Clinical Senior Lecturer, DM[1]

Affiliation:

Research Institute for Primary Care and Health Sciences, Keele University,

United Kingdom

***Corresponding author:**

James A. Prior, BSc, MSc, PhD

Research Institute for Primary Care and Health Sciences,

Keele University,

Staffordshire,

United Kingdom,

ST5 5BG

E-mail: j.a.prior@keele.ac.uk

Tel: +44(0)1782 734847

Fax: +44(0)1782 733911

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Abstract

***Objectives*:** To determine the prevalence of anxiety and depression in gout, examine associations between gout characteristics and these comorbidities and determine the role of allopurinol in any such relationships.

***Method*:** As part of a prospective cohort study, a baseline questionnaire was sent to 1,805 participants with gout aged ≥18 years from UK primary care. Participants had a gout diagnosis or prescriptions for allopurinol or colchicine in their medical records two years prior to baseline. Prevalence of anxiety was defined using the Generalised Anxiety Disorder questionnaire and depression using the Patient Health Questionnaire. Logistic regression was used to examine any association between gout characteristics (12-month attack frequency, oligo/polyarticular gout and gout duration) and the presence of anxiety or depression. Crude and adjusted associations were reported as Odds Ratios (OR) and 95% Confidence Intervals (CI). Adjusted gout characteristics were stratified by allopurinol use.

***Results*:** 1,184 participants responded to baseline (65.6%). Prevalence of anxiety and depression were 10.0% and 12.6% respectively. There was no association between gout characteristics and anxiety. However, there was an association between attack frequency and depression amongst those gout patients using allopurinol (2.87 (1.2 to 6.6)) and also between oligo/polyarticular gout and depression (2.01 (1.2 to 3.3)), irrespective of allopurinol use (2.09 (1.1 to 4.0)) or not (2.64 (1.0 to 6.8)).

***Conclusion*:** Patients experiencing frequent gout attacks or attacks in multiple joints are likely to experience depressive symptoms, even when using allopurinol. Depression

may influence medication adherence and participation in routine reviews, hence impacting adversely on gout management outcomes.

Keywords: Allopurinol, Anxiety, Comorbidity, Depression, Gout, Primary Care

Introduction

Gout is experienced by 2.5% of UK adults, making it the most common form of inflammatory arthropathy [1]. The primary risk factor for gout is an elevated serum urate level (hyperuricaemia), leading to monosodium urate (MSU) crystal deposition in and around joints, acute attacks of crystal synovitis and progressive joint damage [2]. Long-term treatment of gout involves using urate-lowering therapies (ULT), typically the xanthine oxidase inhibitor allopurinol [3].

Comorbidity is common in people with gout [4] and whilst the association with physical conditions has been widely investigated [5-7], research into the potential association between gout and psychological comorbidity (including anxiety and depression) remains limited. In particular there is sparse information on the prevalence of either anxiety or depression in gout patients in primary care, the setting where the majority of gout patients are managed and treated [8]. A small study of 50 gout patients undertaken in a Singapore Rheumatology department reported the prevalences of anxiety and depression, defined using the Hospital Anxiety and Depression Scale (HADS), to be 6% and 20% respectively [9]. The prevalence of depression (defined using the Patient Health Questionnaire (PHQ-9)) in adults aged 60 years or older with gout was 13.5% in the 2009-2010 National Health and Nutrition Examination Survey (NHANES) study, an estimate that was similar to that in the general population [10].

We have previously examined the incidence rate of general practice consultation for anxiety and depression in gout patients in UK primary care [11]. In this population, we found no association between a diagnosis for gout and a subsequent consultation for these psychological comorbidities, when compared to primary care consulters matched by age, gender, year of consultation and general practice. However, this research was based on historical medical consultation for either anxiety or depression, both of which

are typically under-reported and under-diagnosed in general practice [12, 13]. Furthermore, owing to the nature of medical consultation data, no consideration of specific gout characteristics was possible, which have been shown to influence the psychological quality of life in gout patients [14].

