Neuropsychiatric Comorbidity in Primary Hyperparathyroidism Before and After Parathyroidectomy: A Population Study

A. Koman1,2 • R. Bränström1,2 • Y. Pernow2,3 • R. Bränström4 • I.-L. Nilsson1,2 • Fredrik Granath5

Accepted: 25 January 2022 / Published online: 5 March 2022 © The Author(s) 2022

Abstract

Background  Primary hyperparathyroidism (PHPT) is often accompanied by neuropsychiatric symptoms. This study aimed to map out psychiatric comorbidity as reflected by medical treatment for psychiatric symptoms.

Methods  A retrospective case–control analysis and a prospective cohort analysis of psychotropic drug utilization before and after PTX. A total of 8279 PHPT patients treated with parathyroidectomy in Sweden between July 1, 2008 and December 31, 2017 compared to a matched control cohort from the total population (n = 82,790). Information on filled prescriptions was collected from the Swedish Prescribed Drug Register (SDR). Socioeconomic data and diagnoses were added by linkage to national patient and population registers. Regression analyses were used to calculate relative drug utilization (OR) within 3 years prior to PTX and relative incidence of drug treatment (RR) within 3 years postoperatively.

Results  Utilization of antidepressant, anxiolytic and sleep medication was more comprehensive in PHPT patients compared with the controls prior to PTX. The most common were benzodiazepines [OR 1.40 (95% CI: 1.31–1.50)] and selective serotonin reuptake inhibitors [SSRI; OR 1.38 (95% CI: 1.30–1.47)]. Postoperatively, the excess prescription rate for anxiolytic benzodiazepines decreased within three years from a 30 to 19% excess and for benzodiazepines for sleep from 31 to 14%. No corresponding decrease in excess prescription rate was observed for SSRI.

Conclusion  PHPT is associated with increased utilization of antidepressive medications and benzodiazepines before PTX. This study implies that psychiatric symptoms should be considered in PHPT patients and continuous medication should be reevaluated after PTX.

Introduction

Today, primary hyperparathyroidism (PHPT) is a common disease that ranks third among endocrine diagnoses [1]. PHPT is often accompanied by a wide array of nonspecific neuropsychiatric symptoms which are often indistinguishable from symptoms related to other conditions. Significant neuropsychiatric symptoms, namely depression, anxiety, cognitive decline, fatigue and sleep disorders may be present even in a biochemically mild disease where an indisputable indication for surgical treatment is lacking. Positive effects on the overall quality of life (QoL) and cognitive function commonly occurs after PTX [1–3]. The
surgical procedure is safe and effective [4–8]. Though the occurrence of neuropsychiatric symptoms related to PHPT is not controversial today, the clinical significance and the pathophysiology is debated [2, 9–12]. Still, it remains challenging to predict if the patient will benefit from PTX [13–15].

Previous knowledge was mainly based on self-reported QoL data and it is thus unknown whether healthcare and drug consumption related to neuropsychiatric comorbidity in untreated PHPT had an impact at a population level. The hypothesis behind this study was that treatment for neuropsychiatric morbidity is more prevalent in patients with PHPT compared with the background population. The specific aim was to investigate the preoperative utilization of psychotropic drugs within three years prior to PTX in comparison with the background population. Second to that, the aim was to analyze any potential implications on psychiatric comorbidity after PTX.

Methods and material

Study population

All patients (n = 8626) registered with PTX between January 1, 2008 to December 31, 2017 in the Scandinavian Quality Register of Thyroid, Parathyroid and Adrenal surgery (SQRTPA) [16] as well as in the Cancer Registers, were collected by the National Board of Health and Welfare [17]. For each case, Statistics Sweden (SCB) selected 10 individuals from the Total Population Register matched by year of birth, gender and county (n = 86,260) [18]. To allow complete analysis of drug allocation within 3 years prior to PTX, 347 patients registered between January and June 2008 and their respective controls (n = 3470) were excluded from analyses resulting in a study population of 8279 PHPT and 82,790 controls (Fig. 1).

Data sources

The SQRTPA was founded in 2004 and has a well-validated database that covers about 95% of all PTX performed in Sweden [16]. SQRTPA comprises detailed information on any underlying causes (e.g., renal failure, multiple endocrine neoplasia 1, lithium) biochemical measures, symptoms, indications for surgery, postoperative complications and pathology reports from the time of referral up until 6 months postoperatively.

PTX patients were identified in SQRTPA and/or the Swedish Cancer Register [17]. Population control subjects were sampled as non-PTX subjects and matched according to patients’ sex, age and county as listed in The Swedish Total Population Registry [18]. Information on specialist care visits and hospital admissions was retrieved from The National Patient Registry, and information on income, education level and country of origin was collected from Longitudinal Integrated Database for Health Insurance and Labor Market Studies [19, 20]. Information on administered prescribed drugs was retrieved from the Swedish Prescribed Drug Register [21] containing continuous information on all filled prescriptions in Sweden. Information on vital status and emigration was collected from RTB [18].

