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AN INITIAL STUDY OF MODIFIABLE AND NON-MODIFIABLE FACTORS FOR LATE-LIFE PSYCHOSIS*

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Abstract

Objective—To determine rates of psychotic symptoms and associated modifiable and non-modifiable factors among elderly long term nursing home residents without prior history of psychiatric illness.

Method—A cross-sectional design using the Scale for the Assessment of Positive Symptoms (SAPS) to measure psychotic symptoms, the Folstein's Mini-Mental State Exam (MMSE), and Mattis Dementia Rating Scale (DRS) to evaluate cognitive impairment. Frequency and rates of global psychotic symptoms and hallucinations, delusions, formal thought disorder, and bizarre behavior were calculated. Logistic regression was used to examine modifiable (e.g., medication use) and non-modifiable clinical characteristics (e.g., older age) associated with late-life psychosis.

Results—There were 15.9% of subjects reporting delusions and 7.3% reporting hallucinations. History of stroke, poorer cognition, and receiving multiple medications showed significant association with late-life psychosis. Only stroke (OR = 9.12; 95% CI: 1.58-52.74) and receiving different classes of medications (benzodiazepines, neuroleptics, and antidepressants) (OR = 13.17; 95% CI: 2.10-85.82) remained significantly associated with psychosis after adjusting for Mattis DRS total score. Further analyses excluding subjects with MMSE scores of 24 or lower ($n = 24$) showed essentially the same results but subjects with better cognitive function suffered a less severe form of psychosis, essentially constituted by one symptom type (i.e., visual hallucinations).

Conclusions—Rates of late-life psychosis in this sample of nursing home residents without previous psychiatric history were high. Simultaneous use of medications including antidepressants, sedatives, and stimulants may be a clinically relevant modifiable factor to be targeted in prevention studies. Severity and type of psychosis is dependent on the severity of cognitive impairment.

Keywords

psychosis; late-life; aging psychiatry; polypharmacy; stroke; cognitive impairment; prescription medications

Late-life psychosis is common among persons with dementia and among individuals living in nursing homes [1]. Not surprisingly, dementia and nursing home placement are risk

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factors for late-life psychosis because cognitive impairment is a primary indication for nursing home placement and as many as 90% of patients with dementia become institutionalized [3]. In addition to being a source of suffering for the affected individual, psychotic symptoms complicate caregiving in the nursing home [4, 5] and are linked to greater caregiver distress [6, 7]. In turn this reduces the quality of life of nursing home residents (e.g., increased residents' agitation [8, 9] and aggression [10, 11]). Classic work in the taxonomy of older age mental disorders included the construct of senile psychosis [12]. Senile psychosis is posited to have onset after age 65 and occurring among individuals without history of schizophrenia or other psychiatric diagnoses while presenting commonly with delusions and hallucinations and on occasion with agitation and bizarre behavior [13]. Symptoms may be related to an under-lying biological condition [13]. Subsequent to these early observations, several investigators have studied the epidemiology of psychosis of late life in several settings [1, 2, 14-17].

Because high rates of behavioral and psychiatric symptoms are reported among nursing home residents [18], the nursing home setting offers an enriched environment for studying factors associated with psychosis of late life as potential mechanisms. In nursing homes, the prevalence of psychotic symptoms ranges from 13% to 60.1% [2, 14, 19, 20]. Both male and female gender have been reported as risk factors [1, 4, 21-24]. Also, studies supported by neuroimaging have found an association between brain damage (e.g., stroke) and late-life psychosis [25, 26]. Association with older age appears plausible based on earlier research [27]. Nonetheless, a recent large scale review reported that the association between late-life psychosis and older age remains controversial [1]. Other commonly reported risk factors for late-life psychosis are hearing impairment and poor general health [28-33].

