Parkinson's Disease Psychosis – Prevalence Patterns Across the EU-5

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Parkinson's disease psychosis (PDP) is a clinical condition that affects patients diagnosed with Parkinson's disease (PD) and has a spectrum of neuropsychiatric symptoms distinct from the hallmark motor symptoms. Although prior studies have reported on the prevalence of PDP in select European nations, variations in study design complicate study-to-study comparisons. In this study, we surveyed 1,667 medical practitioners across France, Germany, Italy, Spain, and the UK (collectively, the EU-5) to estimate the prevalence of PDP or symptoms of psychosis among patients with PD. Analysis of the survey data suggest approximately 29% of the general PD population in the EU-5 exhibit signs of PDP. Among the PD population, country-specific rates of PDP are estimated at 30% in France, 27% in Germany, 34% in Italy, 30% in Spain and 21% in the UK. These rates appear in line with those reported in prior country-specific studies. Results from the subset of 437 neurologists who proceeded to take the full survey suggest the symptoms of PDP are disruptive to patients or their respective caregivers in approximately 53% of cases. These results provide a resource that enables cross-country comparison of PDP rates across these major European nations.

Keywords

Parkinson's disease, psychosis, prevalence, epidemiology, Europe

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Parkinson's disease (PD) is a chronic, progressive, neurological disorder; diagnosis is based on its hallmark motor symptoms which include resting tremor, bradykinesia, rigidity and postural instability.[1–3] It is the second most common neurodegenerative disease after Alzheimer's disease, affecting over 1 million individuals across Europe and more than 10 million worldwide.[3,4]

Parkinson's disease psychosis (PDP) is a distinct non-motor clinical condition that commonly manifests in patients following a primary diagnosis of PD. The condition is characterised by a spectrum of symptoms associated with psychosis such as illusions, false sense of presence, hallucinations and delusions.[5] Hallucinations in PD are typically visual, unlike in schizophrenia where hallucinations are often auditory.[6] PDP diagnostic criteria developed by the US-based National Institute of Neurological Disorders and Stroke (NINDS)/National Institute of Mental Health (NIMH) work group include having a prior diagnosis of PD and one or more of the aforementioned psychotic symptoms that persist for one month or longer and are not explained by other causes or diagnoses.[5] Treatment guidelines from European healthcare authorities generally recommend use of clozapine or quetiapine if withdrawal of add-on medications and dose adjustment for PD medications are insufficient to control the symptoms of psychosis; however, there are safety and efficacy concerns with the use of these drugs.[7–9]

Understanding the epidemiology of PDP is important, in part, because the chronic, progressive and debilitating condition can magnify the clinical, humanistic and economic burden of PD on patients, communities and healthcare systems. Risk factors for PDP include new medications and changes to existing PD medications, older age, advanced or late-stage PD, dementia, as well as vision and sleep disorders.[10] Symptoms of PDP vary in severity and can be disruptive to the patient. Studies in patients with PD have associated symptoms of psychosis with increased odds of reporting suicidal or death ideation[11,12] and increased mortality risk.[13,14] Multiple studies have also reported positive associations between PDP and dementia, as well as with neuropsychiatric symptoms such as depression and anxiety, suggesting patients with PDP are likely to have high comorbidity burdens.[15–17] The symptoms of PDP can also be disruptive to caregivers. Family members are often the party to take on caregiver responsibilities for patients with PDP.[18] Multiple studies have found that caregivers of patients with PDP report higher burdens, increased depression and lower quality of life compared with caregivers of PD patients without psychosis.[16,19,20] Finally, studies in patients with PD have identified psychosis as one of the most common reasons for hospitalization[21,22] and hallucinations as the strongest predictor of placement into nursing homes[23,24] suggesting patients with PDP are likely to incur higher healthcare resource utilisation than patients without psychosis.

Though prevalence data on PDP in European nations already exist, estimates vary widely by country and study. Variations in study design, such as data-gathering methods, study inclusion/exclusion

criteria, definitions of PDP and symptoms of psychosis complicate study-to-study comparisons, which can make aggregate epidemiological data from a meta-analysis difficult to interpret. A key prospective longitudinal study in Norway has reported the cumulative prevalence of PDP at 60% among 230 patients with PD followed over the 12-year study, with point prevalence rates ranging from 18–49%.[25]

We surveyed medical practitioners in France, Germany, Italy, Spain and the UK (collectively, the EU-5) to gain a clearer picture of PDP epidemiology and treatment patterns across this region. The current study presents estimates on the prevalence and severity of PDP among patients with PD in the EU-5 based on the survey data. Trends identified within this region could potentially predict trends across the broader EU.