Previous research from English primary care and US secondary care populations found little influence of gout on psychological health, when compared to the influence on physical health [15-17]. However, when classification by gout characteristics was applied, such as by the number of painful joints [18], number of attacks in a 12-month period [14, 18-20] or disease duration [20], associations were found between gout and poorer general psychological health (as measured using the SF12 or SF36). This suggests that different gout characteristics may be important in identifying those patients more likely to experience poorer psychological health. However, it remains unclear whether the prevalence of anxiety and depression is associated with specific gout characteristics in UK primary care. The only paper to have considered the association between gout and psychological comorbidity was conducted by Khanna et al in a US secondary care sample. They found the prevalence of depression, determined from record review, to be greater in patients experiencing ≥2 flares in a 12-month period, even in patients treated with ULT [21].

The specific objectives of this study were i) to establish the prevalence of anxiety and depression amongst UK primary care gout patients, ii) to investigate the association between gout characteristics and anxiety and depression and iii) to examine the role of allopurinol use on any association with these psychological comorbidities.

Patients and methods

Study design and population

The study uses baseline data from a prospective primary care-based cohort study of people with gout [22]. Gout patients aged 18 years and older were recruited from 20 research-active General Practices across the West Midlands, UK. Participants were selected based on the presence of Read codes for a previous consultation for gout or a prescription of allopurinol or colchicine in the electronic medical records within the two years preceding the baseline questionnaire. Participants were mailed a postal questionnaire, with a two-staged reminder system in place for initial non-responders. With participant consent, questionnaire data were linked to participants' medical records. Approval was obtained from the North West – Liverpool East Research Ethics Committee (Ref no: 12/NW/0297).

Baseline survey measures

The prevalence of anxiety and depression within the gout sample was assessed using two validated measures included in the baseline questionnaire. Anxiety status was determined using the Generalised Anxiety Disorder (GAD-7) questionnaire [23]. The GAD-7 consists of seven questions designed to identify cases of generalised anxiety disorder. Depression was assessed using the Patient Health Questionnaire (PHQ-9) [24], a nine-question measure developed for use in primary care to identify the presence of depression. The GAD-7 and PHQ-9 have both been shown to be capable of screening for their respective conditions and are valid measures of clinically diagnosed anxiety and depression [23, 24]. Scores of <10 represent 'no anxiety' or 'no depression' and scores of ≥10 represent the presence of anxiety or depression for each measure [23, 24].

The baseline questionnaire also collected data on age, gender, body mass index (BMI) and deprivation status. BMI was calculated from self-reported weight and height and deprivation status was assessed using the Indices of Multiple Deprivation (IMD), which is a neighbourhood level deprivation measure [25]. Other data collected included the frequency of alcohol consumption and self-reported comorbidities including hypertension, hyperlipidaemia, diabetes mellitus, angina, myocardial infarction, kidney stones, transient ischaemic attack, kidney failure or stroke.

Gout-specific characteristics recorded included: the frequency of gout attacks in the last 12 months, whether gout had ever been experienced in more than one joint at the same time (oligo/polyarticular gout), the age at which the diagnosis of gout had been made (gout duration), whether the participant was currently experiencing a gout attack, and whether the patient was currently using allopurinol.

Statistical analysis

The characteristics of the study sample were initially summarised using descriptive statistics. The mean age (Standard Deviation (SD)) and gender were reported. IMD was categorised into tertiles (the least deprived, mid-deprived and most deprived). BMI was categorised by those with a score i) <25.0 (healthy weight), ii) 25.0-29.9 (overweight), iii) 30.0-34.9 (obese) or iv) ≥35.0 (severely obese). The frequency with which alcohol was consumed was categorised as ; i) never, ii) occasionally, iii) 1-3 times per month, iv) 1-2 times a week, v) 3-4 times a week or vi) daily/almost daily.

The GAD-7 and PHQ-9 were reported as the proportion of respondents with or without anxiety symptoms, or with or without depression symptoms, by dichotomising each measure into either a score of <10 (condition not present) or ≥10 (condition present) [23, 24]. Subsamples with anxiety or depression were not mutually exclusive and the

same patient could be included in each of these two comorbid disease groups. Frequency of gout attacks in the last 12 months was categorised by 0, 1-2 or ≥3 attacks. Use of allopurinol and history of oligo/polyarticular attacks were each dichotomised into 'yes' or 'no'. Gout duration was calculated by subtracting the age at diagnosis from the participant's current age and was categorised into quartiles as; ≤2 years, 3-8, 9-17 or 18≥ or more years.

