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Review article

Defining delirium in idiopathic Parkinson's disease: A systematic review

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ABSTRACT

Background: Parkinson's disease patients may be at increased risk of delirium and developing adverse outcomes, such as cognitive decline and increased mortality. Delirium is an acute state of confusion that has overlapping symptoms with Parkinson's dementia, making it difficult to identify. This study aimed to determine the diagnostic criteria, prevalence, management strategies and outcomes of delirium in Parkinson's through a systematic review of the literature.

Methods: Seven databases were used to identify all articles published before February 2017 comprising two key terms: "Parkinson's Disease" and "delirium". Data were extracted from studies meeting predefined inclusion criteria.

Results: Twenty articles were identified. Delirium prevalence in Parkinson's ranged from 0.3 to 60% depending on setting; a diagnosis of Parkinson's was associated with an increased risk of developing delirium. Delirium was identified/diagnosed using seven different criteria. Delirium may be associated with an increased length of hospital stay and worsening motor symptoms. We did not identify any studies examining the management of delirium in Parkinson's.

Discussion: This review highlights the paucity of well-designed, appropriately powered studies investigating delirium in Parkinson's. The results suggest that delirium is a significant issue in people with Parkinson's and that having delirium may be a risk factor for adverse outcomes, particularly in inpatient settings. Further prospective research is needed to accurately determine the prevalence of delirium in Parkinson's, its management strategies and outcomes, and to evaluate diagnostic criteria to differentiate between the overlapping symptoms of Parkinson's and delirium.

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder defined by motor symptoms. However, it is now recognised that PD comprises a number of non-motor symptoms, which include neuropsychiatric features such as hallucination, delusions, anxiety and depression [1]. Cumulatively, 80% of patients with PD will develop dementia (PDD) [2]; this is associated with chronic impaired but fluctuating attention, psychotic symptoms and delusions [3]. In addition, it is suspected that PD patients with and without dementia are at increased risk of delirium [4].

Delirium is an acute neuropsychiatric syndrome that is common in older adults admitted to hospital [5]. Delirium is associated with an altered level of consciousness, confusion and impaired attention [6]. Delirium can be distressing for both the person with delirium and their families. Delirium in older adults has been associated with both short term and long term adverse consequences, such as increased risk of falls, cognitive decline, nursing home placement and higher rates of death [7,8]. Occurrence of delirium is also associated with prolonged hospital stay [9] and higher costs per patient per admission [5]. In the only population-based study exploring the impact of delirium on cognitive outcomes, delirium was associated with an eight-fold increased risk of future dementia [10]. However, delirium may be preventable in a third of cases [11,12]. Therefore, early detection and diagnosis could lead to improved outcomes for patients and reduced hospital costs.

There may be an overlapping clinical phenotype of PD and delirium. Commonly reported PD symptoms, such as attentional dysfunction, cognitive fluctuations, hallucinations, sleep disturbance and daytime

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somnolence are also common in delirium [4,6], making it difficult to distinguish PD symptoms from delirium. Therefore, previous studies may have either underestimated or overestimated the prevalence of delirium in people with PD. Additionally, the management of delirium in PD is complex. Dopaminergic medication may predispose to delirium; neuroleptic medication, often used to treat delirium in older adults, may worsen motor symptoms resulting in increased rigidity and bradykinesia, which in turn can cause falls, impaired swallowing, aspiration and dehydration.

Patients with PD may be at increased risk of developing delirium and adverse outcomes. Understanding the relationship between delirium and PD could help guide clinical practice. The aim of this systematic review was to: i) determine how delirium has been defined/diagnosed in PD patients in previous studies, ii) describe common presentations of delirium in people with PD, iii) establish the therapeutic strategies used to manage delirium in PD, and iv) determine the outcomes of delirium in people with PD.

2. Methods

2.1. Search strategy

We searched seven databases: Medline, Embase, PsychINFO, Cochran, Scopus, Web of Knowledge and the Cumulative Index to Nursing and Allied Health Literature (CINAHL). The search comprised two key terms: “Parkinson's Disease” and “delirium”. For each key term, a list of synonyms were compiled (Table 1); where available, MeSH terms were used. The search included all articles published before February 2017. In addition, we examined references of articles from the search for articles not identified in the searches, but may be suitable for inclusion.

A central database was compiled using articles from the search; RAL removed all duplicates. Reviewers (RAL and CM) reviewed the titles and abstracts independently. The full text was reviewed where it was unclear whether the paper met inclusion criteria.

2.2. Inclusion and exclusion criteria

Articles were included if PD and delirium were referred to in the title or abstract, the paper was written in English and the full text was available. Articles were excluded if they included subjects with non-idiopathic parkinsonism, including multiple system atrophy, progressive supranuclear palsy, dementia with Lewy bodies (DLB), vascular PD, drug induced PD, subjects with a diagnosis of PD for less than one year, and could therefore meet the criteria for DLB, or where subjects had a history of brain injury or brain tumour. Review articles and case series were excluded.

2.3. Data extraction

A data extraction form was generated which included study setting, study population, how participants were selected/identified, duration of study and follow up period. Key outcomes were also included on the data extraction form, including how delirium was diagnosed, the prevalence of delirium in PD, presenting symptoms of delirium, how delirium was managed and clinical outcomes associated with delirium, for example, duration of hospital admission, change in motor symptoms or cognitive function and mortality.

