Antipsychotic Use in Hospitalized Patients: Rates, Indications, and Predictors

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Abstract

Background/Objectives—Although antipsychotics are used for treatment of delirium/agitation in hospitalized patients, the scope of use is unknown. We investigated patterns and predictors of use in hospitalized patients.

Design—Retrospective cohort study.

Setting—Academic medical center.

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Participants— 18 years old, hospitalized 8/2012–8/2013. We excluded patients admitted to obstetrics/gynecology, psychiatry, or with a psychotic disorder.

Measurements—Use ascertained from pharmacy charges. Potentially excessive dosing defined using guidelines for long-term care facilities. A review of 100 records was performed to determine reasons for use.

Results—Our cohort included 17,775 admissions, median age 64 years. Antipsychotics were used in 9%, 55% of which were initiations. The most common reasons for initiation were delirium (53%) and probable delirium (12%). Potentially excessive dosing occurred in 16% of exposed. Among admissions with antipsychotic initiation, 26% were discharged on these medications. Characteristics associated with initiation included: age   75 years (RR 1.4 [1.2–1.7]); male sex (RR 1.2 [1.1–1.4]); black race vs. white (RR 0.8 [0.6–0.96]; delirium (RR 4.8 [4.2–5.7]); dementia (RR 2.1 [1.7–2.6]); admission to a medical service (RR 1.2 [1.1–1.4]); intensive care unit stay (RR 2.1 [1.8–2.4]); and mechanical ventilation (RR 2.0 [1.7–2.4]). Characteristics associated with discharge on antipsychotics among initiators included: age   75 years (RR 0.6 [0.4–0.7]); discharge to any location other than home (RR 2.5 [1.8–3.3]) and class of in-hospital antipsychotic exposure (RR 1.6 [1.1–2.3] for atypical vs. typical; RR 2.7 [1.9–3.8] for both vs. typical).

Conclusion—Antipsychotic initiation and use were common during hospitalization, most often for delirium, and patients were frequently discharged on these medications. We identified several predictors of use on discharge, suggesting potential targets for decision support tools prompting consideration of ongoing necessity.

INTRODUCTION

Delirium is common in hospitalized patients, occurring in 15 to 26 percent of hospitalized older adults.[1–3] Although both conventional and atypical antipsychotics are commonly used off-label for treatment of behavioral symptoms associated with delirium and/or dementia, their effectiveness for this purpose is controversial.[4, 5] A recent systematic review noted an almost complete lack of rigorous studies examining the effectiveness of these medications for the treatment of delirium. However, severe acute agitation and/or psychosis can pose important psychological and physical risks to a patient – particularly in the hospital setting where intravenous lines and urinary catheters may become traumatically dislodged – and other treatment options in this setting are limited and often not feasible given time and resource constraints. Nonetheless, any benefit from these medications must be balanced against a growing number of documented risks, including falls,[6, 7] pneumonia,[8–10] and death.[11, 12] Overuse of these medications in hospitalized patients could contribute to excess adverse outcomes.

Given the frequency of delirium and the lack of guidelines or regulatory oversight for prescribing of antipsychotic medications in hospitalized patients, use could be substantial. To our knowledge, the scope of antipsychotic use in the hospital setting has not been previously investigated. We sought to investigate prescribing patterns and predictors of new

initiation and subsequent discharge on these medications in a large cohort of hospitalized patients.

METHODS

Setting and Data Collection

We conducted a retrospective cohort study of patients admitted to a large, urban academic medical center in Boston, Massachusetts from August 1, 2012 through August 31, 2013. The study was approved by the institutional review board at Beth Israel Deaconess Medical Center, and granted a waiver of informed consent. Data were collected from electronic medical information databases maintained at the medical center and supplemented by chart review where noted. These electronic databases, collected prospectively for clinical and administrative purposes, contain patient-specific information related to each admission during the study time period.

Inclusion and Exclusion Criteria

All admissions at least 18 years of age were eligible for inclusion. We excluded patients admitted to a psychiatry service or with a primary or secondary discharge diagnosis of a psychotic disorder (defined by the Elixhauser comorbidity "Psychoses:" 295.00–298.9, 299.10–299.11), since we were interested in use of antipsychotics for conditions other than primary psychiatric disorders. We also excluded patients admitted to the obstetrics and gynecology (Ob/gyn) service owing to the non-representativeness of this patient population for the general hospitalized patient. We excluded patients with a missing preadmission medication list (defined below), to allow differentiation of in-hospital initiation from preadmission use.

Antipsychotic Medication Utilization

We categorized antipsychotic medications as typical (haloperidol, loxapine, thioridazine, molindone, thiothixine, pimozide, fluphenazine, trifluoperazine, chlorpromazine, and perphenazine) and atypical (aripiprazole, asenapine, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone) based on the classification of the Food and Drug Administration.[13] We excluded prochlorperazine (Compazine) from our typical antipsychotic definition, as this medication is almost exclusively used in the hospital setting as an antiemetic rather than as an antipsychotic.

