

# BMJ Open Frequency of non-motor symptoms in Parkinson's disease presenting to tertiary care centre in Pakistan: an observational, cross-sectional study

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## ABSTRACT

**Objective** To determine the frequency of non-motor symptoms (NMS) in patients of Parkinson's disease (PD) presenting to a movement disorder clinic at a tertiary care centre in Pakistan, and how frequency of NMS is different in male and female patients.

**Study design** Observational, cross-sectional study.

**Setting** Tertiary care centre.

**Participants** Out of 102 patients, 85 were included. Inclusion criteria were patients with PD diagnosed according to the UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria, age  $\geq 18$  years, able to give consent and have no difficulty in answering questions. Exclusion criteria were diseases that resemble PD, stroke, dementia, patients unable to provide information and history of antipsychotic use.

**Results** The NMSQuest revealed a mean of nearly seven different NMS per patient. Autonomic problems such as constipation (56%) and nocturia (49%) were the most common NMS, while urinary urgency was reported by 35% of patients. Low mood and feeling sad were reported by 47%, whereas feeling anxious/panicky was reported by 36%. Problem with memory was reported by 45% of patients. Feeling of light-headedness and dizziness was reported by 40% of patients. Problems with sexual relationship were reported by 30% of patients. The most common sleep problem was difficulty falling sleep (29%). Pain not related to the musculoskeletal system was reported by 30% of patients. Loss or change in the ability to taste or smell was reported by 29% of patients. The rest of NMS were less than 25% in frequency. Feeling sad or blue, feeling light-headed/dizzy, unexplained pain, unpleasant sensations in the legs, difficulty in swallowing and faecal incontinence were more common in female participants, while problems with sex were more common in male participants.

**Conclusion** NMS are quite prevalent in PD in our population. Certain NMS are more common in women as compared with men. There is a need for a large-scale study to look for the association of different NMS with sex.

## INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disorder, after Alzheimer disease. It is characterised by motor symptoms that include resting tremor,

## Strengths and limitations of this study

- This is the first study on this subject done in Pakistan (of 102 patients, 85 were included in the study) showing 7 non-motor symptoms (NMS) per patient.
- The study compared NMS between male and female patients.
- Limitations are its relatively small sample size and that it is a single-centre study.

bradykinesia, rigidity and postural problems.<sup>1</sup> About 1–2 persons per 1000 of the population suffer from PD. The prevalence of PD tends to increase with ageing population, and 1% of the population above 60 years is affected by PD.<sup>2</sup> Non-motor symptoms (NMS) of PD include a variety of symptoms such as neuropsychiatric problems (cognitive impairment, anxiety, depression, psychosis, compulsive disorders and apathy), autonomic manifestations (bowel problems such as constipation, urinary complaints and sexual dysfunction), sleep disorders, fatigue and sensory symptoms.<sup>3</sup>

As much as 90% of people with PD report NMS from early to advanced stages of the disease.<sup>4</sup> A number of studies have shown a negative correlation between NMS and quality of life.<sup>5</sup>

Some NMS of PD are well recognised, such as dementia, dysautonomia, depression and sleep problems, but symptoms such as weight changes, dribbling of saliva, visual problems and sexual problems may not be well appreciated.<sup>6</sup> Many NMS such as pain, apathy, bowel incontinence, difficulties with sexual relationship and sleep problems may not be disclosed to attending physicians mainly due to embarrassment or patients may be unaware that the symptoms are linked to PD.<sup>7</sup> Up to 50% of patients with PD may have dementia after 15 years of disease period,<sup>8</sup> with prevalence increasing to as high as 80%–90% by the age

of 90 years and above.<sup>9</sup> Neuropsychiatric manifestations, mainly psychosis and depression, are prevalent at all stages of the disease and lead to significant disability.<sup>10</sup> Many of the drugs that are used for treatment of PD, such as dopamine therapy, can lead to many NMS, such as drug-induced psychosis or hallucinations, postural hypotension and dopamine dysregulation syndrome.<sup>11</sup> NMS of PD may be very troublesome and the quality of life of both patients with PD and their relatives or caregivers is badly affected.<sup>12</sup>