Logistic regression analysis (conducted using STATA, version 12), was used to assess the association between the gout characteristics of i) frequency of gout attacks, ii) oligo/polyarticular gout and iii) disease duration, with the presence of anxiety and depression symptoms. Associations were reported as Odds Ratios (OR) with 95% Confidence Intervals (CI) between these three gout characteristic and the presence of either anxiety or depression symptoms. Each association was initially examined as a crude analysis, then initially adjusted for age, gender and deprivation status, followed by a further stage of additional adjustment for BMI, comorbidities, alcohol consumption and gout characteristics. Adjustment for gout characteristics varied for each analysis depending on which characteristic was the focus. For example, frequency of gout attacks was adjusted for oligo/polyarticular gout and duration of gout.; oligo/polyarticular gout was adjusted for frequency of gout attacks and duration of gout and so on. All gout characteristics were adjusted for a current gout attack, Finally, once each of the three gout characteristics had been adjusted they were stratified by 'use of allopurinol'.

Results

Sample characteristics

Of the 1,805 gout patients mailed the baseline questionnaire, 1,184 responded (65.6%). Non-responders to the baseline questionnaire tended to be younger than responders,

they were also more likely to be male and live in more deprived areas [26]. The mean age of responders was 65.6 years (SD 12.5). 81.5% were male, 73.0% were either overweight or obese and 23.4% of the sample drank alcohol on a daily basis (**Table 1**). Mean gout duration was 11.9 years (SD 12.1), 36.8% had experienced oligo/polyarticular attacks, 64.5% had experienced at least one attack of gout in the last 12 months and 56.3% were currently taking allopurinol (**Table 2**).

Prevalence of anxiety and depression

Of the baseline questionnaire responders, 1,094 completed the GAD-7. Of these 10.0% (n=109) scored above ≥10 and were classified as having generalised anxiety. 1,042 of the baseline questionnaire responders had completed the PHQ-9, with 12.6% (n=131) scoring above >10 and defined as having depression.

Association between gout characteristics and anxiety and depression

In crude analysis, compared to those having no gout attacks in the preceding 12 months, anxiety (OR 2.67 (95% 1.6 to 4.4)) and depression (3.25 (2.0 to 5.3)) were more common in those experiencing ≥3 gout attacks within a 12-month period, but no more common in those experiencing only 1-2 attacks (**Tables 3 and 4**). This association was retained for both anxiety and depression after initial adjustment, but was subsequently attenuated when adjustment was made for other gout characteristics (anxiety: 1.60 (0.8 to 3.1); depression 1.83 (0.9 to 3.5)). When frequency of gout attacks was stratified by those who used allopurinol and those who did not, there were no associations with anxiety. However, there was an association between attack frequency and depression amongst those gout patients using allopurinol (2.87 (1.2 to 6.6)).

Compared to those with no oligo/polyarticular attacks, those who answered yes were significantly more likely to experience anxiety and depression within crude analysis and this was retained after adjustment for age, gender and deprivation status. With the additional adjustment for BMI, comorbidity and alcohol consumption the association between oligo/polyarticular gout and anxiety was lost. However, a history of oligo/polyarticular attacks was associated with depression, even after all our adjustments (2.01 (1.2 to 3.3)). Furthermore, when stratified, this association was retained for both those who were currently using allopurinol (2.64 (1.0 to 6.8)) and those who were not (2.09 (1.1 to 4.0)). No associations were found between gout duration and the presence of anxiety or depression symptoms at any stage of regression analysis.

Discussion

This primary care-based study examined the prevalence of anxiety and depression in people with gout, identifying the association between these psychological comorbidities, specific gout characteristics and the role of allopurinol in such relationships. We found that 10.0% of gout patients had generalised anxiety and 12.6% had depression, as defined by validated diagnostic instruments commonly used in primary care. Though there were initial relationships between gout characteristics and anxiety, these were attenuated after adjustment. However, certain gout characteristics were initially associated with depression and were retained after adjustment. Gout patients using allopurinol and experiencing frequent gout attacks over a 12-month time-period (≥3), compared with no attacks had nearly a three-fold increase in the odds of reporting symptoms of depression. There was also an association between those with a history of oligo/polyarticular attacks and depression.