Study design

The index date was defined as the time of PTX for patients and the same date for the matched population controls. The primary outcome measure was the utilization of psychotropic drugs. Second to that, a selection of diagnoses (ICD-10) which were deemed relevant for the research question (e.g., cognitive and psychiatric diagnoses, gastrointestinal, kidney stone and chronic musculoskeletal diseases) was mapped for both cohorts during one and five years prior to index date. Socioeconomic status, educational level and household income the year before the index date were considered as confounders in addition to the matching variables. The retrospective case–control study comprehended drugs according to ATC codes designated to match the treatment of neuropsychiatric disorders. Data on prescriptions filled and administered by a pharmacy during a period of 3 years before and after index date were retrieved, which was considered relevant to detect any change of clinical significance. The retrospective case–control study comprehended drugs according to ATC codes designated to match the treatment of neuropsychiatric disorders and cognitive deficiency. The prevalence of utilization within one and three years before index date was assessed and compared between patients and controls. Interactions in relation to calcium levels, age and gender of the patient were analyzed. In the prospective cohort study, the study subjects were divided into incident and prevalent users based on whether they filled at least one prescription during the year before the index date. End of follow-up was defined as date of death, date of emigration or December 31 2019, whichever occurred first. Administrations of psychotropic drugs three years after the index dates were compared by calculating the incidence of at least one administered filled prescription per six months period.

Power calculations were based on the assumption of a Poisson. The population was estimated to guarantee 80% statistical power at a 95% confidence level for the presence
of risk factors between 0.5–30% among controls in the retrospective case–control analyses and an incidence 0.5–10% among controls in the prognostic cohort study.

Base-line characteristics are presented as median and interquartile range for continuous variables and as proportions for categorical variables. The cohorts were stratified into age groups: <50 years, 50–64 years, 65–79 and >80 years.

Drug utilization (filled prescriptions) preoperatively was compared by conditional logistic regression, and results are presented as odds ratios (OR) together with 95% confidence intervals (95% CI). Effect modification by calcium levels, in quartiles, was assessed by an appropriate interaction term. Analyses of the prescription rates after PTX in 6 months periods in patients and controls were analyzed with repeated measurement Poisson regression models. Comparisons were adjusted for age, gender, region, income, ethnicity and education. Trends in the RR's over time were tested by including time as a continuous variable. The results are presented as prescription rates and as rate ratios (RR) with 95% CI. \( p \) values less than 0.05 were considered significant. Analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA) and SPSS version 27.

Results

Baseline characteristics at index date, including age distribution, information on education, employment, and country of birth are presented in Table 1. Clinical characteristics of the 7177 individuals registered in SQRTPA are presented in Table 2. Among patients with data available for calcium levels, \( n = 6932 \), 95.4% remained normocalcemic six months postoperatively.

The retrospective analysis revealed that the utilization of psychotropic drugs was more extensive in patients prior to PTX than in the average population within 3 years prior to PTX (Table 3). Compared to the background population, the relative prevalence of treatment for sleep and anxiety in patients was greater the year prior to PTX as compared to a look back at the third year before index date (Fig. 2). The most common were benzodiazepines [\( \text{OR} 1.40 \ (95\% \ CI \ 1.31–1.50) \)] and SSRI [\( 1.38 \ (1.30–1.47) \)] for which ORs were highest among younger patients and patients with lower calcium levels; \( p < 0.001 \) (Table 3, Suppl.1). No significant gender-specific difference was observed. In the elderly (80 years of age and older), the utilization of antidepressive medication was similar in patients as compared to the background population, though there was
increased use of benzodiazepines [OR 1.25 (95% CI 1.05–1.49)] in the PHPT cohort.

Both somatic and psychiatric diagnoses were more prevalent in the PHPT patient group. Psychiatric disorders (ICD-10; F06-F99) were more than twice as common before PTX with 8.7% among patients and 3.7% among the controls within the year prior to index date [OR 2.51 (CI 95% 1.31–2.73)]. In retrospect, the difference was less over a period of five years preoperatively [OR 1.67 (CI 95% 1.56–1.79)] (Table 4).

Figure 3 and Supplemental Table 2 illustrate initiation and continuation of drug use after PTX. Patients initiating treatment showed a significantly higher initiation rate after PTX than the controls for all substances during the first year after surgery, yet remained elevated at three years only for SSRI and benzodiazepine (sleep). Prevalent users showed the same prescription rate for patients and controls, with the exception of SSRI where patients show significantly lower usage than the controls.

Lithium treatment accounted for a relatively small proportion but was markedly over-represented in the patient cohort [OR 5.74 (CI 4.76–6.93)] which remained unaffected postoperatively (Table 3, Fig. 3, Suppl. Table 2).