Most of the times NMS are overlooked during routine patient encounters, and such under-recognition may lead to deleterious implications on the quality of care as many NMS are potentially treatable.<sup>7</sup> A study conducted in the USA reported that treating physicians in over 50% of consultations did not recognise existing anxiety, depression, fatigue and sleep problems in over 40% of encounters.<sup>13</sup> Recognition of NMS is of utmost importance as many of the NMS of PD are treatable and patients may get better with dopaminergic drugs.<sup>10</sup>

The NMS questionnaire is a comprehensive 30-item self-assessment screening instrument comprising nine NMS domains meant for rapid screening of NMS, empowering both caregiver/relative and patients to raise relevant NMS that are not otherwise discussed in routine clinical visits.<sup>14</sup>

The validity, feasibility and acceptability of the NMS questionnaire have been assessed in a pilot validation study, which has been published, and the questionnaire has undergone independent validation and is hence recommended by the Department of Health in the UK for use in clinical practice.<sup>7</sup>

There have been many studies conducted to date that described different NMS in different populations, but very few studies were conducted in this part of the world. The main idea that motivated this research project was to see the pattern of NMS in our population and see if there is any difference between male and female patients in regard to the frequency of the different NMS.

## PATIENTS AND METHODS

This was a cross-sectional, observational and descriptive study. It was conducted on patients with PD presenting to a movement disorder clinic, Lahore General Hospital, Lahore (a tertiary care centre) from 1 August 2015 to 31 December 2016. The inclusion criteria were patients with PD diagnosed according to the UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria,<sup>15</sup> age  $\geq 18$  years, able to give consent, and have no difficulty in answering questions independently or with the help of a family member or a doctor. The exclusion criteria were diseases that resemble PD (Parkinson's plus others), patients with stroke, patients who were unable to provide information, dementia and history of antipsychotic use. Seventeen patients were found to have Parkinson's plus, concurrent stroke and history of taking antipsychotics, and hence were not included in the study. Informed

consent was obtained. All participants of the study were required to fill in a PD NMS questionnaire either himself or with the help of a family member. In cases where there was a language problem, doctors helped patients in filling in the PD NMS questionnaire. Responses were recorded in a yes or no fashion. Patients only marked yes if he or she had experienced the said symptom/problem in the past 1 month. Drug history and routine demographic details were also recorded. Declaration of NMS by patients with PD led to proper management of reported symptoms.

G\*Power V.3.1 statistical software was used for sample size determination. By using one-sample t-test, 'NMS' score was assumed as an outcome variable. The mean and SD of NMS were considered at  $35.21 \pm 21.85$ .<sup>16</sup> The calculated effect size and power ( $1-\beta$ ) were 0.80 and 0.95, respectively. An aggregate of 85 samples would be quite enough for our study parameters.

## Patient and public involvement statement

No patient was involved in the design or conduct of the study, but the results of the study will be shared to patients coming for follow-up.

## Data analysis

After the questionnaires were filled in by all of the patients, data were entered and analysed using Statistical Package for Social Sciences (SPSS) V.22. The mean and SD were calculated for numerical variables. Categorical data were expressed as frequency and percentage. With regard to the reliability of NMS among items, a Cronbach's alpha value of 0.72 reflected good reliability. The frequency of each NMS was calculated by computing the number of yes response and calculating the percentage related to the number of patients in the sample. Analysis was done to calculate the frequency of all NMS among the enrolled patients. To find out the association of NMS symptoms with respect to male and female patients,  $\chi^2$  test/Fisher's exact test was applied and  $p \leq 0.05$  was considered significant.