To date, evidence about the association between anxiety and depression in patients with gout has been limited, particularly in primary care where the majority of patients are exclusively managed. Previously Mak et al had reported the prevalence of anxiety and depression in gout patients to be 6% and 20%, respectively. Our study found a higher prevalence of anxiety (10%) and lower prevalence of depression (13%) which may reflect the different study populations (Singapore *vs.* England) or the diagnostic definitions used for both conditions (GAD-7 and PHQ-9 *vs.* Hospital Anxiety and Depression Scale (HADS)) [27, 28]. In contrast, other research using a large, nationally representative US population-based sample to examine depression in different chronic disease groups, found gout patients reported a prevalence rate of 13.5% when defined through the PHQ-9, comparable to our finding of 12.6%[10]. Our findings are also similar to the prevalence of anxiety in the (male) general UK population (8%), but slightly higher for depression (13%) [29].

Though initial associations between the experience of 3≥ gout attacks in 12 months and both anxiety and depression were found, and retained after several adjustments, this did not remain after adjustment for other gout characteristics. This suggests that gout severity, in this case a combination of several poor gout characteristics, influences mental health. In particular, currently experiencing a gout attack has been associated with poorer general mental health in gout patients previously [20]. As our findings were not maintained after this adjustment, this suggests that though frequently experiencing attacks may contribute to some gout patients experiencing anxiety or depression, it alone is not enough to lead to these mental health comorbidities.

Though there was an initial association between oligo/polyarticular gout attacks and anxiety, this was attenuated by confounders, including BMI, comorbidity and alcohol consumption. As such, anxiety in gout patients experiencing attacks in multiple joints

may be primarily related to other health factors. In contrast, the initial odds of gout patients who have experienced oligo/polyarticular attacks having depression were three-times that of those without multi-joint attacks, even after adjustment this association remained. Our findings concur with previous research which had found a correlation between the number of painful joints and poorer general psychological health [18].

As no causal relationship can be established from this cross-sectional analysis, it remains unclear whether experiencing these gout characteristics places an additional strain on the mental health of gout populations, of which depression may be a consequence, or whether depression may result in more severe gout characteristics. Both mechanisms are possible, frequently experiencing attacks of gout across multiple joints may have negative impacts upon psychosocial factors, such as a reduction in social activity, regular absences from work and additional strain on relationships with family and friends [30], which may all be association with depressive symptoms. Conversely, depressive symptoms could plausibly lead to poor adherence to treatments [31] and as such may result in sub-optimal ULT and more frequent gout attacks. Allopurinol had a mixed influence on these two gout characteristics. Patients with frequent gout attacks who were using allopurinol were 2.87 times more likely to be depressed than those experiencing no attacks. However, there was no association between frequency of gout attack and depression in those not using allopurinol. Though counterintuitive, this result is in-line with Khanna et al who found that 38% of gout patients undergoing optimal ULT continued to have ≥2 flares per year and that these patients were more likely to have depression [21]. An explanation for such findings may be that ULT is being focused on those with the most 'severe' gout who are also more vulnerable to depression. In comparison, patients with oligo/polyarticular gout,

whether they use allopurinol or not, remain over twice as likely to experience symptoms of depression as those who experience gout attacks in one joint only.

These two specific characteristics present a clear sub-group of gout patients who can be identified reasonably easily and may benefit either from being managed through ULT, if already using ULT, being managed more effectively through regular titration or simply being better education on ULT to ensure adherence [32].

In addition, a future option may be to screen for depression in oligo/polyarticular gout patients [33]. In a study of US veterans, people with gout attended mental health clinics less frequently than those without gout [17]. This may lead to under-diagnosis of these gout-associated mental health comorbidities in a specialist setting. Additional identification and subsequent management of depression could result in reduction in pain and improvement in physical, as well as psychological health, as previously observed in an arthritis population [34]. Benefits of screening may come in two forms, the first from improved treatment adherence, as those who have an overall poorer health status and who struggle to express emotional problems have reduced adherence to treatment for gout [35]. The second benefit may be from decreased cost, with depressive comorbidity being a factor in increased costs related to care provision [36].