Discussion

This study aimed to map out the burden of mental illness in a population by means of analyzing data on the utilization of psychotropic drugs [22]. Thus far, the impact of PHPT

| Table 1 Characteristics of 8279 patients with primary hyperparathyroidism subjected to parathyroidectomy and 82,790 controls from the background population matched for age, gender and region |
| Characteristics | PHPT patients (n = 8279) | Control population (n = 82,790) |
|-----------------|--------------------------|-------------------------------|
| Median age at index date, IQR | 62 (53, 71) | 62 (53, 71) |
| Age | n | % | n | % |
| < 30 | 186 | 2.2 | 1860 | 2.2 |
| 30–39 | 337 | 4.1 | 3370 | 4.1 |
| 40–49 | 942 | 11.4 | 9420 | 11.4 |
| 50–59 | 1820 | 22.0 | 18,220 | 22.0 |
| 60–69 | 2451 | 29.6 | 24,510 | 29.6 |
| 70–79 | 1943 | 23.5 | 19,430 | 23.5 |
| 80+ | 598 | 7.2 | 5980 | 7.2 |
| Gender | | | | |
| Female | 6374 | 77.0 | 63,740 | 77.0 |
| Male | 1905 | 23.0 | 19,050 | 23.0 |
| Education | n | % | n | % |
| Elementary school | 1972 | 23.8 | 20,643 | 24.9 |
| Upper secondary school | 3598 | 43.3 | 35,418 | 42.8 |
| Post-secondary education | 2612 | 31.6 | 25,347 | 30.6 |
| Data not available | 106 | 1.3 | 1382 | 1.7 |
| Occupational status | n | % | n | % |
| Employed | | | | |
| < 65 years | 3385 | 75.6 | 34,949 | 78.1 |
| 65+ years | 503 | 13.2 | 5008 | 13.2 |
| Unemployed, declared | | | | |
| < 65 years | 248 | 5.5 | 2508 | 5.6 |
| Country of birth | | | | |
| Sweden | 6897 | 83.1 | 69,063 | 83.4 |
| Nordic countries (except Sweden) | 445 | 5.4 | 3809 | 4.6 |
| Europe (except Nordic countries) | 475 | 5.7 | 5224 | 6.3 |
| Outside Europe | 480 | 5.8 | 5224 | 5.3 |
| Unknown | 0 | – | 2 | – |

PHPT primary hyperparathyroidism
on neuropsychiatric morbidity in relation to the background population has remained largely unknown. To our knowledge, this is the first large-scale population-based study of psychiatric comorbidity in PHPT patients prior to surgical treatment and the impact of PTX.

This analysis revealed that both the prevalence of psychiatric diagnoses and the utilization of psychotropic drugs were significantly more comprehensive in patients with PHPT before PTX as compared to the background population. The most commonly used drugs were SSRI.
Table 3 Users by age groups and gender within 3 years prior to index date in the PHPT patients compared to the control population