3. Results

The database searches identified 5672 potentially relevant articles (Fig. 1). After duplicates were removed (n = 1278), 4394 articles were identified. The title and abstract of the potentially relevant articles were screened and 4337 were excluded. We reviewed the full text of the remaining 56 articles. Thirty-nine articles were excluded because: the full text was not available in English (n = 4), they were a conference abstract and no full text was available (n = 19), the key outcomes identified by this systematic review were not available from the papers (n = 15), or the paper was a systematic review (n = 1). In addition to the 17 papers identified in the search which met inclusion criteria, three additional papers were identified by reviewers [13–15] by reviewing references of articles from the search and a previous review [4], yielding a total of 20 papers which were eligible for data extraction

Table 1
Search terms used database search.

	Parkinson's disease	Delirium
Medline	Parkinson* MeSH HEADING: Parkinson disease MeSH HEADING: Lewy body disease	Deliri* MeSH HEADING: delirium MeSH HEADING: confusion
Embase	Parkinson* MAIN TERM: Parkinson disease	Deliri* MAIN TERM: delirium
PsychINFO	Parkinson* MAIN TERM: Parkinson's Disease	Deliri* MAIN TERM: delirium
Cochran	Parkinson*	Deliri*
Scopus	Parkinson* parkinson* disease or "paralysis agitans" or "idiopathic parkinson*" or "parkinson dementia complex" or "lewy body dementia" or "lewy body disease" or "parkinsonsim primary" or "primary parkinsonism" or "lewy body parkinson*"	Deliri* delirium or "acute confus*" or confus* or "delirium subacute" or "delirium of mixed origin" or "subacute delirium*" or bewilderment or "confusion post ictal" or "confusion post-ictal" or "confusion reactive" or disorientation or "confusional state*" Delirious
Web of Knowledge	Parkinson* parkinson* disease or "paralysis agitans" or "idiopathic parkinson*" or "parkinson dementia complex" or "lewy body dementia" or "lewy body disease" or "parkinsonsim primary" or "primary parkinsonism" or "lewy body parkinson*"	Deliri* delirium or "acute confus*" or confus* or "delirium subacute" or "delirium of mixed origin" or "subacute delirium*" or bewilderment or "confusion post ictal" or "confusion post-ictal" or "confusion reactive" or disorientation or "confusional state*" Delirious
CINAHL	Parkinson* (MH "Parkinsonian Disorders+") Kufor-Rakeb Syndrome Lewy Body Disease Parkinson Disease	Deliri* (MM "Delirium") OR (MH "Delirium, Dementia, Amnestic, Cognitive Disorders+")

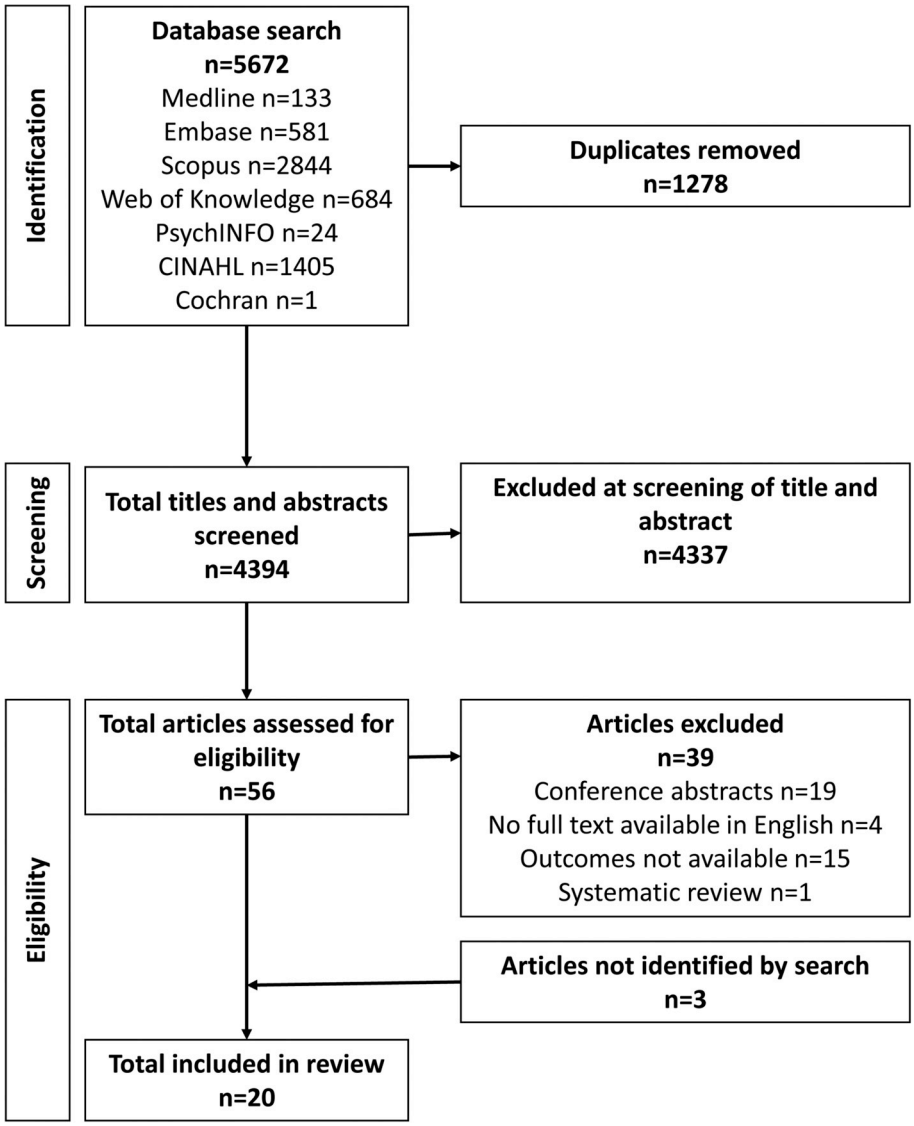

Fig. 1. PRISMA diagram presenting the search yield for the systematic review.