The strengths of this study lie in the examination of a large sample of gout patients from primary care and the use of validated tools of psychological morbidity that are widely used in this setting and compare well to the diagnostic gold standard (structured clinical interview) [23, 37]. Use of these measures, rather than reviewing the medical records for previous mental health diagnoses is important as anxiety and depression are typically under-reported and under-diagnosed in primary care, with diagnosis often only being made when patients consult for other reasons [38].

Limitations of this work include a potential response bias. Only a selection of gout characteristics was examined, there would have also been benefit in examining the association between the presence of tophi, serum uric acid levels or time with pain between attacks of gout and anxiety and depression, but this information was either not originally included at baseline, or where available was insufficiently reported.

In conclusion, 1 in 10 gout patients attending UK primary care will also have anxiety or depression symptoms. This is a high proportion of patients when compared to male UK primary care patients of a similar age (60-69 years), where prevalence of anxiety and depression is estimated at 4.6% and 6.5% respectively [39, 40]. However, though anxiety may present periodically in gout patients during an attack, it is depression which is associated with particular gout characteristics. In particular, patients who experience attacks in more than one joint are particularly vulnerable to experiencing depression. In addition to the subsequent negative influence of depression on the psychological health of the gout patient, the presence of depression may also influence adherence to gout medication and participation in routine reviews and hence impact adversely on the outcome of gout management. Whilst there is currently insufficient evidence to support the routine screening of patients with gout for depression, clinicians should be aware that gout and depression often coexist and as this may adversely impact on health outcomes they should take a more aggressive approach to the treatment of this sub-group of gout patients.

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Table 1: Characteristics of gout patients (n = 1,184).

	Frequency n (%)
Age (mean, SD)	65.6 (12.5)
Gender (Male %)	990 (83.6)
Neighbour Deprivation Status (Tertiles)	
Least deprived	384 (32.4)
Mid-deprived	398 (33.6)
Most deprived	402 (34.0)
BMI (kg/m^2)	
<25.0	221 (19.8)
25.0-29.9	511 (45.7)
30.0-34.9	260 (23.2)
≥35.0	127 (11.4)
Alcohol consumption	
Daily/almost daily	273 (23.4)
3-4 times per week	263 (22.5)
1-2 times per week	254 (21.8)
1-3 times per month	109 (9.3)
Occasionally	155 (13.3)
Never	113 (9.7)
Comorbidity	
Hypertension	731 (61.7)
Hyperlipidaemia	508 (42.9)
Diabetes mellitus	205 (17.3)
Angina	147 (12.4)
Myocardial infarction	119 (10.0)
Kidney stones	81 (6.8)
Transient ischaemic attack	62 (5.2)
Kidney failure	56 (4.7)
Stroke	37 (3.1)

Figures are n (%) unless otherwise stated.
SD: Standard Deviation, BMI: Body Mass Index

Table 2: Gout-specific characteristics.

Characteristics	**Frequency n (%)**
Gout duration (n = 1,095) (mean years, SD)	11.9 (12.1)
Gout attack(s) in last 12 months (n = 1,123)	
0	398 (35.4)
1-2	418 (37.2)
≥3	307 (27.3)
Currently experiencing a gout attack (n = 1,135)	
No	1,003 (88.4)
Yes	132 (11.6)
Currently using Allopurinol (n = 1,120)	
No	490 (43.7)
Yes	630 (56.3)
Ever experienced gout in more than one joint (n = 1,131)	
No	695 (61.5)
Yes	436 (38.5)