## RESULTS

From August 2015 to 31 December 2016, 102 patients were screened. Out of those patients, 85 were found eligible for study based on the inclusion and exclusion criteria. The average age was  $57.61 \pm 10.64$  years, the youngest being 35 years old and the oldest being 77 years old. In our study, men dominated in number ( $n=70$ , 82%) as compared with women ( $n=15$ , 18%). The NMS score revealed a mean of nearly seven different NMS per patient. Gastrointestinal complaints were the most frequent. Out of a total of 85 patients, 48 (56%) reported constipation. Only 24 (28%) patients reported troublesome sialorrhoea. Urinary symptoms were next in frequency, with nocturia being the second most common symptom as reported by 42 (49%) patients, while urinary urgency was reported by 30 (35%) patients. Neuropsychiatric symptoms were also quite frequent as low mood and feeling

sad were reported by 40 (47%) patients, whereas feeling anxious and panicky was reported by 31 (36%). Problems with memory were reported by 38 (45%) patients. Problems with libido were reported by 12 (14%) patients and 26 (30%) patients admitted difficulty with sexual relationships. Among autonomic symptoms, feeling of light-headedness and dizziness while standing from lying or sitting position was reported by 35 (40%) patients. Difficulty falling sleep and staying asleep was reported by 25 (29%) patients. Pain not related to the musculoskeletal system was reported by 26 (30%) patients. Change in the ability to taste or smell was reported by 25 (29%) patients. Excessive sweating, unpleasant sensation in the legs, frightening dreams and unexplained change in weight were reported by 21 (24%), 19 (22%), 19 (22%) and 18 (20%) patients, respectively. The rest of the NMS were less than 20% in frequency. The frequency of all NMS is listed in table 1.

The most common NMS in men included constipation (54%), getting up regularly to pass urine at night (50%) and problems with short-term memory (48%). The most common NMS in women included feeling sad or blue (80%), unexplained pain (67%), feeling light-headed or dizzy (73%), feeling anxious or panicky (61%), and feeling unpleasant sensations in the legs while at rest (47%). The frequency of all NMS in both sexes is shown in figure 1.

We observed that a significant association of NMS symptoms was found as compared with men and women in feeling sad or blue, feeling light-headed/dizzy, unexplained pain, problems with sex, unpleasant sensation in the legs, difficulty in swallowing food or drink or problems with choking, and faecal incontinence (table 2). However the small number of female patients (n=15) was a major limitation of our study.

