Antipsychotic medication treatment for mild hallucinations in Parkinson's disease: Positive impact on long-term worsening

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Abstract

To test if antipsychotic medication treatment of Parkinson's disease (PD) patients with mild hallucinations and retained insight delays deterioration to delusions or hallucinations without insight. We identified subjects at the time they developed their first hallucination, based on documented progression in their UPDRS thought disorder (TD) score from <2 to 2 ("benign" hallucinations with insight retained). We registered TD scores at follow-up visits and their hallucination treatment: antipsychotic medication, PD medication reduction, or observation. The primary outcome measure was the time from the first TD = 2 until the TD score worsened to 3 (hallucinations with loss of insight) or 4 (delusions, psychosis). The effect of antipsychotic medication treatment on transition hazard rate was modeled by proportional hazards regression (Cox model) with antipsychotic medication use as a time-dependent covariate. Of 64 patients, 31 received antipsychotic medication during the study (mean group follow-up 31 months). Of the 38 subjects who reached endpoint, eight subjects had been treated with antipsychotic medication compared to 30/33 in those not treated with antipsychotic medication. Antipsychotic medication treatment reduced the risk of deterioration [hazard ratio = 0.156, CI = (0.067-0.363), $P < 0.0001$] compared to treatment without antipsychotic medications. The median time from

the introduction of antipsychotic medication to the conversion from TD = 2 to TD > 2 was 39 months in subjects on antipsychotic medication compared to 12 months in patients treated otherwise. Until randomized treatment trials provide definitive information, early antipsychotic medication treatment for mild hallucinations should be considered with the combined goal of improving current hallucinations and reducing risks of later deterioration. © 2008 Movement Disorder Society

ARTICLE TEXT

Hallucinations, primarily visual, are a frequent and disabling complication in chronically treated Parkinson's disease (PD) patients.[1][2] Prospective, longitudinal studies confirm that hallucinations are progressive over time and are a risk factor for nursing home placement and its associated morbidity and mortality.[3][4] A number of atypical antipsychotic medications are used to treat hallucinations, although the only one with established efficacy based on randomized placebo-controlled trials is clozapine.[5][6] Because antipsychotic medications are dopaminergic receptor antagonists, aggravated Parkinsonism is a potential class-effect risk, along with other side effects including sedation, orthostasis, and dyslipidemia.[6] In this context, the question of when antipsychotic medications should be clinically prescribed for treating mild hallucinations is a practical dilemma. It is well accepted that hallucinations in PD generally start as visual perceptions that are recognized by the patient as false and are often not disturbing in content.[1] These hallucinations, traditionally termed mild or "benign" because patients retain insight to their false nature, might be considered safe without need for treatment. A recent study documented, however, that untreated benign hallucinations progress into hallucinations with loss of insight and often into delusional psychosis.[7] On the basis of this longitudinal observation, we hypothesized that patients treated proactively with antipsychotic medication at the time when their hallucinations began in the context of fully retained insight would have less risk of progressing to severe forms of hallucinations compared with those treated without antipsychotic medication.

PATIENTS AND METHODS

In our tertiary care university-based practice, all PD patients are rated with the Unified Parkinson's Disease Rating Scale (UPDRS) motor examination on every visit as part of regular care. In addition, the thought disorder (TD) item that assesses hallucinations on the UPDRS is always complete (0 = none; 1 = vivid dreaming; 2 = benign hallucinations with insight retained; 3 = hallucinations without insight; 4 = delusions or florid psychosis).[8] All visits on all patients are catalogued in a computer-based data repository. Entry criteria to this study were PD subjects defined by UK Brain Bank criteria, whose first hallucinations could be clearly identified by a progression in their UPDRS TD score from less than 2 to 2 (benign hallucinations with insight retained). All subjects had signed consent to have their data placed in the research repository, and the study was approved by the Rush University Institutional Review Board. We followed

these subjects' TD scores at each follow-up visit, (4- to 6-month intervals), each time categorizing patients according to whether their neurologist treated them with observation, lowering of PD medications or with antipsychotic medication. The primary outcome measure was the time from the first TD = 2 until the TD score increased to 3 (hallucinations with loss of insight) or 4 (delusions, florid psychosis). The effect of treatment (observation, PD medication reduction, or antipsychotic medication) on hazard rate for this transition was modeled by proportional hazards regression (Cox model) with treatment use as a time-dependent covariate. This approach allowed us to examine the influence of treatments that changed over time and is different from a standard survival analysis that would apply if patients were assigned to one treatment that was continued throughout the observation period. We also assessed the acute response to antipsychotic medications in terms of hallucinations and Parkinsonism by comparing the TD and UPDRS motor scores at the time of antipsychotic medication prescription with the next outpatient visit. For comparisons of medication regimens, we used the following " levodopa (L-dopa) equivalent" calculation: L-dopa mg as carbidopa/L-dopa + (0.8 × mg L-dopa in CR preparation) + 100 × mg pergolide) + 100 mg pramipexole) + 30 × mg ropinirole).[9] For antipsychotic medications, we also expressed doses as chlorpromazine equivalents, where 1 mg chlorpromazine = 0.5 mg clozapine = 0.75 mg quetiapine.[10][11]