Most research evaluating risk factors for late-life psychosis among persons living in nursing homes has focused on non-modifiable risk factors (e.g., age, sex) [1]. Whereas most studies were cross-sectional, some were prospective [1], but few have examined the role of modifiable factors including use of prescription medications and substance abuse [34]. The concomitant use of multiple medications either of same or different classes (i.e., polypharmacy) is common among the elderly and is associated with adverse outcomes [35-37]. The present study examines the association between specific classes of medications and concomitant use of multiple prescription medications and late-life psychosis among residents of Iowa nursing homes. Other demographic and clinical factors (e.g., age, sex, and cognitive impairment) were included in the analyses to examine the amount of variance explained by use of multiple medications against reported predictors of late-life psychosis.

METHODS

Study Sample

The sample for this study has been described in previous studies [38, 39] and included 69 residents of three rural nursing homes in the state of Iowa. The sample is constituted of subjects who participated in a comprehensive assessment of psychiatric/behavioral symptoms, cognitive and functional status. To be enrolled in the study, a subject had to be over age 60 and be a long-term resident of a nursing home. Inclusion criteria broadly permitted the participation of the nursing home residents regardless of medical illness or physical disability provided they were able to cooperate with the study interview. Exclusion criteria were history of or current schizophrenia, bipolar disorder, and mental retardation ascertained through exam and medical records. Regarding the sample selection procedures, in this study recruitment proceeded by reviewing the study with the directors of nursing of each facility. The directors then determined which residents were appropriate to approach in terms of ability to cooperate, and obtained permission from the potential subject or legal decision maker. On the basis of their assessment of persons as not appropriate,

approximately 20 potential subjects were unable to cooperate because of aphasia or profound cognitive impairment. Some potential participants *also* had to be excluded because their decision maker was not available for consent. Subjects or their legal representatives signed written informed consent after the study protocol as approved by the University of Iowa Human Subjects Committee was discussed. Twenty-three subjects (of 69) had their legal representatives sign the consent form for them after they had given verbal consent. The remaining 46 subjects completed and signed the consent forms after reviewing the documents with the research nurses. The cognitive and symptom data were collected by a trained research assistant who had established reliability in symptom and neuropsychological assessment through training with the Iowa Mental Health Clinical Research Center and who regularly attended training sessions to periodically recalibrate on rating scale procedures to ensure absence of rater drift over time. The symptom ratings were obtained by direct interview and assessment of the participants themselves, with additional information gained from the nursing documentation and interview of the facility nurses.

Background Clinical Data and Measurement Instruments

General medical history and demographic data including sex, age, and education were recorded. Medical history information was obtained by reviewing the nursing home charts including the clinician progress notes, nursing documentation, laboratory measures, and consultation reports. Medications received by patients were ascertained from their medical record. Medical history information was also obtained by interview with the participant and nursing staff to achieve the most complete information possible. Psychotic symptoms were assessed using the Scale for the Assessment of Positive Symptoms (SAPS) [40], an instrument successfully used to assess psychotic symptoms [41, 42] with good validity and reliability [43]. Cognitive functioning was measured with the Mattis Dementia Rating Scale (DRS) [44] and Folstein's Mini-Mental State Exam (MMSE) [45].

Variables

The dependent variable in this present study is psychosis, derived from the global rating score of psychotic symptoms including hallucinations, delusions, formal thought disorder, and bizarre behavior [40]. The global rating score for each spectrum of psychotic symptoms as described in SAPS [40] is based on the duration and severity of each symptom-spectrum and as such is not simply the sum total of the different psychotic symptoms subscales. In the SAPS, the global rating scores may range from 0 to 5 (0 = none, questionable, mild, moderate, marked, and 5 = severe). The present study used a conservative approach to classify subjects as having psychosis purported to be of clinical relevance. Moderate, marked, and severe scores were used to classify subjects as *with psychosis* whereas a score of less than moderate signified "no psychosis." The independent variables included age, sex, and education. Education and age were analyzed as continuous variables. Medical conditions including stroke, hypertension, and visual and hearing impairment were also used as independent variables. The two variables assessing cognitive impairment (DRS and MMSE scores) were both analyzed as continuous variables. For parsimony's sake, medications were grouped into antidepressants, sedatives (including benzodiazepines, antipsychotics and/or other sedative medications), stimulants, and multiple medications categories. The multiple medications category signified that subjects in the study received at the same time any combination of antidepressants, stimulants, and sedatives. Each category/variable was dichotomized (received versus did not receive).