Figures are n (%) unless otherwise stated

Table 3: Association between anxiety and gout characteristics

	Anxiety		Crude OR (95% CI)	Adjusted OR (95% CI)		Adjusted OR (95% CI), stratified by use of allopurinol	
	No (%)	Yes (%)		Age, gender & deprivation status	Age, gender, deprivation status, BMI, comorbidity, alcohol consumption & gout characteristics	No	Yes
Frequency of gout attacks							
0	347 (93)	26 (7)	Ref	Ref	Ref	Ref	Ref
1-2	355 (92)	29 (8)	1.09 (0.6 to 1.9)	0.95 (0.5 to 1.7)	0.68 (0.4 to 1.3)	0.57 (0.2 to 1.8)	0.76 (0.3 to 1.8)
3≥	240 (83)	48 (17)	**2.67 (1.6 to 4.4)***	**2.23 (1.3 to 3.7)***	1.60 (0.8 to 3.1)	2.07 (0.6 to 7.4)	1.72 (0.7 to 4.3)
Oligo/ polyarticular gout							
No	595 (92)	53 (8)	Ref	Ref	Ref	Ref	Ref
Yes	351 (87)	51 (13)	**1.63 (1.1 to 2.4)***	**1.53 (1.0 to 2.3)***	0.96 (0.6 to 1.6)	1.04 (0.4 to 3.0)	0.94 (0.5 to 1.9)
Gout duration (years)							
≤2	248 (89)	31 (11)	Ref	Ref	Ref	Ref	Ref
3-8	232 (91)	23 (9)	0.79 (0.4 to 1.4)	0.86 (0.5 to 1.5)	0.74 (0.4 to 1.5)	0.57 (0.2 to 1.6)	0.96 (0.3 to 3.3)
9-17	196 (92)	17 (8)	0.69 (0.4 to 1.3)	0.85 (0.4 to 1.6)	0.87 (0.4 to 1.8)	0.34 (0.1 to 1.4)	1.90 (0.6 to 6.3)
18≥	243 (88)	32 (12)	1.05 (0.6 to 1.8)	1.51 (0.8 to 2.7)	1.48 (0.7 to 3.0)	0.77 (0.2 to 3.1)	2.99 (0.9 to 9.8)

*** = p ≤0.05**

Table 4: Association between depression and gout characteristics

	Depression		Crude OR (95% CI)	Adjusted OR (95% CI)		Adjusted OR (95% CI), stratified by use of allopurinol	
	No (%)	Yes (%)		Age, gender & deprivation status	Age, gender, deprivation status, BMI, comorbidity, alcohol consumption & gout characteristics	No	Yes
Frequency of gout attacks							
0	333 (92)	28 (8)	Ref	Ref	Ref	Ref	Ref
1-2	325 (89)	39 (11)	1.43 (0.9 to 2.4)	1.33 (0.8 to 2.2)	1.03 (0.6 to 1.9)	0.64 (0.2 to 1.9)	1.49 (0.7 to 3.4)
3≥	212 (79)	58 (21)	**3.25 (2.0 to 5.3)***	**2.95 (1.8 to 4.8)***	1.83 (0.9 to 3.5)	1.16 (0.3 to 4.1)	**2.87 (1.2 to 6.6)***
Oligo/ polyarticular gout							
No	565 (92)	50 (8)	Ref	Ref	Ref	Ref	Ref
Yes	308 (80)	75 (20)	**2.75 (1.9 to 4.0)***	**2.70 (1.8 to 4.0)***	**2.01 (1.2 to 3.3)***	**2.64 (1.0 to 6.8)***	**2.09 (1.1 to 4.0)***
Gout duration (years)							
≤2	230 (87)	34 (13)	Ref	Ref	Ref	Ref	Ref
3-8	222 (89)	27 (11)	0.82 (0.5 to 1.4)	0.83 (0.5 to 1.4)	0.65 (0.3 to 1.2)	0.46 (0.2 to 1.3)	1.27 (0.4 to 3.8)
9-17	176 (89)	22 (11)	0.85 (0.5 to 1.5)	0.95 (0.5 to 1.7)	0.87 (0.4 to 1.7)	0.45 (0.1 to 1.7)	2.11 (0.7 to 6.4)
18≥	223 (85)	38 (15)	1.15 (0.7 to 1.9)	1.33 (0.8 to 2.2)	1.12 (0.6 to 2.2)	0.92 (0.3 to 3.2)	2.11 (0.7 to 6.3)

*** = p ≤0.05**