RESULTS

The repository identified 64 patients (32 men, 32 women) who fit entry criteria. Their mean age at the time of first hallucinations (first TD = 2) was 72 years (SD 8.5) with a mean PD duration of 12 years (SD 7.9). Their mean UPDRS "on" motor score at the time of first hallucination was 40 (SD 8.3) and their mean daily L-dopa equivalent was 802 (SD 389.1) mg. Subsequent to the development of hallucinations, 31 received antipsychotic medication treatment during the study period. Twelve were treated with antipsychotic medications alone, and 19 had antipsychotic medications introduced as well as reductions in PD-related medications. Thirty-three were not treated with antipsychotic medications, 13 received reductions in dopaminergic drugs, and the remaining 20 received nonmedication interventions ("observed"), including education, counseling, keeping lights on at night and improved sleep hygiene recommendations without pharmacological alterations (Figure in supplemental materials). Although in all cases, the treating clinician noted the TD score at each visit and documented the choice of treatment among the three options, the decision-making process could not be extracted from the chart note.

At the time of first hallucinations, neither the demographic profiles nor medication treatments differed significantly between subjects who received antipsychotic medications vs. those who did not. Of the 31 patients treated with antipsychotic medication, eight patients started clozapine (mean starting dose 14.1, SD = 4.4) and 23 patients started quetiapine (mean starting dose 16.8, SD = 6.1). In chlorpromazine equivalents, the mean starting dose for the antipsychotic medication-treated subjects was 23.9 mg/day (SD 8.5). The mean maximum clozapine dose utilized was 39 mg/day (N =

8, SD = 37.3), and 26.6 mg/day (N = 24, SD = 15.8) quetiapine, or mean 46.7 mg/day (SD 44.6) chlorpromazine equivalents. Patients started on clozapine or quetiapine remained on these drugs with the exception of three patients who transiently switched to aripiprazole (2.5 mg/day); one of these returned to quetiapine because of increased sedation, although her TD score did not worsen, and the other two met endpoint criteria on aripiprazole. In patients treated with PD medication reduction, the mean initial treatment decrease at the time of first TD = 2 was 111.9 mg/day (SD 72.4) and the mean maximum reduction was 130.4 mg/day (SD 87.1). No patient in the study received cholinesterase inhibitors.

Follow-up was ongoing or until the patient met the target end-point of TD > 2 (hallucinations with loss of insight or delusions, florid psychosis). The mean follow-up time was 31 months (median, 27 months; range, 2-110). During the study period, 38 of the 64 patients reached endpoint, and their hallucinations deteriorated from hallucinations with retained insight to those with loss of insight or delusions. Among those treated with antipsychotic medications, 8/31 reached endpoint, compared to 30/33 of those not treated with antipsychotic medications.

The time of transition to hallucinations with loss of insight or delusional psychosis was significantly influenced by intervention. Proactive antipsychotic medication treatment of benign hallucinations strongly reduced progression of hallucinations [hazard ratio = 0.156, CI = (0.067-0.363), $P < 0.0001$]. The median time from the introduction of antipsychotic medications to the conversion to TD > 2 after antipsychotic medication was introduced was 39 months (range, 15-90), compared to 12 months (range, 2-54) in patients who did not receive antipsychotic medication. When PD medications were reduced without introduction of antipsychotic medication, the median transition time was 9 months (range, 2-33) and when observation alone was used as treatment, the median time to deterioration was 12 months (range, 2-54). Because the number of patients treated with clozapine (N = 8) was small, we did not examine differential effects of this drug vs. quetiapine. Of the eight antipsychotic-treated subjects who reached endpoint from first time TD reached 2, the median conversion time was similar between those treated with (N = 4; median, 39 months; range, 25-48) or without (N = 4; median, 38 months; range, 19-50) additional PD medication reductions ($P = 1.000$, Wilcoxon rank sum test).