Statistical Analysis

Data were analyzed using SAS version 9.2. The freq procedure was used to calculate frequency and rates, while means were calculated using the means procedure. Odds ratios were calculated using *logistic regression* methods as appropriate for dichotomous dependent

variables (presence or absence of psychosis). The model building included the following steps. The association of psychosis and variables was first assessed in univariate logistic regression analyses. Variables with a p -value ≤ 0.10 were selected for multivariable analysis. The model with the surviving variables was fitted. The final model included variables significant at $p < 0.05$ level. Additional analyses were computed to compare the rates of psychotic symptoms between subjects with cognitive impairment (i.e., MMSE ≤ 24) and subjects without cognitive impairment (i.e., MMSE > 24).

RESULTS

The sample was primarily composed of widowed women with legal guardians (Table 1). Mean age was 87.5 years ($SD = 7.7$, range 62.0-102.0 years) and mean education 12.9 years ($SD = 2.9$, range 4-20 years). Mean MMSE was 19.5 ($SD = 8.0$), while mean for the Mattis DRS was 90.7 ($SD = 34.9$). Mean weight was 62.7 kg ($SD = 17.1$, range 54.6-117 kg).

Rates of Psychosis

Proportions of subjects with psychotic symptoms including hallucinations, delusions, bizarre behavior, and thought disorder are presented in Figure 1. There were $N = 18$ (26.1%) subjects who showed at least one psychotic symptom. Percentage of subjects reporting moderate to severe global score for delusion were more than double (15.9%) the percentage of subjects reporting moderate to severe global score for hallucinations (7.3%). Subjects reported more persecutory delusions than any other type of delusions. Visual hallucinations were the most common hallucinations, present in 26.0% of subjects. The rates for bizarre behavior and thought disorder were 17.4% and 20.3% respectively.

Univariate Analysis

Odds ratios (OR) and 95% confidence intervals (CI) for risk factors for psychosis are presented in Table 2. In univariate logistic regression analyses, concurrently receiving different classes of medications (sedatives, stimulants, and antidepressants), history of stroke, and poorer cognition (i.e., lower Mattis DRS and MMSE scores) were associated with late-life psychosis. Visual and hearing impairment showed a non-significant association with psychosis. There was no significant association between sex or education and late-life psychosis. Older age, on the other hand, was marginally negatively associated with late-life psychosis ($p = 0.06$), therefore met criteria to be included in the multivariate regression.

Multivariable Analysis

Age, Mattis DRS total score, history of stroke, and multiple medication use were independent variables entered in the multivariate model. Receiving different classes of medications (sedatives, stimulants, and antidepressants) and history of stroke were independently associated with psychosis (see Table 2). In order to further assess the effect of cognitive impairment on the relationship between polypharmacy and psychosis, additional multivariate analyses were carried out excluding subjects with MMSE scores of 24 or lower ($n = 24$). Factors associated with psychosis in these analyses were essentially the same as in the analyses carried out using the entire sample. However, only 13.3% of subjects with MMSE > 24 reported psychotic symptoms compared to 60.0% among individuals with cognitive impairment (MMSE ≤ 24). Nursing home residents with MMSE > 24 reported only one psychotic symptom type (e.g., visual hallucinations) whereas almost 29.0% of subjects with cognitive impairment showed multiple psychotic symptoms. Table 3 shows the rates of psychotic symptoms in cognitive impaired (MMSE ≤ 24) and non-cognitive impaired subjects (MMSE > 24). Rates of delusions, thought disorder and bizarre behavior were significantly lower in subjects without cognitive impairment (Table 3).

DISCUSSION

In the present study, over one-fourth of subjects showed at least one psychotic symptom, a result consistent with earlier research [16]. Rates of hallucinations (7.3%) and delusions (15.9%) in the present report were comparable to most previous studies evaluating late-life psychosis [1, 2, 14, 16, 46]. One study [14] that followed nursing home residents over two years reported notably higher rates (32.8% for hallucinations and 56.0% for delusions). Consistent with the present study, a population-based study including both nursing home and community-dwelling individuals reported hallucination rates of 6.9% [17]. The present study is also consistent with the Webster and Grossberg study [13] reporting higher rates of visual compared to auditory hallucinations (Figure 1).