(Table 2).

3.1. Characteristics of studies and participants

Of the 20 studies identified, ten were prospective, nine were retrospective and one was a case-control study (Table 2). The majority of studies were in an inpatient setting (n = 17) with two studies conducted in outpatients [16,17] and one in residential and nursing homes [18].

The samples ranged in size from 15 to 182,859 subjects with PD [14,19]. The largest studies were retrospective review of medical databases [14,20,21]. Older adults were the focus of the research in three studies, of which a proportion of subjects had PD [18,22,23]. Eight studies included postoperative subjects with PD (Table 2), five of which included PD patients who had undergone deep brain stimulation (DBS) surgery [13,19,24–26].

Participants with PDD were included in eight studies [14,15,18,20,22,23,27,28] but were excluded from seven (Table 2) [13,24–26,29–31]. The remaining studies did not give explicit details as to whether PDD participants were included in the study [16,17,19,21,32].

3.2. Defining and diagnosing delirium

The criteria used to diagnose or identify delirium varied between studies (Table 2). Three studies used validated diagnostic criteria to diagnose delirium (Table 3). These comprised the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) [16,28] and the International Classification of Diseases 10th Revision (ICD-10) [14]. Three studies used the Confusion Assessment Method (CAM), a validated assessment tool designed to allow non-specialists to identify delirium [22,30,31]. In addition, Boorsma, et al. [18] used an adjusted version of the Nursing Home-CAM retrospectively by matching data from the Resident Assessment Instrument, a database used in Dutch nursing and residential care. However, the papers did not specify how these criteria were applied and what methods were used to assess specific criteria, such as attention.

The definition of delirium varied more widely between the remaining studies. Delirium was diagnosed by expert opinion by Golden et al. [29] and Woodford and Walker [15]. Broader definitions of delirium were employed, which comprised “transient post-operative confusion” [19] and any event of hallucinations, delusions, or disorientation to circumstance [24]. Lange et al. [25] defined delirium as “an altered mental state of reduced cooperation due to fear, psychomotor agitation and impaired or lost orientation.” Oichi et al. [21] used

Table 2
Summary of studies that met inclusion criteria.

Reference	Type of study	Study setting	Participant characteristics	Participants with PDD included?	Delirium definition	Prevalence of delirium	Symptoms of delirium present	Outcomes associated with delirium	Main findings
Boorsma et al., 2012 [19]	Retrospective study	Multicentre, residential and nursing homes in the Netherlands	Older adults n = 2193 after exclusions, of which n = 83 were PD	Yes	Nursing Home –Confusion Assessment Method (NH-CAM)	Older adults: n = 176 (8.2%) PD: n = 12 (14.5%)	Not stated	Not stated	PD in nursing home residents was associated with increased risk of delirium 2.4 (1.0–5.9). PD in residential home residents was not significantly associated with delirium
Carlson et al., 2014 [25]	Retrospective study	Single centred study, USA. Hospital inpatients post DBS	Consecutive surgical patients (n = 59) receiving DBS for advanced idiopathic Parkinson's disease. Two surgeries 1) stereotactic implantation of electrodes under light sedation, 2) DBS generator and extension leads placed under general aesthetic.	No, PDD excluded	Retrospective chart review. Delirium was broadly defined as the occurrence of any event of hallucinations, delusions, or disorientation to circumstance, even if apparently benign.	13/59 (22%) following first surgery 6/59 (10%) following second surgery 2/13 participants with delirium at first surgery also had delirium following second surgery	Hallucinations in 46% (n = 6) participants with delirium vs. 8.7% (n = 4) participants without delirium	Prolonged stay following 1st surgery was related to uncontrolled delirium in n = 7 (12%) participants. Prolonged stay secondary to delirium following second surgery was observed in 4 patients	Development of delirium was associated with age, pre-operative hallucinations, longer disease duration, lower opioid medication use and delays in PD medication administration
Gerlach et al., 2013 [33]	Prospective study	Single centre, hospital inpatients in the Netherlands (DBS patients excluded)	52 admissions from n = 40 patients with PD	Not stated	Not defined	24%	Not clearly stated, reported as confusions/ delirium	Not stated but patients with complications (including delirium) did have decline in UPDRS III scores	Patients had significantly worse motor scores at discharge, which was associated with infections and medication errors
Golden et al., 1989 [30]	Retrospective study	Single centre, hospital post-operative inpatients in the USA	Hospital records of PD (n = 25) patients who had surgery over 2 year period.	No	Clinical diagnosis	15/25 (60%). Observed incidence of delirium CI = 39–79%.	Confusion/ disorientation: 15/25; Day-night reversal 1/25; hallucinations 9/25; Fluctuations 1/25	Delirium onset ranged from 1 to 7 days post-surgery; 70% episodes of delirium were delayed onset. Delirium duration ranged from 1 to 4 days in nine participants, remaining were discharged before delirium resolved.	Authors estimate post-operative relative risk of delirium in PD patients was between 2.8 and 8.1
Holroyd et al., 2001 [17]	Prospective study	Single centre, out-patient tertiary clinic in USA	102 consecutive patients attending movement disorder clinic diagnosed with PD	Unclear	DSM-IV criteria for delirium	3.9% (n = 4)	Patients with delirium were identified from patients reporting hallucinations or delusions	Not stated	Visual hallucinations are common symptoms in Parkinson's disease and are most likely of multifactorial origin. Only a minority in the outpatient setting were secondary to delirium
Kahn et al., 2012 [20]	Prospective study	Single centre, hospital in patients post DBS in USA	15 early PD patients 47 advanced PD (retrospective review)	Unclear (but unlikely as relative contra-indication to DBS)	No formal diagnosis - transient post-operative confusion	26.7% (4/15 early PD patients)	Transient confusion	Not stated	There were a number of transient adverse events from DBS which included confusion
Kim et al., 2016 [31]	Prospective study	Single centre, hospital	77 PD patients enrolled in study. 17 patients with postoperative delirium	No, PDD excluded	Confusion Assessment Method (CAM)	22.1% (17/77 patients)	Not stated	No significant differences were observed for post-	No significant differences were observed for age, sex,