Methods

Survey design

An online survey was developed and targeted to medical practitioner specialists in the EU-5 nations between 21 May 2015 and 24 June 2015 as part of a broader study to address evidence gaps related to PDP epidemiology and treatment patterns among those in the neurologist specialty. The evidence gaps were previously identified from a targeted literature review covering the epidemiology and current treatment paradigm for PDP (unpublished findings).

Measures taken to encourage survey participation included honoraria for respondents who were deemed qualified to take the full survey, and recruitment via email, telephone and fax using large physician databases. All surveys were translated and administered in the local language.

Preliminary qualitative research identified medical practitioners in the neurology specialty who practiced in office and hospital settings as the key providers of treatment to patients with PD. Findings were used to optimise survey targeting and recruitment. The survey was designed with 18 screener questions to help limit the full survey (made up of 65 questions around patient records) to medical practitioners who were most likely to diagnose and provide care for patients with PDP in a manner that is representative of their country of practice. Eligibility to take the full survey was based on participant responses to the screener questions. The screening criteria are presented in *Table 1*.

The full survey included questions about the percentage of the neurologists' patients with PDP who had disruptive versus non-disruptive symptoms of psychosis, the percentage of patients with disruptive PDP who had severe versus mild-to-moderate PD motor symptomology, and the rates of dementia and cardiovascular disease (CVD) among the patients with disruptive PDP.

Results from both the screener questions and full patient records survey were provided to investigators at Analysis Group in an anonymised aggregated dataset, and were analysed using Microsoft Excel 2010.

BluePrint Research Group, an independent market research firm commissioned by ACADIA Pharmaceuticals Inc., conducted the survey in compliance with data protection legislation and privacy laws, and the codes of conduct of the Market Research Society (MRS) and British Healthcare Business Intelligence Association (BHBIA).

Data analysis

The diagnosis of PDP and symptoms of psychosis were based on the assessment of the medical practitioner. An analysis of responses to two of the screener questions (Q10 and Q11) was used to estimate the prevalence of PDP among the broader PD population. These questions were as follows.

Table 1: Medical practitioner screening criteria

Board certified, in practice full time
In clinical practice for 3–30 years
Area of specialisation is neurology
Seen at least 200 patients (for any condition) in the last year
Seen at least 40 PD patients in the last year
Seen at least 12 PDP patients in the last year
Personally makes drug treatment decisions for PDP
Primary practice setting is office, clinic, hospital or nursing home

PD = Parkinson's disease; PDP = Parkinson's disease psychosis.

Q10. Of the total patients you have seen/treated in the last 12 months, how many have PD?

Q11. Of the patients you have seen/treated for PD in the last 12 months, how many have PDP, or symptoms of psychosis associated with their PD (which may manifest as a result of PD progression or treatment)?

Q10 and Q11 both included instructions to not multi-count patients who the surveyed medical practitioner has seen multiple times in the last 12 months. To minimise confounding from neuropsychiatric conditions with overlapping symptomology, Q11 also instructed the respondent to exclude patients with PD who have symptoms of psychosis due to other conditions such as schizophrenia, schizo-affective disorder or bipolar disorder.

Respondents who did not answer both screener questions were excluded from the analysis for estimating PDP prevalence. Rates of PDP by country and across the EU-5 were calculated based on the sum of self-reported patient numbers from Q11 divided by the sum of self-reported patient numbers from Q10.

An analysis of neurologist-provided responses to four questions from the full survey (Q1, Q3, Q5 and Q6) was used to estimate the frequency at which PDP symptoms are disruptive to patients and their respective caregivers, as well as the rates of severe and mild-to-moderate PD motor symptomology, dementia and CVD among these patients. Q1 and Q3 also were complemented with a question asking the neurologist to rank the top five features they considered when assessing the disruptiveness of psychosis symptoms and severity of PD motor symptomology (Q2).

Questions 1, 2, 3, 5, and 6 were as follows:

Q1. Of all your patients with PDP, what percentage belong to each of the following categories regarding the disruptiveness of their symptoms of psychosis? (Categories were 'non-disruptive' and 'disruptive').

Q2. Please rank the top 5 features that you consider when determining the severity of PD psychosis symptoms.

Choices for Q2 were as follows:

i. The degree to which the patient's psychosis interferes with his/her ability to sleep at night.
ii. The degree to which the patient's psychosis interferes with the caregiver's ability to sleep at night.
iii. The degree to which the patient is bothered by his/her symptoms of psychosis (unrelated to sleep).