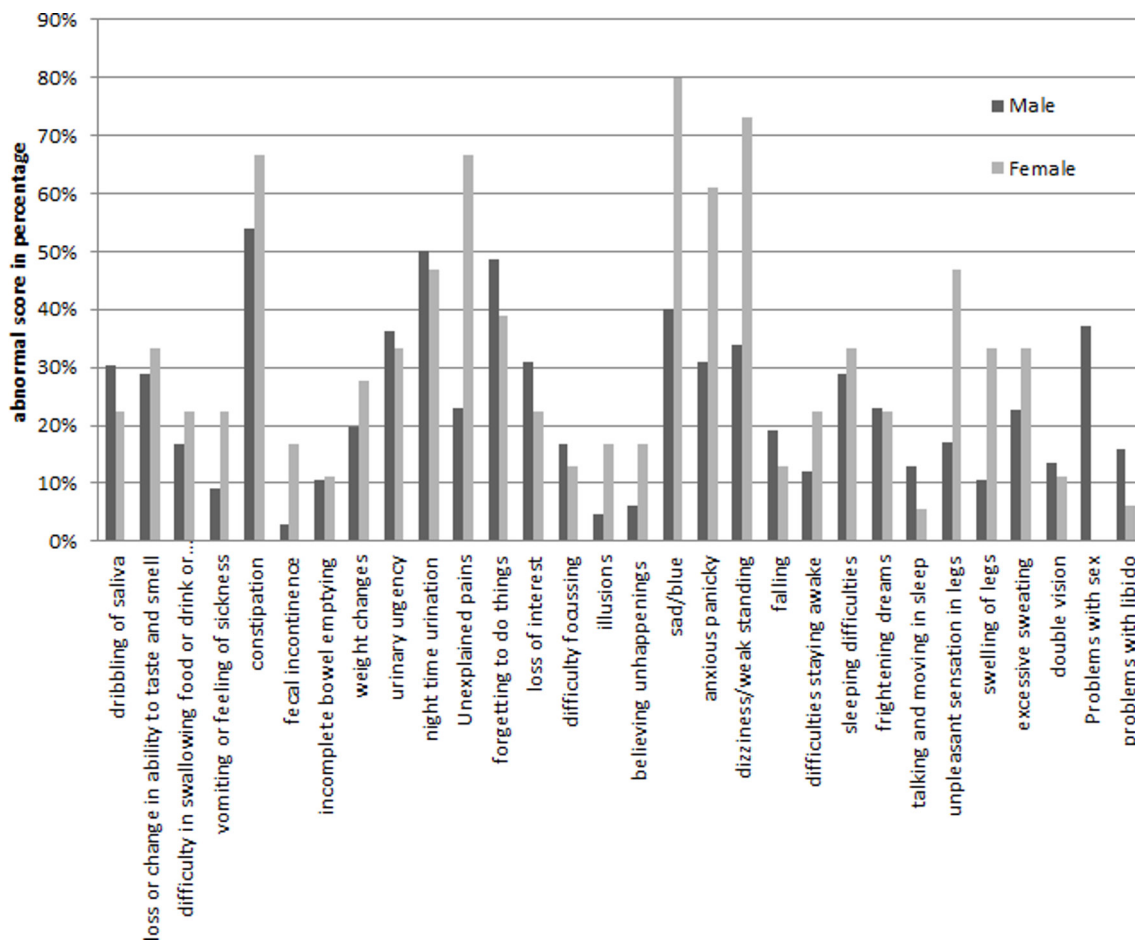
## DISCUSSION

In this study we have shown the high frequency of NMS in patients with PD in Pakistan. Overall the most frequent NMS was constipation (56%). In our clinical practice, constipation is in fact a very common complaint. Stocchi and Torti<sup>17</sup> described the prevalence of constipation in PD ranging from 24.6% to 63% depending on different diagnostic criteria. In PD it is due to slow colonic transit and it can be relieved by polyethylene glycol and lubiprostone, along with dietary modifications.<sup>18</sup> Nocturia is second in frequency (49%), while urinary urgency was reported by 35% of patients. Chaudhuri *et al*<sup>7</sup> reported nocturia to be the most common NMS (65%) in their study. Weerkamp *et al*<sup>19</sup> described nocturia in 57% of nursing home residents. Yeo *et al*<sup>20</sup> described nocturia as the most common urinary tract complaint in patients with PD (>60%) and attributed it to detrusor muscle overactivity, while urgency was found at 33%–54%. Rana *et al*<sup>21</sup> reported a significant association between anxiety and nocturia in patients with PD, with greater significance found for male patients as compared with female patients, and suggested that addressing anxiety may help nocturia.

**Table 1** Prevalence of individual non-motor symptoms (NMS) items

NMS symptoms	Percentage (frequency)
Constipation	56 (48)
Nocturia	49 (42)
Feeling sad or blue	47 (40)
Forgetting to do things	45 (38)
Feeling light-headed/dizzy	40 (35)
Feeling anxious or panicky	36 (31)
Urinary urgency	35 (30)
Unexplained pain	30 (26)
Problems with sex	30 (26)
Difficulty sleeping	29 (25)
Loss or change in ability to taste or smell	29 (25)
Loss of interest in surroundings	29 (25)
Dribbling of saliva	28 (24)
Excessive sweating	24 (21)
Unpleasant sensation in the legs	22 (19)
Frightening dreams	22 (19)
Unexplained change in weight	20 (18)
Falling	19 (15)
Difficulty in swallowing food or drink or problems with choking	17 (15)
Difficulty concentrating or staying focused	16 (14)
Swelling in the legs	14 (12)
Daytime somnolence	13 (11)
Double vision	14 (12)
Decreased/increased libido	14 (12)
Talking or moving in sleep	11 (10)
Incomplete bowel emptying	11 (10)
Vomiting or feeling of sickness	10 (9)
Delusions	8 (7)
Illusions	8 (7)
Faecal incontinence	6 (5)