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Table 2 (*continued*)

Reference	Type of study	Study setting	Participant characteristics	Participants with PDD included?	Delirium definition	Prevalence of delirium	Symptoms of delirium present	Outcomes associated with delirium	Main findings
		inpatients in South Korea	were compared to 17 age and sex matched patients without delirium					operative medications or ICU admissions between patients with and without postoperative delirium	motor UPDRS, parkinsonian medication, MMSE and CDR (at last follow-up), operation time, pre-operative medications between patients with and without postoperative delirium. Pre-operative olfaction and operation time predicted development of delirium (odds ratio [OR] 0.25; 95% confidence interval [CI] 0.07–0.86; P = 0.03) and (OR 1.02; 95% CI 1.00–1.02; P = 0.04) respectively
Klein et al., 2009 [28]	Retrospective study	Single centre, community hospital inpatients in Israel	143 patients with PD (243 admissions) admitted to Department of Neurology over five years	Yes 41%	Not stated	Not clear. Psychosis in 24% (n = 34) which included delirium n = 12 (8%); frightening visual hallucinations n = 4 (3%); persecutory delusions with agitation and frightening hallucinations n = 18 (13%). In addition, fever due to urinary tract infection or bronchopneumonia, with confusion and agitation: n = 22 (15%); dehydration with hallucinations: n = 8 (6%); brain concussion due to a fall injury, with confusion: n = 6 (4%)	Not stated	Delirium associated with extended hospital stay and recurrent admissions	Reasons for hospital admissions in PD patients included motor complications (37%), psychosis (24%), general medical problems (14%), and a combination of motor and psychiatric (25%). Drug-induced psychosis was the most significant cause of repeated and prolonged admissions (29%)
Krack et al., 2003 [14][a]	Prospective study	Single centre, France. Hospital inpatients. Five year follow up (at 1, 3 and 5 years)	49 consecutive PD patients who received DBS	Not at baseline. 3 developed dementia by 3 years	Not stated	24.4% (n = 12)	Not clearly stated described as "ranging from temporospatial disorientation to psychosis"	Not stated	Patients with PD who were treated with bilateral stimulation of the subthalamic nucleus had marked improvements over five years in motor function. There was no control group, but worsening of akinesia, speech, postural stability, freezing of gait, and cognitive function between the first and the fifth year is consistent with the

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Table 2 (*continued*)