|                      | PHPT patients (n = 8279) | Control population (n = 82,790) | OR   | 95% CI          |
|----------------------|--------------------------|---------------------------------|------|-----------------|
|                      | n                        | %                               | n    | %               |
| SSRI N06AB All patients |                          |                                 |      |                 |
| Age                  |                          |                                 |      |                 |
| – 49                 | 278/1465                 | 19.0                            | 1677/14,650 | 11.4 | 1.81 (1.57–2.09) |
| 50–64                | 516/3012                 | 17.1                            | 3627/30,120 | 12.0 | 1.53 (1.38–1.70) |
| 65–79                | 424/3204                 | 13.2                            | 3730/32,040 | 11.6 | 1.17 (1.05–1.30) |
| 80+                  | 98/598                   | 16.4                            | 970/5980    | 16.2 | 0.98 (0.78–1.23) |
| Sex M                | 189/1905                 | 9.9                             | 1414/19,050 | 7.4  | 1.37 (1.17–1.61) |
| F                    | 1127/6374                | 17.7                            | 8590/63,740 | 13.5 | 1.38 (1.29–1.48) |
| SNRI, other N06AG, N06AX All patients |                      |                                 |      |                 |
| Age                  |                          |                                 |      |                 |
| – 49                 | 132/1465                 | 9.0                             | 805/14,650 | 5.5  | 1.73 (1.42–2.10) |
| 50–64                | 292/3012                 | 9.7                             | 2099/30,120 | 7.0  | 1.45 (1.27–1.65) |
| 65–79                | 244/3204                 | 7.6                             | 1977/32,040 | 6.2  | 1.26 (1.09–1.44) |
| 80+                  | 47/598                   | 7.9                             | 515/5980    | 8.6  | 0.90 (0.65–1.23) |
| Sex M                | 141/1905                 | 7.4                             | 888/19,050 | 4.7  | 1.65 (1.37–1.99) |
| F                    | 574/6374                 | 9.0                             | 4508/63,740 | 7.1  | 1.31 (1.19–1.43) |
| Tricyclic antidepressive N06AA All patients |                      |                                 |      |                 |
| Age                  |                          |                                 |      |                 |
| – 49                 | 58/1465                  | 4.0                             | 306/14,650 | 2.1  | 1.93 (1.44–2.58) |
| 50–64                | 169/3012                 | 5.6                             | 1083/30,120 | 3.6  | 1.61 (1.36–1.91) |
| 65–79                | 122/3204                 | 3.8                             | 1126/32,040 | 3.5  | 1.11 (0.91–1.34) |
| 80+                  | 25/598                   | 4.2                             | 208/5980    | 3.5  | 1.17 (0.76–1.81) |
| Sex M                | 47/1905                  | 2.5                             | 317/19,050 | 1.7  | 1.48 (1.08–2.03) |
| F                    | 327/6374                 | 5.1                             | 2406/63,740 | 3.8  | 1.39 (1.24–1.57) |
| Antihistaminergic N05BB All patients |                      |                                 |      |                 |
| Age                  |                          |                                 |      |                 |
| – 49                 | 171/1465                 | 11.7                            | 915/14,650 | 6.2  | 1.99 (1.67–2.38) |
| 50–64                | 281/3012                 | 9.3                             | 1943/30,120 | 6.5  | 1.51 (1.32–1.72) |
| 65–79                | 230/3204                 | 7.2                             | 1802/32,040 | 5.6  | 1.30 (1.13–1.51) |
| 80+                  | 34/598                   | 5.7                             | 363/5980    | 6.1  | 0.93 (0.65–1.35) |
| Sex M                | 104/1905                 | 5.5                             | 749/19,050 | 3.9  | 1.42 (1.15–1.75) |
| F                    | 612/6374                 | 9.6                             | 4274/63,740 | 6.7  | 1.48 (1.36–1.62) |
| Anxiolytic, benzodiazepine N05BA All patients |                      |                                 |      |                 |
| Age                  |                          |                                 |      |                 |
| – 49                 | 157/1465                 | 10.7                            | 800/14,650 | 5.5  | 2.09 (1.74–2.52) |
| 50–64                | 349/3012                 | 11.6                            | 2452/30,120 | 8.1  | 1.51 (1.33–1.70) |
| 65–79                | 464/3204                 | 14.5                            | 3784/32,040 | 11.8 | 1.28 (1.15–1.42) |
| 80+                  | 127/598                  | 21.2                            | 1225/5980 | 20.5 | 1.06 (0.86–1.31) |
| Sex M                | 181/1905                 | 9.5                             | 1224/19,050 | 6.4  | 1.58 (1.34–1.87) |
| F                    | 916/6374                 | 14.4                            | 7037/63,740 | 11.0 | 1.37 (1.27–1.48) |
| Sleep, benzodiazepine N05CF All patients |                      |                                 |      |                 |
| Age                  |                          |                                 |      |                 |
| – 49                 | 208/1465                 | 14.2                            | 1229/14,650 | 8.4  | 1.82 (1.55–2.14) |
| 50–64                | 604/3012                 | 20.1                            | 4438/30,120 | 14.7 | 1.47 (1.34–1.62) |
| 65–79                | 816/3204                 | 25.5                            | 6909/32,040 | 21.6 | 1.25 (1.15–1.36) |
| 80+                  | 233/598                  | 39.0                            | 2013/5980 | 33.7 | 1.25 (1.05–1.49) |
| Sex M                | 294/1905                 | 15.4                            | 2127/19,050 | 11.2 | 1.48 (1.29–1.70) |
| F                    | 1567/6374                | 24.6                            | 12,462/63,740 | 19.6 | 1.36 (1.28–1.45) |
anxiolytic and sleep medication. Psychiatric comorbidity was found to be continuously increasing over at least three years of observation prior to PTX as compared to the background population indicating a progress of symptoms along with the duration of PHPT. The relative over-use in patients was found to be represented mainly in patients of up to 65 years of age. In the elderly, use of antidepressants was equivalent to the controls while sleep medication was slightly more common. However, neuropsychiatric symptoms were reported equally in the quality register SQRTPA irrespective of age. This may indicate that somatic symptoms tend to be more of a focal point in the elderly or in the restrictions on medication in order to await the effect of surgery [23].

Following PTX, prevalent users showed the same prescription rate for patients and controls, with the exception of SSRI where patients show a significantly lower prescription rate than the controls. In line with previous clinical studies, this supports the fact that curative PTX may have an effect on neuropsychiatric aspects of the disease even at a population level [4]. Contrarily, the initiation rates were higher for all substances up to one year postoperatively, yet remained significantly elevated at three years only for SSRI and benzodiazepine for sleep. However, numerically the initiation rates were low postoperatively; for SSRI 1.7% in patients and 1.0% in the controls and for benzodiazepines for sleep 2.4% and 1.3%, respectively, over six months after PTX.