We assessed the acute response of hallucinations to the three possible interventions by comparing TD scores one visit after changes were prescribed by the treating physician. At the visit immediately after antipsychotic medication introduction, 48% of patients had an improved TD score (<2), and the rest remained with stable TD = 2 scores with no patient progressing to higher scores and meeting endpoint criteria. In patients whose hallucination treatment involved reduction in PD medication doses but no antipsychotic medications, 38% had improved TD scores on the next visit, 54% remained with TD scores of 2, and 8% worsened and met endpoint criteria. In the 20 patients whose treatment involved only observation without antipsychotic medications and without reduction in PD medications, one visit after the first documentation of hallucinations, 15% had improved TD scores <2, 60% remained with TD scores of 2, and 20% worsened and met endpoint criteria.

To determine if the acute antipsychotic medication treatment negatively influenced Parkinsonism, we assessed the UPDRS motor scores one visit after initial antipsychotic medication introduction. The UPDRS change scores for these two visits were not significantly different (mean pretreatment 40 (SD = 8.3), vs. posttreatment 40 (8.7), $P = 0.90$, signed rank test). The same comparison for subjects whose hallucinations were treated by reduction in PD medications showed that the UPDRS increased slightly, though with statistical significance (mean pretreatment 44 (9.0), vs. posttreatment 45 (9.1), $P = 0.031$, signed rank test). No changes occurred in association with observation (mean pretreatment 39 (SD = 7.8), vs. posttreatment mean 40 (SD = 7.8), $P = 0.35$).

The severity of Parkinsonism at the end of the study was compared by examining the change score between the UPDRS motor exam at the time of antipsychotic medication introduction and the last follow-up visit in those exposed to antipsychotic medications and the change score from first intervention (reduction in PD medications or observation alone) to last follow-up visit in subjects treated with reduction in PD medications or observation alone. UPDRS scores increased over time, but the change scores did not differ by treatment intervention ($P = 0.16$ Kruskal-Wallis test). At last follow-up visit, the mean L-dopa equivalent dose was 857.5 mg/day (SD 340.73) for the entire cohort. The end-of-study L-dopa equivalent dose did not differ significantly between those prescribed antipsychotics (mean 912.3 mg/day, SD 331.2) and those not prescribed antipsychotics (mean 805.9 mg/day, SD 346.5, Wilcoxon signed rank $P = 0.24$). Among the antipsychotic medication-treated subjects, all patients the mean end-of-study medication doses were 39.5 mg/day clozapine (N = 6, SD 43.4), 24.5 mg/day quetiapine (N = 23, SD 13.9), and 2.5 mg/day aripiprazole (N = 2, SD = 0).

DISCUSSION

Hallucinations are a frequently encountered nonmotor complication of chronically treated PD.[1][2] They are primarily visual and may be vague sensations of another person's presence in the room, a fleeting de passage vision, or, more characteristically, well-formed and highly stereotypic images of people or animals.[12] Other sensory modalities can be involved, but usually occur within the context of visual hallucinations.[1] Risk factors for hallucinations include cognitive impairment and depression, and some studies document patient age or PD duration as additional liabilities.[1][2] Whereas visual hallucinations have been most commonly observed in patients with well-established PD, they can be seen early in treatment,[13] although hallucinations at the very beginning of therapy should also alert the clinician to alternative diagnoses.[14]

Hallucinations occur across a clinical continuum that begins with preserved insight, progresses to hallucinations without insight, and can deteriorate to the point of paranoia, delusional thinking, and florid psychosis.[1][2] The standard rating scale used for evaluating PD severity, the UPDRS, operationalizes this progression in the TD question (item 2) of the scale. Clinical experience has long accepted the relatively innocuous condition of hallucinations with preserved insight, since patients recognize them and are often even pleasantly amused by these visions. The term benign hallucination has been

applied to this state, although we have previously emphasized the ambiguity of the term. Indeed, though hallucinations with retained insight may be benign for the moment, they naturally progress to more severe forms of hallucinations.[7] In a series of 48 patients with hallucinations in the context of retained insight (benign hallucinations, TD score = 2) 81% progressed to hallucinations with loss of insight or to delusional psychosis over 3 years. When we considered not only hallucination severity as an index of progression, but also added consequent treatment interventions, either introduction of antipsychotic medications or reduction in PD medications as end points, both carrying risks of aggravated Parkinsonism, 96% of the sample met the criteria of progression. As such, we suggested that benign hallucinations be deleted from the operative vocabulary of PD, because the hallucinations in fact carry a malignant prognosis.