Reference	Type of study	Study setting	Participant characteristics	Participants with PDD included?	Delirium definition	Prevalence of delirium	Symptoms of delirium present	Outcomes associated with delirium	Main findings
									natural history of Parkinson's disease
Lange et al., 2015 [26]	Retrospective study	Single centre, hospital inpatients in Germany	38 consecutive patients undergoing DBS surgery. Compared anaesthesiology regimes DBS: I) asleep wake asleep (n = 16) or II) awake sleep awake (n = 22)	No, PDD excluded	An altered mental state of reduced cooperation due to fear, psychomotor agitation and impaired or lost orientation. Identified three types of delirium: intraoperative delirium (that began during surgery, but resolved before the next morning), postoperative delirium (that began after the day of surgery) and perioperative delirium (beginning during surgery and lasting for more than 24 h)	10.5% (n = 3 intraoperative delirium in Group I and n = 1 postoperative delirium in Group II)	Delirium resolved, duration of delirium < 24 h for intraoperative delirium and < 30 h for postoperative delirium. No deaths.	Delirium resolved, duration of delirium < 24 for intraoperative delirium and < 30 for postoperative delirium. No deaths	Intraoperative delirium was associated with the amount of intraoperative sedative and anaesthetic drugs
Low et al., 2015 [15][a]	Retrospective study	Multi-centre, hospital inpatients in England in four year period	49,874,100 admissions, 324,055 Parkinson's disease admissions in 182,859 patients	Yes	Diagnosis were coded using ICD 10 classification.	0.3% (n = 622) reason for admission. However reason for admission stated as "senility" n = 5465 (3%), "disorientation" n = 2027 (1%), "hallucination" n = 386 (0.2%)	Not stated	Not stated	PD patients have higher rates of emergency admissions compared to other admissions, in addition to longer duration in hospital, high costs and in-patient mortality
Lubomski et al., 2015 [21]	Retrospective study	Multi centre, hospital inpatients in Australia	5637 patients with PD vs. 8143 controls. Data from Admitted Patient Data Collection (APDC) from the New South Wales Ministry of Health database over five years	Yes	Not stated	Encephalopathy/delirium in PD 10.6% vs. 1.8% in controls	Not stated	Not stated	Patients with PD are more likely to suffer serious health problems, including delirium, adverse drug reactions, syncope, falls and fractures than controls
Nishikawa et al., 2009 [18]	Prospective interventional study	Single centre, out-patients in Japan	78 consecutive patients on stable dose of amantadine	Unclear	Not stated	3.8%, 3 cases of delirium	All three cases had hallucinations as adverse event, unclear if related to delirium	Delirium resolved on cessation of the drug, between 3 and 5 days.	All the delirious patients had a plasma concentration of amantadine greater than 3000 ng/ml
Oh et al., 2016 [23]	Prospective study	Single centre, hospital inpatients in USA	431 patients undergoing hip repair, n = 13 had PD	Patients with dementia included	Confusion Assessment Method (CAM)	34.1% in cohort, prevalence unavailable in PD participants. Having PD was associated with increased risk of delirium, OR = 3.18 (1.02–9.89)	Not stated	Not stated	Men are at higher risk of postoperative delirium after hip fracture repair than women. Their higher risk of postoperative delirium may be due to their underlying preoperative disease severity
Oichi et al., 2017 [22]	Retrospective matched pair cohort study	Multi centre, hospital inpatients in Japan	1423 patients with prescribed antiparkinsonian	Unclear	Patients with newly prescribed antipsychotic drugs (quetiapine, risperidone, trazodone,	30.3% (n = 431) compared to controls 4.3% (n = 77)	Not stated	Not stated	Postoperative delirium was the most frequently observed complication

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Table 2 (*continued*)

Reference	Type of study	Study setting	Participant characteristics	Participants with PDD included?	Delirium definition	Prevalence of delirium	Symptoms of delirium present	Outcomes associated with delirium	Main findings
			medication and 5498 controls		mianserin, and haloperidol) postoperatively				in patients with PD following spinal surgery
Schupbach et al., 2005 [27]	Prospective study	Hospital in-patients undergoing DBS in France with five year follow up	37 PD patients	No, excluded PDD	Not stated	n = 6 (16%) postoperative	N = 3 (8%) patients had postoperative hypomania, which may indicate hypoactive delirium.	Not stated	PD patients had marked improvement of motor function that was sustained over five year's post-DBS. Moderate motor and cognitive decline was observed which was possibly due to disease progression
Serrano-Duenas and Bleda 2005 [32]	Prospective study	Single centre, hospital inpatients in Ecuador. Follow up every six month for five years (11 assessments)	A consecutive series of 21 patients with PD who met criteria for delirium. Two control groups were used: 1) 21 PD patients without delirium and 2) 21 control group	No, patients with dementia at baseline were excluded	Confusion Assessment Method (CAM): the presence of (i) acute onset and fluctuating course; (ii) Inattention; (iii) disorganized thinking; and (iv) altered level of consciousness. The diagnosis of delirium requires the presence of features (i) and (ii) and either (iii) or (iv)	Cannot be ascertained from this paper.	As part of diagnostic criteria for delirium, participants had acute onset and fluctuating course and inattention plus disorganized thinking and/or altered level of consciousness. Delirium was the agitated type in 16 patients; in 6 patients do not have altered level of sensorium	Mortality: 10 deaths in patients with PD and delirium vs. four in PD group vs. two in controls. Survival and regression analysis showed delirium was associated with death. Cognitive function: decline in all groups over time, but PD with delirium significantly worse than PD or controls. No significant difference in PD vs. control group. Disease severity: UPDRS scores declined across both PD groups; PD with delirium had significantly poorer scores than PD group	People with PD and delirium are at increased risk of developing dementia, more severe motor impairment and death
Umemura et al., 2014 [29]	Nested case control study	Single centre, hospital inpatients in Japan	80 PD patients; 26 with systemic inflammation, 54 controls	Yes	Retrospectively diagnosed in accordance with DSM-IV criteria using medical records	38.8% (31/80); 81% with systemic inflammation vs. 18.5% of controls	Nursing staff recorded disturbances/ fluctuations in consciousness, cognition and perception at 2 h intervals, prevalence of symptoms or duration not recorded	Delirium significantly associated with motor deterioration at six month follow up (OR = 15.9, 95% CI 3.2–78.1)	In PD patients with systemic inflammation, delirium and high body temperature were risk factors for subsequent motor deterioration which could can persist for over 6 months
Vida et al., 2006 [24]	Prospective study	Multi centre, emergency department in Canada	256 older adults, n = 33 with PD (12.9%)	Yes n = 22 (8.6%)	Confusion Assessment Method (CAM)	16/33 people with PD (48.4%); vs. 85/223 (38.1%) of older adults	Not stated	Not stated	There is an interaction between delirium, dementia and chronic medical problems, including PD