Table 2: Survey participants by geography and primary specialty area

Country	Total	Neurology*	Psychiatry**	GP/FP/IM	Geriatrics	Other
France	255	213 (84%)	13	13	4	12
Germany	379	314 (83%)	20	28	7	10
Italy	327	252 (77%)	8	43	8	16
Spain	286	237 (83%)	9	35	0	5
UK	271	181 (67%)	24	27	20	19
Total	1,518	1,197 (79%)	74	146	39	62

Covers general neurology, movement disorder specialists, and nervenärzte (Germany only);Covers general psychiatry and geriatric psychiatry. GP = general practice; FP = family practice; IM = internal medicine.*

iv. The degree to which the patient's caregiver is bothered by the patient's symptoms of psychosis (unrelated to sleep).
v. The frequency of symptoms of psychosis.
vi. The type of symptoms of psychosis the patient is experiencing (i.e., illusions versus visual hallucinations versus delusions).
vii. Whether the patient has insight on his/her psychosis.
viii. The degree to which the patient's psychosis interferes with his/her daily activities.
ix. The degree to which the patient's psychosis negatively impacts his/her quality of life.
x. The degree to which the patient's psychosis interferes with the caregiver's quality of life.
xi. Other (specify).

Q3. Of all your PDP patients with disruptive symptoms of psychosis, what percentage belong to each of the following categories regarding PD motor symptomatology? (Categories were 'severe' and 'mild-to-moderate').
Q5: Of all your PDP patients with disruptive symptoms of psychosis AND mild-to-moderate PD motor symptomatology, what percentage have the following comorbidities? (Categories were 'dementia', 'CVD' and 'none of these').
Q6: Of all your PDP patients with disruptive symptoms of psychosis AND severe PD motor symptomatology, what percentage have the following comorbidities? (Categories were 'dementia', 'CVD' and 'none of these').

Estimated frequency of symptoms and comorbidities were based on the weighted mean of neurologist-provided estimates to Q1, Q3, Q5 and Q6. Neurologist-provided responses to these questions were weighted according to the estimated prevalence of PDP in each country.

Reported percentages for Q2 are unweighted and based on the frequency at which neurologists ranked each parameter as among the top five they considered when determining the disruptiveness of symptoms of psychosis. The frequency was calculated by dividing the total number of instances where a parameter was ranked as among the top five considered divided by the number of surveyed neurologists.

Results

Survey metrics

A total of 1,667 medical practitioners across the EU-5 participated in the survey. Of these, 1,518 responded to both screener questions related to PDP prevalence (Q10 and Q11) and were included in the analysis to estimate prevalence. In this subset, 1,197 (79%) described their primary specialty as neurology and 74 (5%) described their primary specialty as psychiatry. The remaining 247 participants (16%) described their primary specialty as general practice, family practice, internal medicine, geriatrics or 'other'. Of the participants included in the prevalence analysis, 758 (50%) primarily practised in the academic/teaching hospital setting, 415 (27%) primarily practised in an office or clinic setting, and 319 (21%) primarily practised at a community hospital. The remaining 26 participants (2%) primarily practised in other settings. Country-specific breakdowns of survey participants by primary specialty areas are reported in *Table 2*.

Table 3: Geographical breakdown of respondents

Country	Screener	Full Survey
France	255	88
Germany	379	90
Italy	327	91
Spain	286	96
UK	271	72
Total	1,518	437

Only 437 participants (26%) were eligible to take the full patient records survey based on their responses to the screener questions. The number of respondents surveyed by country is reported in *Table 3*.

Parkinson's disease psychosis prevalence

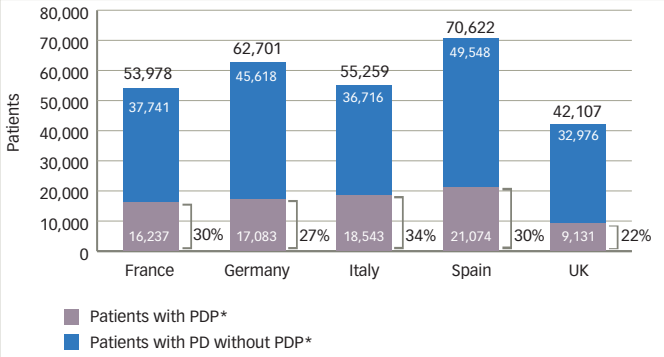
The 1,518 survey respondents reported seeing and/or treating approximately 285,000 patients with PD over the past 12 months. Participants reported approximately 82,000 of their patients as having a diagnosis of PDP or symptoms of psychosis associated with PD, suggesting a prevalence rate of 29% within the sampled EU-5 cohort. Estimated prevalence rates of PDP or symptoms of psychosis among the PD patient population in each of the five surveyed countries were 30% in France, 27% in Germany, 34% in Italy, 30% in Spain and 21% in the UK. Prevalence and patient numbers by country are presented in *Figure 1*.

