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Editorial to "Increases in institutionalization, healthcare resource utilization, and mortality risk associated with Parkinson disease psychosis: retrospective cohort study" by Friedman et al.

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When things go wrong in chronic diseases, there are always two sets of problems. One is how to fix what's wrong. The second is what this problem portends. Parkinson's disease (PD) offers a number of ways in which things can go wrong, both from disease progression, as well as from iatrogenic complications, which usually, indirectly, reflect disease progression. Psychotic symptoms in PD are, unfortunately common, affecting about 20–30% of treated patients [1] and increasingly prevalent as the disease advances, with up to 60% [2] developing symptoms by the time of death.

The appearance of hallucinations or delusions first affects how the patient is treated, often requiring a reduction in medications, limiting additional treatment of motor symptoms, or the addition of an antipsychotic drug. In addition, the appearance of these psychotic features increases caregiver stress [3], the risks of hospitalization [4], nursing home placement [5], and dementia [6]. The observation that psychotic symptoms increased mortality was illustrated by the double blind, multi-centered, placebo controlled trial of low dose clozapine to treat psychosis. The drug was effective, but 10% of the subjects were dead within three months [7] of the end of the 4 week trial, with none of the deaths attributed to the study drug. This increased mortality has been confirmed in larger studies [8,9].

Why does this happen and what can we do about it? The second question is easier to answer, at least in the short run. We now have antipsychotics that are safe and relatively effective for treating psychosis, but we don't yet know the impact these drugs on long term outcome. Although people do not die from psychotic symptoms, their stress-inducing behavior and increased need for institutionalization may partly account for increased mortality, but probably not all. Psychotic symptoms reflect the interaction of worsened brain pathology with medication, leading to increasingly vulnerable patients.

In the current issue of Parkinsonism & Related Disorders, Wetmore and colleagues [9] analyze the association between PD psychosis (PDP) and long-term custodial care, death, and health care costs. Data was extracted from the Medicare database between January 2007 to September 2015 resulting in a sample size of 53,765 persons with PD. The selected outcomes included custodial care, defined as an institutionalization stay longer than 100 days, and death before the end of the study period. Data was also collected on associated direct costs including inpatient, outpatient and emergency consultations, and pharmacy medication dispensing. Overall, 19.6% of the PDP required custodial care in comparison to 6.5% of PD patients without psychosis. In addition, PDP patients had a shorter time to first institutionalization and longer admission durations. Cumulative incidence showed that within 1 year of PDP diagnosis, 12.1% of PDP required custodial care. PDP was also associated with a higher risk of death. After the adjusted Cox proportional hazard regression analysis, the authors reported that PDP was associated with a hazard ratio 3.38 for custodial care, and of 1.34 for death. Factors associated with custodial care were age ≥ 90 years and female sex. Interestingly, the same factors were associated with death. Finally, annualized health care resource utilization and associated costs were almost double for the PDP patients.

While the authors did not directly address PD dementia (PDD); they did report that the presence of a dementia claim prior to PD diagnosis was one of the most common comorbidities associated with both custodial care and death in the multivariate models.

Given confirmation of the association of dementia with psychosis, that psychosis is associated with an increased risk of “custodial care” and an over 30% increased risk of mortality as outlined by Wetmore et al., research should focus on predicting and then ameliorating dementia among PD patients. Recent research identified biomarkers for dementia risk in PD making it possible to prospectively identify patients for potential interventions [10,11]. Aside from our basic lack of understanding of the mechanisms for the onset or progression of PD itself, we face larger problems for our understanding of dementia in PD, with 15–20% of demented PD brains having concomitant Alzheimer's disease, one third having moderate to severe tau pathology and over half having moderate or greater amyloid beta pathology [12]. Dementia in PD not only increases the risk of psychosis, but also the risk of other behavioral problems and death. Studies to reduce incipient dementia in PD should assess subsequent development of psychosis,

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institutionalization and mortality. Further, given theories that neural plasticity is prolonged in humans, it is also possible that aggressively treating psychosis early, would reduce severe or treatment refractory psychosis incidence and potentially reduce the associated risks of custodial care and mortality. Some authors have discouraged the use of the term “benign hallucinations” for just this reason [6]. Current evidence is lacking to support aggressive psychosis management and therefore future research should address early treatment of psychosis and longer term outcomes. Some data suggest that treatment response is the same for demented and non-demented PDP patients [7,13], but the numbers are small. Future studies for psychosis treatment in PD should include those with dementia since this is a strong risk factor for psychosis. It follows from Wetmore et al. [9] that studies of psychosis treatment in PD that do not include those with dementia may have less applicability in our patient population. Mixed pathologies will continue to confound all our studies for the forseeable future, but these large population studies are nevertheless crucial for understanding the impact of interventions for long term outcome as well as for better health care planning.

Potential conflicts of interest

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Janis M. Miyasaki: Royalties Up to Date (Functional Movement Disorders), Associate Editor, Parkinsonism and Related Disorders.

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