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Table 2 (*continued*)

Reference	Type of study	Study setting	Participant characteristics	Participants with PDD included?	Delirium definition	Prevalence of delirium	Symptoms of delirium present	Outcomes associated with delirium	Main findings
Woodford and Walker 2005 [16][a]	Retrospective study	Single centre, England. Hospital emergency admissions	246 admissions by 129 PD patients with 324 reasons for admission (246 primary 78 secondary)	Yes	Expert opinion	Primary reason for admission n = 12 (5%), secondary reason for admission n = 1	Not stated	Not stated	PD patients have longer average length of stay in hospital and an increased discharge to nursing homes in comparison to non-PD patients admitted to elderly care wards

PD = Parkinson's disease, PDD = Parkinson's disease dementia, DBS = Deep brain stimulation, OR = Odds ratio, CI = Confidence interval; DSM-IV = Diagnostic and Statistical Manual of Mental Disorder.

[a] Papers identified by researchers that were not identified in the database search.

the prescription of antiparkinsonian medication as a marker for PD, and classified patients as having delirium if they were newly prescribed antipsychotic drugs postoperatively, which included quetiapine, risperidone, trazodone, mianserin and haloperidol. Six studies did not explicitly state how delirium was defined or diagnosed [13,17,20,26,27,32].

3.3. Prevalence of delirium

The prevalence of delirium varied between studies and ranged from 0.3 to 60% (Table 2). This likely reflects the variation in study design including setting, patient populations and definitions of delirium used across studies. Studies reporting primary and secondary reasons for hospital admissions reported the lowest prevalence rates (0.3–5%) [14,15]. This method most likely underestimates the prevalence of delirium. Delirium is frequently secondary to an acute illness such as infections or hip fractures. The acute illness triggering delirium is more likely to be reported as the reason for admission rather than the concurrent delirium. This is demonstrated by the higher rates of delirium reported among medical inpatients. Studies that prospectively reviewed patients to identify delirium or retrospectively reviewed case notes for evidence of delirium reported prevalence of 22–48%. Similarly, studies that assessed the prevalence of delirium in PD patients undergoing surgery reported prevalence rates of 11–60% in PD subjects (Table 2) [13,19,22,24–26,29]. The prevalence of delirium was lower in patients undergoing DBS (11–27%) compared to other surgeries (22–60%).

Delirium prevalence in outpatient settings was lower at 4% [16,17]. This likely reflects a population among which acute undercurrent illness was less common.

The prevalence was unclear in some studies due to the indistinct definitions of delirium applied [20,27]. The prevalence of delirium in PD could not be ascertained by two studies [22,31], although Oh et al. [22] reported that having PD was associated with a threefold increased risk of developing delirium (Table 2). Three other studies suggested having PD was associated with an increased risk of delirium [18,20,21]. Subjects with PD were five times as likely to be treated for delirium in inpatient settings [20], and residents in a nursing home with PD were more than twice as likely to suffer from delirium. Postoperatively, Oichi, et al. [21] found delirium was 8 times more likely in patients with PD undergoing spinal surgery than patients without PD undergoing the same surgery.

3.4. Symptoms of delirium

Eleven studies presented findings pertaining to symptoms of delirium in PD subjects [16,17,19,24–26,28–32]. Confusion and disorientation were the most commonly reported symptoms of delirium [19,25,29,31,32]. Hallucinations and/or delusions were also commonly reported symptoms [16,17,24,29], although the two symptoms were not necessarily differentiated between. Golden et al. [29] reported hallucinations in 36% of PD participants following DBS. Hallucinations were reported in all PD subjects with delirium by Nishikawa et al. [17], but it was not clear whether hallucinations were directly related to delirium. Disturbances and fluctuations in consciousness, cognition and perception were symptoms associated with delirium [28,29]. Golden et al. [29] was the only study which reported day-night reversal although this was only in one subject. However, studies did not systematically assess or report these symptoms, thus it was not possible to draw conclusions as to their frequency.

Three studies hinted at delirium phenotype. Serrano-Duenas and Bleda [31] identified 76% of PD subjects with delirium as “agitated type” delirium, while Lange et al. [25] and Schupbach et al. [26] reported that a small proportion of subjects (n = 5 and n = 3, respectively) had postoperative hypomania. However, this should be viewed

Table 3
Delirium criteria.