Disruptiveness and comorbidity rates

Based on responses from the 437 neurologists surveyed, an estimated 53% of patients with PDP in the EU-5 cohort exhibit symptoms of psychosis that are disruptive to the patient or their respective caregivers. In the subset of patients with disruptive PDP, an estimated 48% have severe underlying PD motor symptomology while the other 52% have mild-to-moderate symptomology. Comorbidity rates are estimated at 10% for dementia and 7% for CVD among patients with disruptive PDP (not mutually exclusive) and were comparable between those with severe or mild-to-moderate PD motor symptomology.

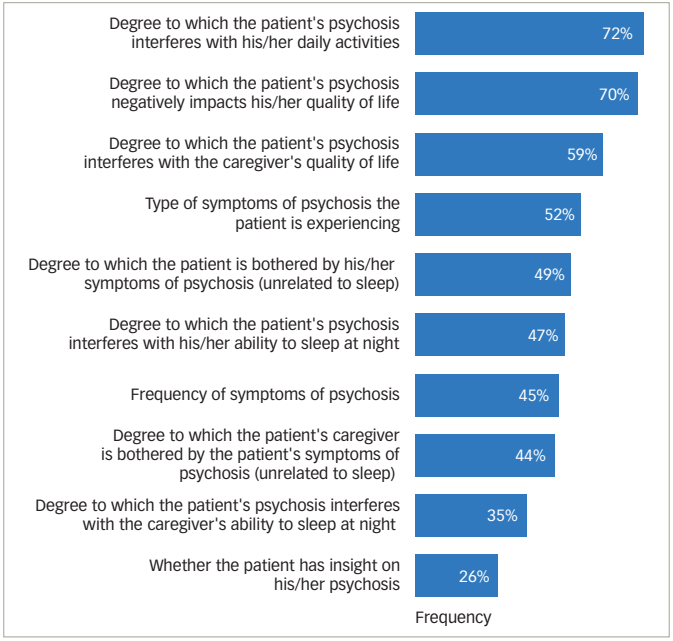
Surveyed neurologists most often cited interference with patient daily activities (72%), negative impact on patient quality of life (QoL) measures (70%), and negative impact on caregiver QoL measures (59%) as among the top five parameters considered when assessing the disruptiveness of PDP symptoms, although country-to-country variations were identified. Detailed results are presented in *Figure 2*. Neurologists in Italy and the UK ranked interference with patient daily activities as the top factor considered when assessing disruptiveness of the symptoms of psychosis, while those in Germany and Spain ranked negative impact on patient QoL measures as the top factor. In France, neurologists ranked negative impact on caregiver QoL as the top factor when assessing the disruptiveness of the symptoms of psychosis.

Figure 1: Geographical breakdown of patients



**Based on estimates reported by medical practitioners. PD = Parkinson's disease; PDP = Parkinson's disease psychosis.*

Figure 2: Frequency of parameters neurologists ranked as among the top five considered for determining disruptiveness of PDP symptoms



PDP = Parkinson's disease psychosis.

For assessing severity of PD motor symptomology, neurologists surveyed cited interference with patient daily activities (69%), negative impact on patient QoL measures (65%) and impact on walking ability (62%) as the top three factors considered.

Discussion

PDP is an under-recognised and under-treated condition that commonly manifests in patients with PD that can magnify the overall burden of PD. Treatment options for PDP are distinct from those used to address the hallmark motor symptomology in PD. Current antipsychotic options recommended by European healthcare authorities have non-ideal therapeutic profiles or mixed evidence of efficacy, suggesting a need for therapies without such shortcomings.[26–31] Clozapine, for example, requires intensive monitoring due to the risk of serious side effects including agranulocytosis and myocarditis.[32] Despite the need, epidemiological data on the prevalence of PDP in Europe are limited, making it difficult for national governments and regulatory authorities to assess the burden of PDP independently from PD, as well as the cost-effectiveness and budget impact of emerging therapies specifically developed to treat PDP. Data on PDP treatment patterns among neurologists in the EU-5 are also limited and are presented in a separate report.[33]

In the current study, the estimated prevalence rates for PDP among patients with PD in the EU-5 nations are in line with those reported in previous studies.