Neuropsychiatric symptoms such as anxiety, low mood and memory problems can lead to significant morbidity and negatively impact quality of life. Feeling anxious was reported by 36% of our patients, while 47% had low mood and 45% had issues with remembering things. Chaudhuri *et al* and Weerkamp *et al* reported anxiety in 42% and 53% and low mood in 49% and 66%, respectively, while 51% of patients had problems with their memory in both studies.<sup>7 19</sup> These symptoms in PD are attributable to intricate pathological changes in various brain regions.<sup>22</sup> Alterations in dopamine, acetylcholine and serotonin levels in subcortical projections and degenerative processes involving the limbic circuits and



**Figure 1** Frequency of different non-motor symptoms (NMS) in both sexes. The x-axis shows different NMS while the y-axis shows the percentage.

cortical connections lead to NMS.<sup>23</sup> Tricyclic antidepressants are effective for depression in PD, and antipsychotic clozapine is effective for psychosis.<sup>24</sup>

Feeling light-headed and dizzy was also a major concern (40%) in our study. Other studies have reported slightly higher incidences (39% and 48%).<sup>7,19</sup> It may be relieved by addressing neurogenic orthostatic hypotension. Management includes patient education, physical manoeuvres, adequate hydration and judicious use of dopaminergic drugs.<sup>25</sup> Specific treatment includes salt supplementation, mineralocorticoids and other empiric medications.<sup>26</sup>

Drooling of saliva is one of the NMS in patients with PD that have negative physical and psychosocial impact on patients and their families. The cause of drooling in PD remains uncertain; however, decreased intraoral salivary clearance is thought to be the major factor in the pathophysiology of drooling.<sup>26</sup> Our study shows that 28% of patients had drooling of saliva, while other studies found a higher number of patients with this complaint (42% and 63%).<sup>7,19</sup> This difference may be due to the difference in age of patients (our cohort being younger) and also the frequent use of anticholinergics in this part of the world. Non-pharmacological measures such as sucking on candies or chewing gum<sup>27</sup> and adjusting

dopaminergic drugs may help some patients.<sup>28</sup> Drug therapy for severe drooling includes muscarinic receptor antagonist, which inhibits salivary secretions. However, keeping in mind their adverse effect profiles, such agents should be used cautiously in elderly patients.<sup>29</sup> Injection of parotid glands with botulinum toxin has been shown to be a safe and effective modality in the treatment of sialorrhoea in patients with PD.<sup>30–33</sup>

Sleep problems in patients with PD comprise problems with initiating sleep, frequent night-time awakening, restless legs syndrome, sleep breathing disorders, rapid eye movement sleep disorders, sleep attacks, drug-induced symptoms and daytime somnolence.<sup>34</sup> In our study 29% of patients had problems with insomnia, 14% had daytime somnolence and 10% had problem with talking or moving in sleep. Treatment of insomnia includes ruling out and treating other sleep-related motor and breathing problems, treating motor complications of PD if present, following proper sleep hygiene and cognitive-behavioural therapy, and melatonin at high dose, and if all ineffective then drugs such as zolpidem, trazodone or doxepin, and eszopiclone could be added.<sup>35</sup>

Anosmia is a common NMS of PD. Anosmia has been shown to occur years before the motor symptoms of PD set in, and autopsy findings have confirmed synucleinopathy