Criteria	Definition
DSM-IV	A) A disturbance in attention (i.e., reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment). B) The disturbance develops over a short period of time (usually hours to a few days), represents a change from baseline attention and awareness, and tends to fluctuate in severity during the course of a day. C) An additional disturbance in cognition (e.g., memory deficit, disorientation, language, visuospatial ability, or perception). D) Disturbances in criteria A) and C) are not explained by another pre-existing, established, or evolving neurocognitive disorder and do not occur in the context of a severely reduced level of arousal, such as coma. E) Evidence from the history, physical examination, or laboratory findings that the disturbance is a direct physiologic consequence of another medical condition, substance intoxication or withdrawal (i.e., because of a drug of abuse or to a medication), or exposure to a toxin or is because of multiple aetiologies.
ICD-10	F05 Delirium, not induced by alcohol and other psychoactive substances Definition: An etiologically nonspecific organic cerebral syndrome characterized by concurrent disturbances of consciousness and attention, perception, thinking, memory, psychomotor behaviour, emotion, and the sleep-wake schedule. The duration is variable and the degree of severity ranges from mild to very severe. Incl.: acute or subacute: • brain syndrome • confusional state (non-alcoholic) • infective psychosis • organic reaction • psycho-organic syndrome Excl.: delirium tremens, alcohol-induced or unspecified (F10.4) F05.0 Delirium not superimposed on dementia, so described F05.1 Delirium superimposed on dementia Incl.: Conditions meeting the above criteria but developing in the course of a dementia (F00-F03). F05.8Other delirium Incl.: Delirium of mixed origin, Postoperative delirium F05.9Delirium, unspecified
CAM	1) Acute onset and fluctuating course 2) Inattention 3) Disorganized thinking 4) Altered level of consciousness. The diagnosis of delirium using the CAM requires the presence of features 1) and 2) and either 3) or 4)

DSM-IV = Diagnostic and Statistical Manual of Mental Disorders 4th Edition [41]; ICD-10 = The International Classification of Diseases 10th Revision [42]; CAM = Confusion Assessment Method [43].

with caution, as hyperactive delirium was not explicitly stated. Of the remaining studies, a description of symptoms of delirium were either unclear or not stated.

3.5. Outcomes of delirium

Accurately defining the outcomes of delirium in patients with PD is challenging due to the limited information available from only nine studies (Table 2) [17,24,25,27–32]. Duration of delirium in PD patients ranged from 24 h or less, to under 30 days [17,25,29]. Two studies showed that delirium was associated with extended hospital stay compared to PD patients without delirium [24,27].

Longitudinal studies suggested that delirium could be associated with a worsening of motor symptoms in PD patients [28,31]. Umemura et al. [28] showed that patients with delirium were more than 15 times more likely to have motor deterioration (OR = 15.9), while Serrano-Duenas and Bleda [31] showed that subjects with PD and delirium had significantly poorer motor scores compared to PD subjects without delirium after five years. Gerlach et al. [32] reported that patient complications while hospitalised, which included delirium, were associated with a decline in motor symptoms, but the contribution of delirium could not be determined.

Whether delirium was associated with future PDD could not be ascertained. Serrano-Duenas and Bleda [31] found delirium was significantly associated with a decline in cognitive function over five years and increased mortality rates compared to age-matched PD patients without delirium and controls. However, these results should be viewed with caution due to the small sample size used (21 PD, 21 PD with delirium and 21 controls), and does not take into account additional hospital admissions or episodes of delirium. In addition, none of the studies assessed interventions for delirium or its associated outcomes.

4. Discussion

Key findings of this review include that the prevalence of delirium in PD varied widely between studies and settings, ranging from 0.3% to 60% of subjects, as did the criteria used to identify or diagnose delirium. In inpatient settings, delirium occurred in 11–60% patients and overall having PD was associated with an increased risk of developing delirium. Findings relating to symptoms and outcomes of delirium in PD patients were limited, but delirium may be associated with increased length of hospital stay and worsening motor symptoms.

The results showed that up to 60% of PD inpatients have delirium, and that having PD was a risk factor for developing delirium [18,20–22]. However, given the wide range of reported prevalence of delirium in PD, some caution should be made when interpreting these results. The variation likely reflects the heterogeneous samples, settings and criteria used to define delirium in PD subjects. Firstly, the sample and study setting varied across studies and included both large retrospective studies and smaller prospective studies. As expected, delirium prevalence was lower in outpatient settings (4%) compared to inpatient settings (22–48%) and postoperatively (11–60%). The proportion of PD patients whose primary reason for admission to hospital was delirium was low (0.3–5%). This likely reflects current coding practices, where the underlying condition leading to delirium is documented as the primary reason for admission; however, this underestimates the proportion of patients whose admission is complicated by delirium. It also does not reflect cases were delirium developed while in hospital [24].

A number of studies excluded patients with PDD; PDD is common and develops in up to 80% of patients [2]. As people with PDD may be most at risk of delirium [18], a key group of people are likely to have been under investigated in previous research. None of the studies stratified for dementia; it is therefore difficult to determine the extent to which PDD or PD alone is a risk factor for delirium. Vida et al. [23] showed that in non-demented older adults, participants with delirium had poorer instrumental activities of daily living (ADL) after 18 months compared to those without delirium, but there was no difference in functional outcomes in demented participants. This may reflect the pre-existing impact of dementia on ADL.

Nine different criteria were to used identify or diagnose delirium,

and in six studies no methods were stated. Only seven studies used existing diagnostic criteria or a validated diagnostic tool to identify delirium in PD. Other studies used broader definitions of delirium, which included symptoms such as confusion or presence of hallucinations. Only a few studies referred to fluctuating cognition, but it was not clear whether this was a feature of cognitive impairment associated with PD or delirium. Use of objective measures, such as repeated cognitive tests, e.g. the Mini Mental State Examination, to determine change in cognition or improvement over time were not reported in the articles. Finally, the validity of the assessment tools, such as CAM, used by non-specialists to identify delirium have not been validated in PD. These issues have the potential to misidentify delirium as these symptoms are not uncommon in PD [3], and several articles were unclear whether these were acute changes or longstanding symptoms associated with PD.