Treatment with lithium, which is a known risk factor for developing PHPT, was found in 2.1% of the patients [24]. As expected, given that the main indication for lithium treatment is chronic psychiatric illness, medication with lithium was found to be stable both pre- and postoperatively. The causality of the observed excessive administration of psychotropic drugs in PHPT is elusive in this model. There are several hypothetical explanations for these results; e.g., symptoms of other origins may have prompted biochemical investigations that led to the diagnosis or prescribing of drugs may continue due to a lack of follow-ups with revision of medication [25].

\[
\text{Table 3 continued}
\]

|                  | PHPT patients       | Control population | OR     | 95% CI          |
|------------------|---------------------|--------------------|--------|-----------------|
|                  | \((n = 8279)\)      | \((n = 82,790)\)   |        |                 |
| **Sleep, other** |                     |                    |        |                 |
|                  | N05CF, N05CH, N05CM |                    |        |                 |
| All patients     | 667/8279 8.1        | 5032/82,790 6.1    | 1.36   | (1.25–1.49)     |
| Age              |                     |                    |        |                 |
| – 49             | 120/1465 8.2        | 658/14,650 4.5     | 1.88   | (1.53–2.31)     |
| 50–64            | 278/3012 9.2        | 1873/30,120 6.2    | 1.54   | (1.35–1.76)     |
| 65–79            | 222/3204 6.9        | 2067/32,040 6.5    | 1.09   | (0.95–1.26)     |
| 80+              | 47/598 7.9          | 434/5980 7.3       | 1.10   | (0.81–1.51)     |
| Sex              |                     |                    |        |                 |
| M                | 119/1905 6.2        | 915/19,050 4.8     | 1.35   | (1.11–1.65)     |
| F                | 548/6374 8.6        | 4117/63,740 6.5    | 1.37   | (1.25–1.50)     |
| **Neuroleptics** |                     |                    |        |                 |
|                  | N05A, except Lithium|                    |        |                 |
| Age              |                     |                    |        |                 |
| – 49             | 58/1465 4.0         | 290/14,650 2.0     | 2.09   | (1.55–2.81)     |
| 50–64            | 138/3012 4.6        | 693/30,120 2.3     | 2.13   | (1.76–2.57)     |
| 65–79            | 109/3204 3.4        | 827/32,040 2.6     | 1.40   | (1.14–1.71)     |
| 80+              | 15/598 2.5          | 245/5980 4.1       | 0.59   | (0.34–1.02)     |
| Sex              |                     |                    |        |                 |
| M                | 73/1905 3.8         | 405/19,050 2.1     | 1.91   | (1.47–2.47)     |
| F                | 247/6374 3.9        | 1650/63,740 2.6    | 1.57   | (1.37–1.81)     |
| **Lithium**      |                     |                    |        |                 |
|                  | N05AN01             |                    |        |                 |
| Age              |                     |                    |        |                 |
| – 49             | 19/1465 1.3         | 44/14,650 0.3      | 4.36   | (2.49–7.62)     |
| 50–64            | 89/3012 3.0         | 118/30,120 0.4     | 8.00   | (6.04–10.59)    |
| 65–79            | 66/3204 2.1         | 139/32,040 0.4     | 4.82   | (3.58–6.49)     |
| 80+              | 3/598 0.5           | 18/5980 0.3        | 1.72   | (0.50–5.89)     |
| Sex              |                     |                    |        |                 |
| M                | 39/1905 2.0         | 56/19,050 0.3      | 7.11   | (4.70–10.77)    |
| F                | 138/6374 2.2        | 263/63,740 0.4     | 5.44   | (4.41–6.72)     |

At least one package administrated of the prescribed drug within the observation time

*PHPT* primary hyperparathyroidism, *SSRI* selective serotonin reuptake inhibitors, *SNRI* serotonin norepinephrine reuptake inhibitors
modulations due to the disease or to long-term symptomatic medication may further be subjects for explanatory hypotheses.

Although calcium is a well-known mediator in cell signaling throughout the nervous system, no convincing correlation between the level of hypercalcemia and

Table 4 Diagnoses registered in The National Patient Register (NPR) within one and five years prior to index date in patients compared to the control population