In prior studies covering the EU-5 nations, reported rates of hallucinations and delusions among patients with PD ranged from 10–45% in France,[34–36] 13–29% in Germany,[37,38] 11–32% in Italy,[39–41] 15–42% in Spain[42,43] and 13–55% in the UK.[17,44–46] These broad reported ranges highlight the difficulty of carrying out cross-study comparisons. Common variations in study design identified from a targeted literature review (unpublished findings) include the criteria for patient selection, the definition of PDP, the symptoms of psychosis that were of interest to study investigators, differences in the methodology used to assess symptoms, and the timeframe over which symptoms were observed. For example, several studies have reported that inclusion of minor phenomena increases the observed prevalence rate of psychosis symptoms among patients with PD[47–49] and that standard assessment tools for PD symptomology, such as the thought disturbance item on the Unified Parkinson Disease Rating Scale (UPDRS) Part I have low sensitivity for capturing such phenomena.[50,51] The prevalence rates in the current study were estimated based on survey data reported retrospectively by medical practitioners. Most respondents are likely to have used standard diagnostic criteria, clinical judgment and assessment tools to diagnose PDP and symptoms of psychosis. The need to modify existing diagnostic criteria and assessment tools for PDP to capture minor phenomena is discussed elsewhere in the literature.[5,47,50]

The 29% estimated prevalence rate for PDP in the EU-5 overall also aligns with the 12-year longitudinal population study in Norway reporting the 18–49% range for point prevalence of PDP,[25] suggesting the current study results could be useful for approximating PDP prevalence in other European nations.

Survey participants were asked to stratify the composition of their respective patient pools by disruptiveness of symptoms, severity of underlying PD motor symptomology and the presence of select comorbidities; such data could facilitate future studies to elucidate differences in treatment patterns based on the presence or absence of these clinical factors. In the current study, the estimated 53% rate for disruptive psychosis among patients with PDP was based on responses from the subset of neurologists who participated in the survey. Multiple studies in patients with PD have documented the negative impact of psychosis on QoL measures in individual European nations,[19,52–55] but to the best of our knowledge, the rates of disruptive versus non-disruptive psychosis among patients with PDP have not been previously reported for the EU-5. Additional areas for future research include stratification by stage of PD and by suspected drivers of PDP symptoms (e.g., drug-induced versus not drug-induced).

Data from the current study suggests the 1,518 respondents to the screener questions extended care to approximately 285,000 patients with PD across the EU-5 nations in the 12 months since they participated in the survey. A 2015 market research study reported an estimated 1.3 million patients with PD in the EU-5 nations,[4] which suggests the current study captured over 20% of the total PD patient population across this region. Together with the current findings, we estimate approximately 370,000 patients with PDP in the EU-5.

It is important to note that estimated prevalence rates from the current study are based on estimates provided by respondents to an online survey, and are retrospective by nature. Moreover, the identification of PDP, its associated symptoms and various comorbidities are based on the assessment of the survey participant and are subject to local and regional variations in clinical practice. The survey did not control for country-specific variations in guideline recommendations, diagnostic criteria and assessment tools that medical practitioners use to diagnose PDP or symptoms of psychosis in their PD patients. In addition, the survey did not control for the possibility of multi-counting patients. It is possible a patient will visit a neurologist for PD motor symptomology and a psychiatrist for psychosis-related symptomology, and it remains possible for survey respondents to multi-count patients who came in for care multiple times over a 12 month timeframe when providing estimates. Although instructions to not multi-count patients from multiple consultations were provided, the level of compliance could not be determined. With respect to survey questions, Q10 from the screener questions asked survey respondents to include patients with symptoms of psychosis associated with PD when providing their estimates, which could be a broader definition of PDP than what is described in current guidelines from European healthcare authorities. Moreover, responses from Q1 and Q3 from the full survey are based on neurologists' assessments of what they consider to be disruptive versus non-disruptive psychosis and severe versus mild-to-moderate PD motor symptomology, which includes a degree of subjectivity. Reasonable efforts were made during the survey design, targeting and analysis steps to preserve the integrity of the collected data. The estimated prevalence from the current study align with those reported in prior studies suggesting survey respondents answered questions in good faith and that data integrity was not significantly compromised.

Conclusion

No other study to date has assessed the prevalence of PDP in the EU-5 using a consistent methodology that would enable straightforward comparison of prevalence rates between countries. Results of the current study provide a resource that enables cross-country comparison of PDP rates across these major European nations and could potentially be used in studies to estimate the prevalence of PDP across the broader EU. The results also could facilitate studies to assess the burden of PDP and cost effectiveness of emerging new therapies independently of PD. A report of survey data related to treatment patterns for patients with PDP in the EU-5 is presented in a separate report.[33] ❑

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