**Table 2** Association of non-motor symptoms (NMS) with sex

NMS symptoms	Male (n=70)	Female (n=15)	P values
Constipation	38 (54)	10 (67)	0.554
Nocturia	35 (50)	7 (47)	0.814
Feeling sad or blue	28 (40)	12 (80)	0.011*
Forgetting to do things	33 (48)	5 (39)	0.751
Feeling light-headed/dizzy	24 (34)	11 (73)	0.012*
Feeling anxious or panicky	22 (31)	9 (61)	0.073
Urinary urgency	25 (36)	5 (33)	0.861
Unexplained pain	16 (23)	10 (67)	0.002*
Problems with sex	26 (37)	0	0.003*
Difficulty sleeping	20 (29)	5 (33)	0.759
Loss or change in ability to taste or smell	20 (29)	5 (33)	0.758
Loss of interest in surroundings	22 (31)	3 (22)	0.536
Dribbling of saliva	21 (30)	3 (22)	0.537
Excessive sweating	16 (23)	5 (33)	0.601
Unpleasant sensation in the legs	12 (17)	7 (47)	0.031*
Frightening dreams	16 (23)	3 (22)	0.999
Unexplained change in weight	14 (20)	4 (28)	0.727
Falling	13 (19)	2 (13)	0.999
Difficulty in swallowing food or drink or problems with choking	12 (17)	3 (22)	0.031*
Difficulty concentrating or staying focused	12 (17)	2 (13)	0.176
Swelling in the legs	7 (11)	5 (33)	0.081
Daytime somnolence	8 (12)	3 (22)	0.401
Double vision	10 (14)	2 (11)	0.999
Decreased/increased libido	11 (16)	1 (6)	0.199
Talking or moving in sleep	9 (13)	1 (6)	0.682
Vomiting or feeling of sickness	6 (9)	3 (22)	0.192
Incomplete bowel emptying	8 (11)	2 (11)	0.999
Delusions	4 (5)	3 (17)	0.101
Illusions	4 (5)	3 (17)	0.101
Faecal incontinence	2 (3)	3 (17)	0.036*

Categorical variables were presented as frequencies (percentages) and  $\chi^2$ /Fisher's exact test was applied.

\*Significant ( $p \leq 0.05$ ).

affecting the olfactory pathways and the anterior olfactory nucleus.<sup>36</sup> In our study 29% of patients reported anosmia and ageusia. Other studies have reported different frequencies (43% and 11%).<sup>7,19</sup> The difference in reported frequencies may be due to different cultures, age of patients, disease stage and different sample sizes.

Sexual dysfunction is an important but unfortunately a neglected NMS of PD. In our study 13% of patients reported problems with libido, while 30% voiced problems with sexual intercourse. Chaudhuri *et al*<sup>7</sup> reported problems with libido in 37% of their patients and 34% of their patients had difficulty with sex. Kummer *et al*<sup>37</sup> reported loss of libido in 65.6% of their patients, and showed advancing age, lower education, female sex and depression were associated with low libido. The underlying

pathology is hypothalamic dysfunction via altered dopamine-oxytocin pathways, which normally promote libido.<sup>38</sup> Varanda *et al*<sup>39</sup> described sexual dysfunction in women with PD and reported it at 86.9%. Interestingly Hu *et al*<sup>40</sup> conducted a study on Chinese male patients and reported sexual dysfunction was found in 41.4% of their patients. A possible explanation of these differences could be due to different cultures, social values and possible biases in reporting. This topic should be addressed with adequate privacy. Also social norms should be given due respect while looking into these problems.

Certain NMS were more common in female patients ( $p \leq 0.05$ ). They include feeling sad or blue, feeling light-headed/dizzy, unexplained pain, unpleasant sensation in the legs, difficulty in swallowing food or drink or problems

with choking, and faecal incontinence. This implies that female patients need to be probed more thoroughly for NMS. Problems with sex were the only NMS that was more frequent in male patients ( $p \leq 0.05$ ). This may be due to reporting bias. Women in Pakistani culture are more conservative and usually do not feel comfortable with discussing such intimate issues.

Our study had some limitations as well. Majority of our patients were male ( $n=70$ , 82%) as compared with female ( $n=15$ , 18%), with a male to female ratio of 4.6:1. This may be due to culture bias, as expected in male-dominant societies where men are more likely to seek medical care. The study group was relatively small in number and was performed at one centre, so the study may have an element of selection bias as well (investigating only patients coming to our movement disorder clinic).

## CONCLUSION

NMS are quite prevalent in PD in our population. Certain NMS are more common in female patients as compared with male patients. There is a need for a large-scale study to look for an association of different NMS with sex. This will lead to better understanding of patients' problems and more vigilant care can hence be provided.

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**Data sharing statement** Data can be shared via email with interested readers.

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