Only limited inference could be made about the repercussions of delirium in PD patients. Increased length of hospital stay was associated with delirium in PD in two studies. This is consistent with studies in older adults, where occurrence of delirium has also been associated with prolonged hospital admission [9] and higher costs per patient per admission [5]. However, duration of hospital admission can be influenced by other factors, such as comorbidities and frailty, which are also risk factors for delirium.

An increasing number of studies have reported that delirium is a predictor of dementia and is associated with worsening of existing cognitive decline [10,33–35]. Only one study has examined the association between delirium and cognitive decline in PD. Serrano-Duenas and Bleda [31] found that PD patients with delirium were at greater risk of cognitive decline five years later. This is in keeping with studies in the general population. A population-based study in older adults found that delirium was associated with an eight-fold increased risk of future dementia [10]. A systematic review in older adults reported that delirium was associated with increased mortality, functional outcomes and institutionalisation [9]. Further research replicating these findings in PD patients is needed.

There are some limitations to be acknowledged. We used a broad search strategy but excluded articles not available in English; however, we believe this review is comprehensive and includes the key findings in this area. The quality and methodological rigour differed between studies. Although some studies used the Queen's Square Brain Bank criteria to identify idiopathic PD, this was not always possible due to the methodology of some studies, for example in retrospective studies. One study used prescribed anti-parkinsonian medication as a surrogate marker for PD [21], however, this could inadvertently include patients with other parkinsonian conditions and patients who used dopaminergic therapy, for other indications such as restless legs syndrome. Retrospective studies of hospital databases and review of medical notes has the advantage of accessing large amounts of existing data. However, it has been shown that medical records are unreliable sources of delirium as delirium is under-diagnosed, inconsistently documented and under-reported [36]. Furthermore, as demonstrated in one paper [20], delirium and encephalopathy can be used interchangeably; therefore, delirium could be misreported in some subjects. Due to the limited number of studies whose focus was delirium in PD, we used broad criteria to identify and consolidate all currently published literature in this area. However, our findings highlights the need of future studies to use validated criteria to verify the diagnosis of idiopathic PD, such as the Queen's Square Brain Bank criteria, and delirium, such as DSM-5 criteria or CAM.

Most noticeably, we did not find any studies examining interventions to prevent or treat delirium in PD. The dopaminergic and cholinergic deficits in PD theoretically make patients more vulnerable to delirium and it remains to be established if conservative measures shown to prevent delirium in general older adults are as effective in PD [11,12]. Furthermore, there are specific challenges to managing delirium in PD. Many of the medications prescribed to PD patients are associated with increased risk of delirium, and guidelines suggest a medication review should form part of the management of delirium in PD [37].

A first approach should be to identify and treat the underlying precipitant (e.g. infection, dehydration etc.). Where conservative measures and treating the underlying precipitant fails, clinicians may be required to alter or suspend PD medication. The consensus is that drugs with the greatest anticholinergic effect should be removed first [4]. Thus, PD medication could be stopped or suspended in the following order: anticholinergics, amantadine, monoamine oxidase inhibitors, dopamine agonists, levodopa. A review of the current evidence, however, shows these guidelines are not based on hard evidence but clinical experience [4]. It must be noted that the sudden withdrawal of dopaminergic medication could increase the risk of patients developing delirium.

Antipsychotic medications are used in patients without PD to control delirium; however, a meta-analysis of randomised controlled trials (RCTs) failed to show any impact of antipsychotics on duration or severity of delirium, or on length of stay or mortality [38]. Most antipsychotics can worsen motor symptoms in PD and are, therefore, relatively contraindicated. Where neuroleptic mediation is necessary, quetiapine is considered the safest choice; however, there are no studies examining its use in PD [4]. Other agents have been considered for delirium, but not specifically in PD. RCTs of cholinesterase inhibitors in older adults have failed to show superiority compared to placebo, and some have suggested increased adverse events in the treatment arm of these studies [39]. Melatonin has been associated with a decreased incidence of delirium in RCTs performed in older patients on medical wards, but not in the surgical setting [40].

In summary, this review highlights that there is a paucity of well-powered studies investigating delirium in PD and its outcomes. Nonetheless, the results suggest that delirium is a significant issue in people with PD; it may occur more frequently in PD than in older adults, particularly in inpatient settings and postoperatively. Given its potential association with worsening PD motor symptoms, cognitive decline and increased mortality rates, it is important that delirium is regularly screened for and its diagnosis recorded appropriately. More research is warranted in this area. We propose that future studies should consider using prospective methods to investigate the prevalence of delirium in PD, its outcomes and management strategies. Studies that accurately characterise delirium in PD and evaluate diagnostic criteria may also be useful to clinicians and researchers to differentiate between the overlapping symptoms of PD and delirium. A better understanding of delirium and its presentation in PD will be important for treatment selection in future clinical trials to treat or prevent delirium.

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Author roles

Dr Lawson was involved with study conception and design, organisation, execution, data search, reviewed manuscripts for data extraction, analysis and interpretation of data and preparation of the manuscript.

Dr McDonald was involved with study design and organisation, execution, data search, reviewed manuscripts for data extraction, analysis and interpretation and preparation of the manuscript.

Professor Burn was involved with study conception and design, analysis and interpretation of data and preparation of the manuscript.

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