The primary findings of the present research were:

1. association between cognitive impairment and psychosis;
2. association between multiple medication use and psychosis;
3. concurrent use of antidepressants, sedatives, and/or stimulants increased by 13-fold the likelihood to suffer late-life psychosis after adjusting for cognitive impairment; and
4. quantitative and qualitative difference between psychosis in individuals with differing degrees of cognitive function.

Before examining the results of the present study, certain limitations must be acknowledged. First, the possibility exists that some differences did not reach significance due to sample size. The present study is cross-sectional, therefore it is unable to demonstrate a causal association between late-life psychosis and associated factors. Data did not include dosage and frequency of medication administration. The study population included nursing home residents without history of bipolar disorder, schizophrenia, or mental retardation. This may limit generalization to the broader population living in nursing homes and may have influenced the rates of psychosis. Prospective studies on late-life psychosis have focused on non-modifiable factors [1], so further studies using prospective designs will be necessary to expand and replicate these initial findings.

These findings have substantial relevance for clinical psychiatry practice. Bassiony and colleagues [47] reported significant independent associations between anxiolytics and antihypertensives treatment and late-life psychosis. Whereas association between multiple medications use and late-life psychosis has been described in clinical commentaries [34], the present study is to our knowledge the first research to empirically show the association between polypharmacy and psychosis in late life. Future studies employing longitudinal designs should examine the extent to which multiple medications are *causal* to psychosis or may result from attempts to control the psychosis.

In the present study, cognitive impairment showed a significant positive association with late-life psychosis, a finding consistent with previous studies [1, 15-17, 48, 49]. The two variables used to assess cognitive functioning (DRS and MMSE) in this study were both strongly associated with late-life psychosis suggesting that dementia and/or delirium may carry significant risk for psychosis. The interplay of dementia, delirium, and multiple medication use may be critical to understanding the mechanism of psychosis in nursing home elderly. For instance, disorganization of severe dementia or agitated delirium may be responsible for bizarre behaviors. Delirium occurring in the context of a dementia is common [50] and frequently presents with psychosis [51]. Risk of delirium is increased among elderly people taking three or more medications [52]. Using single photon emission computerized tomography (SPECT), Miller and colleagues [53] reported that subjects with

late-life psychosis showed hypoperfusion in the temporal or frontal brain regions. Consistent with previous studies [22, 26], the present study showed a significant association between prior stroke and late-life psychosis, suggesting that a poorly vascularized and brittle brain may constitute a critical risk factor to develop late-life psychosis.

Whereas on the one side multiple medications use may be responsible for delirium [54], on the other polypharmacy was significantly associated with psychosis when controlling for cognitive impairment and among residents who had better cognitive abilities. In the present study, subjects with better cognitive functioning and psychosis showed only one symptom type (i.e., visual hallucinations) and showed significant lower rates for delusions, thoughts disorder, and bizarre behaviors (i.e., a less severe psychosis) compared to individuals with worse cognitive functioning. This suggests that that polypharmacy-associated psychosis in late life is less severe among subjects with better cognitive abilities. This is consistent with previous findings [17] and suggests that cognitive impairment and polypharmacy exert an additive effect onto psychosis in late life. Consistent with prior research [55], association with individual use of antidepressants, stimulants, or sedatives was not statistically significant. An earlier study reported increased rates of psychosis among elderly taking stimulants [13], but this finding was not replicated in the present study.