|                              | PHPT cohort (n = 8279) | Control population (n = 82,790) | OR  | 95% CI      |
|------------------------------|------------------------|---------------------------------|-----|-------------|
|                              | n          | %       | n          | %       |             |
| **Diagnoses ICD-10 registered within the period of one year prior to index date** |            |          |            |           |             |
| Dementia, cognitive disorder, F00-F03 | 49          | 0.59    | 435        | 0.53    | 1.13 (0.84–1.52) |
| Psychiatric disorder, F06-F99   | 721         | 8.7     | 3032       | 3.7     | 2.51 (1.31–2.73) |
| Nervsystem, G00-G99             | 1549        | 18.7    | 11,583     | 13.0    | 1.42 (1.33–1.50) |
| Gastrointestinal disease, K20-K99 | 878       | 10.6    | 4493       | 5.4     | 2.07 (1.92–2.23) |
| Kidney stone, N20-N22           | 492         | 5.9     | 272        | 0.3     | 19.6 (16.5–22.26) |
| Musculoskeletal disease, M00-M79 | 1837      | 22.2    | 8684       | 10.5    | 1.43 (2.30–2.57) |
| **Diagnoses ICD-10 registered within the period of five years prior to index date** |            |          |            |           |             |
| Dementia, cognitive disorder, F00-F03 | 58          | 0.7     | 855        | 1.3     | 0.68 (0.52–0.88) |
| Psychiatric disorder, F06-F99   | 1082        | 13.1    | 6821       | 8.4     | 1.67 (1.56–1.79) |
| Nervsystem, G00-G99             | 3206        | 38.7    | 27,018     | 32.6    | 1.30 (125–1.37) |
| Gastrointestinal disease, K20-K99 | 2052      | 24.8    | 13,254     | 16.0    | 1.73 (1.64–1.82) |
| Kidney stone, N20-N22           | 770         | 9.3     | 971        | 1.2     | 8.65 (7.84–9.53) |
| Musculoskeletal disease, M00-M79 | 3278      | 39.6    | 21,876     | 26.4    | 1.83 (1.74–1.91) |

By the National Board of Health and Welfare

**PHPT** primary hyperparathyroidism, ICD international classification of disease
neuropsychiatric symptoms in biochemically mild to moderate PHPT has been found [26]. The significant inverse correlation between excessive drug use and calcium levels found in this study is interesting. One possible explanation is that patients with psychiatric symptoms may have been prioritized for diagnostic work-up and treatment of PHPT.

The strength of this study is the large-scale population-based analysis of virtually comprehensive and valid data. The longitudinal study design allowed analysis of both the natural course of neuropsychiatric morbidity prior to PTX as well as the effects of treatment. In contrast to previous studies of self-reported QoL, this study comprehended objective registry-based data. The Swedish personal identification numbers enabled overlapping linkage between several well-validated national population registers, adding information on diagnoses, drug administrations and handling socioeconomic and demographic confounders [18, 27]. The measure of administered, prescribed drugs has previously been stated to constitute the best available proxy to estimate burden of disease in population-based studies and is considered more valid than diagnoses by ICD [22]. There are some arguments for this. For one, ICD codes tend to accumulate over time and inconsistent coding of diagnoses may lead to misclassification. In this setting, diagnose codes were not covered for primary care, which is of importance regarding conditions usually treated by general practitioners. In the Swedish health care system all psychotropic drugs are subsidized prescription-only, administered via pharmacies and thus completely covered in the drug register. Furthermore, the access to data from The Swedish Quality Register for Endocrine Surgery (SQRTPA) made it possible to include specific disease-related phenotypic characteristics in the analysis.

There are shortcomings in this study. Most importantly, the patients were already selected for treatment by various indications for surgery. Surveillance due to neuropsychiatric morbidity or other conditions are likely to infer selection bias. This aside, undiagnosed PHPT patients or patients treated conservatively were not captured by the data and this may have weakened the results. For these reasons, the generalizability is limited and the results in this study can only refer to patients already subjected to PTX. Moreover, data on the doses and the size of packages were not available for analyzing the magnitude of treatment. This was discussed. Based on the clinical fact that antidepressants, anxiolytics and sleep medication often are exchanged to a similar drug with different dosages or another brand, we considered that at least one allocation of a generic substance within 6 months as representative for estimating drug usage for continuous users. Nor can we say with certainty that the medication actually had been consumed. However, as this fact does not differ between patients and controls, the risk of affecting the result is minimal. Nevertheless, this new knowledge shines a light on the importance of penetrating the history of mental symptoms and taking them into account when assessing patients diagnosed with PHPT.

Fig. 3 Proportion of PTX patients (red line) and population controls (green dashed line) filling prescriptions during three years after index date (i.e., date of surgery). Top panel shows incident users defined as subjects without filled prescriptions during the year before index date, and the bottom panel shows prevalent user defined as subjects with at least one filled prescription during the year before index date. Uncertainty intervals for the patients not intersecting the dashed green line indicates a significant ($p < 0.05$) difference in prescription rates between patients and controls.
Conclusion

PHPT is associated with increased medication for depression, anxiety and sleeping disorders. Prevalence of neuropsychiatric comorbidity should be assessed and considered in order to choose an optimal treatment for PHPT. Psychiatric status and the need for continuous medication should be reevaluated and followed up postoperatively.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00268-022-06485-1.

Acknowledgements The authors are grateful to all co-workers, from all healthcare regions in Sweden, for their provision of data used for this study. The authors Anna Koman, Fredrik Granath and Inga-Lena Nilsson were responsible for the concept and design of the study. All co-authors contributed to the intellectual process and writing of the manuscript.