The present study expanded on this earlier observation and posed the question of whether this natural progression of hallucinations with insight to more severe forms of hallucinations could be aborted or delayed by early treatment with antipsychotic medications. Because antipsychotic medications are dopamine receptor antagonists, they carry the potential risk of aggravating Parkinsonism.[15][16] Further, the only antipsychotic medication that has been shown to be effective in improving hallucinations in a randomized, placebo-controlled trial is clozapine, an agent that carries the risk of blood dyscrasias.[5] Nonetheless, because hallucinations are a risk factor for nursing home placement and its attendant morbidity and mortality,[3][4] the potential stabilizing effects of antipsychotic medications on progressive deterioration in hallucinations could justify their early use and be an important therapeutic intervention for long-term benefits.

Our analytic approach involved the use of a proportional hazards regression model with treatment intervention as a time-dependent covariate. This method is not a survival analysis, because patients were not assigned to one treatment, but instead could change treatment (observation, PD medication reduction, or antipsychotic medication) at each visit. The statistical technique allowed us to examine the impact of observation alone, medication reduction, and antipsychotic medication treatments in all combinations and to estimate the impact of each on the progression of hallucinations to more severe forms.

We found that early treatment of hallucinations at the point when they occurred with retained insight not only acutely resolved hallucinations in nearly half the treated patients but more importantly positively influenced long-term progression of hallucinations into hallucinations with loss of insight and delusional psychosis. The same rate of acute improvement occurred with PD medication reduction, but did not prevent the long-term progression of hallucinations. The conversion time was actually slightly shorter (median 9 months) in subjects treated with PD medication reduction compared to those observed without pharmacological intervention (median 12 months), but given that the sample size was relatively small and that most follow-up visits were spaced at 3- to 4-month intervals, we do not consider this difference clinically pertinent.

At least acutely, antipsychotic medication treatment did not aggravate Parkinsonism. Although we found a statistically significant acute exacerbation of Parkinsonism in association with PD medication reduction, the mean UPDRS change was only one point,

and we do not consider that change clinically significant. Over the follow-up period, UPDRS motor scores increased similarly regardless of intervention, and we suggest that this deterioration likely reflects disease progression. Overall, the study findings favor the introduction of antipsychotic medications early in the course of hallucinations in terms of hallucinations and Parkinsonism.

The data were collected prospectively in the context of active clinical practice, and we acknowledge the limitations of a retrospective analysis and the nonrandomized nature of the patient assignment to antipsychotic medications or other treatments. We cannot state the exact day or week of hallucination onset, but the frequent visit schedule and the regular assessment of TD scores allows us to ensure that we captured the first hallucinations within the time period of one follow-up visit. It is possible that unassessed factors like cognitive status, financial concerns, or other medical comorbidities influenced the physician's decision to introduce antipsychotic medications or to select a more conservative approach. The patients were derived from a single university practice involving six academic movement disorder specialists and the distribution of patients by group was strongly associated with individual physicians, three of the physicians accounting for 75% of the antipsychotic medication-treated cohort. Whereas the disposition to treat with antipsychotic medications, reduce PD medications, or observe without medication changes was clearly indicated in the chart, the decision-making process could not be extracted, and there were no prespecified guidelines for best medical care of hallucinations. Further, we did not gather information on the frequency or severity of hallucinations within a given category on the TD item from the UPDRS. The Movement Disorder Society Task Force on Rating Scales in PD has recently critiqued available rating scales for hallucinations and psychotic behaviors, and it is possible that more refined measurement tools will be recommended for detecting changes within the broader UDPRS-derived categories.[17] The fact that the medication-reduction group did not uniformly deteriorate indicates that the medication reduction was not substantial, and it is possible that further reductions might have achieved similar long-term benefits as seen with the antipsychotic medications. Finally, whereas we are confident that the worsening of hallucinations is positively delayed by early treatment with antipsychotic medications, we cannot comment presently on whether early antipsychotic medication exposure alters the responsiveness of patients to antipsychotic medication use once a TD score of 3 or 4 is reached. Our sample size of patients on antipsychotic medications who deteriorated remains sufficiently small to preclude a full analysis of responsivity after hallucinations worsen. It is possible that early treatment would predict a brisk response to higher antipsychotic medication doses but conversely, the worsening of hallucination in the pharmacological context of antipsychotic medication exposure could represent an " antipsychotic medication resistant" behavior. The study group is currently being followed to address this question. We concur that the ultimate disposition on using antipsychotic medications to delay or halt the progression of hallucinations can only be firmly established with a prospective, randomized clinical trial with long-term follow-up. Until this type of program can be initiated, we offer these data to clinicians, as they consider therapeutic interventions from both a short-term as well as long-term outcome in PD.

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