Several studies have evaluated the association between age and late-life psychosis [8, 11, 25, 47, 55, 56]; while some of these studies reported an association [8, 25, 47], others found no significant association [11, 55, 56]. A recent publication reviewing 55 studies on late-life psychosis among Alzheimer's disease patients was unable to draw conclusions and noted that 12 studies found an association with older age, while 13 reported no association [1]. In the present study, there was a marginal negative association between age and late-life psychosis in univariate regression (signifying that subjects with relatively younger age were at risk for psychosis), this association (perhaps explainable by a selection among older age survivors of persons without psychoses) did not remain significant in multivariate regression. Differences among studies may be related to the specific characteristics of the study samples, sample size, and perhaps to a non-linear effect of age on psychosis. This issue warrants further examination with larger and inclusive samples and exploration of non-linear trends for the association psychosis and older age. In this sample of nursing home residents without history of major psychiatric disorders, there was no association between late-life psychosis and sex, a finding consistent with 17 of the 55 studies reviewed by Ropacki and Jeste [1]. Ropacki and Jeste [1] also remarked that seven studies showed an association between sex and late-life psychosis, and among these studies, four found women at greater risk for late-life psychosis [23, 57-59] while three reported greater risk for men [55, 60, 61].

In summary, these findings contribute to the understanding of late-life psychosis while giving critical information useful for potential prevention and treatment. In light of the aging of baby boomers and aging of the modern world, psychotic illness in late-life will become in the upcoming decades a pressing clinical issue. For this reason, there is a great need to understand the multiple factors contributing to the development of psychosis in late-life focusing on modifiable factors and prevention.

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Figure 1.

Psychotic symptoms.

Symptoms rates assessed with the Scale for the Assessment of Positive Symptoms (SAPS) are presented. Any given symptom was considered present if assessed as moderate or higher severity. The global score for each spectrum of psychotic symptoms reflects duration and severity of each symptom-spectrum [40].

Table 1

Demographic Characteristics

Variable	Variable category	Frequency	Proportion
Sex	1. Male	14	20.3
	2. Female	55	79.7
Marital status	1. Never married	4	5.8
	2. Married	19	27.5
	3. Divorced	3	4.4
	4. Widowed	43	62.3
Guardian	1. Guardian	52	75.4
	2. No guardian	17	24.6

Table 2

Univariate and Multivariate Logistic Regression of Independent Variables on Psychosis

Variables	Univariate analysis		Multivariate analysis	
	OR ^a (95% CI ^b)	p-Value	OR ^a (95% CI ^b)	p-Value
Age	0.94 (0.88-1.01)	0.06		
Sex	0.76 (0.21-2.74)	0.67		
Education	0.88 (0.72-1.06)	0.17		
Mattis DRS	1.19 (1.01-1.04)	< 0.01		
MMSE	1.03 (1.19-1.30)	< 0.01		
Stimulants	1.01 (0.26-3.75)	0.98		
Sedatives	1.24 (0.41-3.74)	0.70		
Antidepressants	1.85 (0.68-5.08)	0.23		
Concurrent medications	7.94 (2.07-30.46)	0.01	13.17 (2.10-85.82)	< 0.01
Stroke	3.16 (1.05-9.50)	0.04	9.12 (1.58-52.74)	0.01
Hypertension	1.21 (0.43-3.42)	0.73		
Visual impairment	1.11 (0.37-3.32)	0.19		
Hearing impairment	1.44 (0.51-4.07)	0.49		

Note: Table shows univariate and multivariate logistic regression analyses with the dichotomous dependent variable (presence or absence of psychosis). Model building was based on univariate analyses. Variables with a *p*-value ≤ 0.10 were selected for multivariate analysis. The final model included variables significant at $p < 0.05$ level.

^aOR = odds ratio.

^bCI = confidence interval.

Table 3

Psychotic Symptoms among Subjects With and Without Cognitive Impairment

Symptoms	Cognitive impaired (N = 45)		Non-cognitive impaired (N = 24)		Chi- square	p-Value
	n	%	n	%		
Auditory hallucinations	4	8.9	1	4.2	1.67	0.20
Visual hallucinations	13	28.9	5	20.8	0.11	0.74
Thought disorder	13	28.9	4	16.7	5.92	0.01
Bizarre behavior	11	24.4	2	8.3	4.48	0.03
Delusions	10	22.1	1	4.2	3.85	0.05

Note: Table shows percentage of subjects with each psychotic symptom in each group. Cognitive impairment is defined as MMSE $\leq$ 24. Odds ratios: Auditory hallucinations = 1.82, Visual hallucinations = 0.14, Thought disorder = 3.84, Bizarre behavior = 4.35; Delusions = 3.83.