Funding Open access funding provided by Karolinska Institute. This study was funded by the Stockholm County Council, Karolinska Institutet.

Declarations

Conflict of interest The authors have no conflict of interest to declare.

Ethical approval Ethical approval was obtained by Regional Ethical Committee in Stockholm EPN Dnr: 2019-02149. Ethical approval was obtained by Regional Ethical Committee in Stockholm (Dnr 2017/192-32 and 2017/2-12).

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

References

1. Wu B, Haigh PI, Hwang R, Ituarte PH, Liu IL, Hahn TJ et al (2010) Underutilization of parathyroidectomy in elderly patients with primary hyperparathyroidism. J Clin Endocrinol Metab 95(9):4324–4330. Epub 2010/07/09. https://doi.org/10.1210/jc.2009-2819. PubMed PMID: 20610600; PubMed Central PMCID: PMC2936062
2. Pretorius M, Lundstam K, Hellström M, Fagerland MW, Godang K, Mollerup C, et al (2021) Effects of Parathyroidectomy on quality of life: 10 years of data from a prospective randomized controlled trial on primary hyperparathyroidism (the SIPH-study). J Bone Miner Res 36(1):3–11. Epub 2020/11/22. https://doi.org/10.1002/jbmr.4199. PubMed PMID: 33125769
3. Roman SA, Sosa JA, Pietrzak RH, Snyder PJ, Thomas DC, Udelsman R et al (2011) The effects of serum calcium and parathyroid hormone changes on psychological and cognitive function in patients undergoing parathyroidectomy for primary hyperparathyroidism. Ann Surg 253(1):131–137. https://doi.org/10.1097/SLA.0b013e3181f66720 (PubMed PMID: 21233611)
4. Caron NR, Pasieka JL (2009) What symptom improvement can be expected after operation for primary hyperparathyroidism? World J Surg 33(11):2244–2255. Epub 2009/03/17. https://doi.org/10.1007/s00268-009-9987-4 (PubMed PMID: 19288279)
5. Ambrogi E, Cetani F, Cianferotti L, Vignali E, Banti C, Viccica G et al (2007) Surgery or surveillance for mild asymptomatic primary hyperparathyroidism: a prospective, randomized clinical trial. J Clin Endocrinol Metab 92(8):3114–3121. Epub 2007/05/29. https://doi.org/10.1210/jc.2007-0219. PubMed PMID: 17535997
6. Cheng SP, Lee JJ, Liu TP, Yang PS, Liu SC, Hsu YC et al (2015) Quality of life after surgery or surveillance for asymptomatic primary hyperparathyroidism: a meta-analysis of randomized controlled trials. Medicine (Baltimore) 94(23):e931. https://doi.org/10.1097/MD.0000000000000931 (PubMed PMID: 26061318; PubMed Central PMCID: PMC4616470)
7. O’Sullivan K, Yen TWF, Doffek K, Dream S, Mazotas I, Evans DB et al (2021) An Institutional experience with primary hyperparathyroidism in the elderly over two decades. Am J Surg. https://doi.org/10.1016/j.amjsurg.2021.01.027
8. Thomas DC, Roman SA, Sosa JA (2011) Parathyroidectomy in the elderly: analysis of 7313 patients. J Surg Res 170(2):240–246. Epub 20110331. https://doi.org/10.1016/j.jss.2011.03.014. PubMed PMID: 21571309
9. Chiodini I, Cairoli E, Palmieri S, Pepe J, Walker MD (2018) Non-classical complications of primary hyperparathyroidism. Best Pract Res Clin Endocrinol Metab 32(6):805–820. Epub 20180618. https://doi.org/10.1016/j.beem.2018.06.006. PubMed PMID: 30665548
10. Liu JY, Saunders ND, Chen A, Weber CJ, Sharma J (2016) Neuropsychological Changes in Primary Hyperparathyroidism after Parathyroidectomy. Am Surg 82(9):839–845 (Epub 2016/09/28. PubMed PMID: 27670574)
11. Weber T, Eberle J, Messelhäuser U, Schiffmann L, Nies C, Schabram J et al (2013) Parathyroidectomy, elevated depression scores, and suicidal ideation in patients with primary hyperparathyroidism: results of a prospective multicenter study. JAMA Surg 148(2):109–115. https://doi.org/10.1001/jamasurg.2013.156
12. Khan AA, Hanley DA, Rizzoli R, Bollerslev J, Young JE, Rejnmark L et al (2017) Primary hyperparathyroidism: review and recommendations on evaluation, diagnosis, and management. a Canadian and international consensus. Osteoporos Int 28(1):1–19. Epub 2016/09/11. https://doi.org/10.1007/s00198-016-3716-2. PubMed PMID: 27613721; PubMed Central PMCID: PMC5206263
13. Banmani S, Christou N, Guerin C, Hamy A, Sebag F, Mathonnet M et al (2018) Effect of parathyroidectomy on quality of life and non-specific symptoms in normocalcaemic primary hyperparathyroidism. Br J Surg 105(3):223–229. Epub 2018/02/07. https://doi.org/10.1002/bjs.10739. PubMed PMID: 29405278
14. Bell CF, Warrick MM, Gallagher KC, Baregian N (2018) Neurocognitive performance profile postparathyroidectomy: a pilot study of computerized assessment. Surgery 163(2):457–462. Epub 2017/11/15. https://doi.org/10.1016/j.surg.2017.09.001. PubMed PMID: 29133114
15. Calo PG, Medas F, Loi G, Pisano G, Sorrenti S, Erdas E et al (2017) Parathyroidectomy for primary hyperparathyroidism in...
the elderly: experience of a single endocrine surgery center. Aging Clin Exp Res 29(Suppl 1):15–21. Epub 2016/11/12. https://doi.org/10.1007/s40520-016-0666-7. PubMed PMID: 27837463

16. The Scandinavian Quality Register of Thyroid, Parathyroid and Adrenal surgery: The Scandinavian Quality Register of Thyroid, Parathyroid and Adrenal surgery; 2019. http://www.thyroid-parathyroidsurgery.com/

17. Barlow L, Westergren K, Holmberg L, Talbäck M (2009) The completeness of the Swedish Cancer Register: a sample survey for year 1998. Acta Oncol 48(1):27–33. https://doi.org/10.1080/02841860802247664 (PubMed PMID: 18767000)

18. Ludvigsson JF, Almqvist C, Bonamy AK, Ljung R, Michaëllson K, Neovius M et al (2016) Registers of the Swedish total population and their use in medical research. Eur J Epidemiol 31(2):125–136. Epub 20160114. https://doi.org/10.1007/s10654-016-0117-y. PubMed PMID: 26769609

19. Ludvigsson JF, Svedberg P, Oleń O, Bruze G, Neovius M (2019) The longitudinal integrated database for health insurance and labour market studies (LISA) and its use in medical research. Eur J Epidemiol 34(4):423–437. https://doi.org/10.1007/s10654-019-00511-8. PubMed PMID: 30929112; PubMed Central PMCID: PMC6451717

20. Ludvigsson JF, Andersson E, Ekborn A, Feychting M, Kim JL, Reuterwall C et al (2011) External review and validation of the Swedish national inpatient register. BMC Public Health 11:450. Epub 20110609. https://doi.org/10.1186/1471-2458-11-450. PubMed PMID: 21658213; PubMed Central PMCID: PMC3142234

21. Wettermark B, Hammar N, Fored CM, MichaelFored C, Leimanis A, Otterblad Olausson P et al (2007) The new Swedish Prescribed Drug Register–opportunities for pharmacoepidemiological research and experience from the first six months. Pharmacoepidemiol Drug Saf 16(7):726–735. https://doi.org/10.1002/pds.1294 (PubMed PMID: 16897791)

22. Slobbe LCI, Fussenich K, Wong A, Boshuizen HC, Nielen MMJ, Polder JJ et al (2019) Estimating disease prevalence from drug utilization data using the random forest algorithm. Eur J Public Health 29(4):615–621. https://doi.org/10.1093/eurpub/cky270 (PubMed PMID: 30608539; PubMed Central PMCID: PMC6660107)

23. Zia P, Daskalaki A, Bountouni I, Sykioti P, Varrassi G, Paladini A (2017) Depression and chronic pain in the elderly: links and management challenges. Clin Interv Aging 12:709–720. Epub 20170421. https://doi.org/10.2147/CIA.S113576. PubMed PMID: 28461745; PubMed Central PMCID: PMC5407450

24. Meehan AD, Humble MB, Yazarloo P, Järhult J, Wallin G (2015) The prevalence of lithium-associated hyperparathyroidism in a large Swedish population attending psychiatric outpatient units. J Clin Psychopharmacol 35(3):279–285. https://doi.org/10.1097/JCP.0000000000000303 (PubMed PMID: 25853371)

25. Casarett D (2016) The Science of choosing Wisely-overcoming the therapeutic illusion. N Engl J Med 374(13):1203–1205. https://doi.org/10.1056/NEJMp1516803 (PubMed PMID: 27028909)

26. Koman A, Ohlsson S, Branstrom R, Pernow Y, Branstrom R, Nilsson IL (2019) Short-term medical treatment of hypercalcaemia in primary hyperparathyroidism predicts symptomatic response after parathyroidectomy. Br J Surg. Epub 2019/10/10. https://doi.org/10.1002/bjs.11319. PubMed PMID: 31595982

27. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekborn A (2009) The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. Eur J Epidemiol 24(11):659–667. Epub 20090606. https://doi.org/10.1007/s10654-009-9350-y. PubMed PMID: 19504049; PubMed Central PMCID: PMC2773709.

Publisher’s Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.