We ascertained preadmission, in-hospital, and discharge use of antipsychotic medications using 3 separate electronic databases maintained at the medical center. Preadmission medications were obtained from an electronic medication reconciliation application, which went into full use at the medical center in 7/2012. Physicians are expected to populate the preadmission medication list at the time of admission for all patients. In-hospital antipsychotic medication use was ascertained from pharmacy charges, reflecting each medication dispensed by pharmacy during the hospitalization. We ascertained whether each medication was ordered on an as needed or scheduled basis by referring to the physician order accompanying each pharmacy charge. Discharge medications are electronically captured from the discharge worksheet completed by physicians at the time of discharge.

Because guidelines for use of antipsychotic agents in hospitalized patients do not exist, we used the existing Centers for Medicare and Medicaid Services (CMS) guidelines for long term care facilities to define measures of potentially excessive dosing in the hospital setting.[14] These guidelines define the daily dosage levels of antipsychotics above which the medical necessity of the higher dose should be explained in the medical record. We defined any daily dosage above these specified levels as a "potentially excessive daily dose."

Characteristics Associated with Use

We selected potential predictors of use based on a priori clinical grounds: 1) demographic variables such as age (65–74, 75 vs. < 65), gender, and race (self-reported by patients at the time of admission); 2) hospitalization characteristic variables, including admission day of the week (weekend vs. weekday), admitting department (medicine vs. non-medicine), whether the patient spent any time in the intensive care unit (ICU), whether they received mechanical ventilation, discharge day of the week (weekend vs. weekday), and disposition location (home vs. not home); 3) variables representing potential indications for use, including delirium, dementia, and insomnia (see Appendix for *ICD-9-CM* codes pertaining to each); 4) for our model of discharge on antipsychotic medication among in-hospital initiators, we additionally included variables representing characteristics of in-hospital use, including type of in-hospital antipsychotic exposure (atypical vs. typical, and both vs. typical), and whether a patient had any order for scheduled antipsychotic medication (vs. as needed only).

Statistical Analysis

We report rates of in-hospital use, rates of potentially excessive use, rates of initiation of antipsychotic medication, defined as in-hospital use in a patient without an antipsychotic medication on their preadmission medication list, and rates of use on discharge.

We investigated predictors of new initiation and discharge on antipsychotic medication using multivariable Poisson regression models with a robust variance estimator,[18] simultaneously including all potential predictors as independent variables. We excluded from our discharge model those patients who died during hospitalization or left against medical advice.

All analyses were carried out using SAS software, version 9.2, Cary, NC.

Subgroup Analysis: Indication for Use

To determine the documented indication for use we performed an extensive review of the inpatient medical records of 100 randomly selected admissions with in-hospital initiation of antipsychotics. We defined delirium as any documentation of "delirium," or "encephalopathy" in the medical record. We defined probable delirium as documentation of the features of delirium (e.g. waxing and waning mental status, altered mental status, confusion, agitation) in the absence of use of the words "delirium" or "encephalopathy."

RESULTS

Admission Characteristics

There were 30,357 admissions age 18 and over from 8/2012–8/2013. After excluding patients admitted to the Ob/Gyn (n = 5,643) and psychiatry (n = 663) services, patients with a psychiatric diagnosis (n = 929) and patients with a missing preadmission medication list (n = 5,347), our cohort included 17,775 admissions. The median age of the cohort was 64 years (range 18–106), and 8,700 (49%) were women. Table 1 shows the characteristics of the admissions in the cohort, stratified by antipsychotic exposure status.

Antipsychotic Use

There were 1,537 (9%) admissions with charges for antipsychotic medications; 704 (8%) of those age 18–64, 252 (7%) of those age 65–74, and 581 (12%) of those age 75 and older. Among exposed: 1,291 (84%) received scheduled antipsychotic medication, while 246 (16%) received as needed only; 1,274 (83%) received atypical and 496 (32%) received typical antipsychotics, with 233 (15%) exposed to both; 842 (55%) were initiations – i.e. use in patients without these medications on their preadmission medication list.

Discharge on Antipsychotics

Overall, 222 (26%) admissions with any antipsychotic initiation were discharged on an antipsychotic medication. Atypical antipsychotics were more likely to be continued at discharge than typical antipsychotics. Among 620 admissions with initiation of an atypical antipsychotic, 178 (29%) were discharged on an atypical antipsychotic. Among 402 admissions with initiation of a typical antipsychotic, 44 (10%) were discharged on a typical antipsychotic.

Use of Specific Drugs, and Potentially Excessive Dosing

Table 2 demonstrates the most commonly used antipsychotic medications, and the rates of potentially excessive dosing. Quetiapine and olanzapine were the most commonly used atypical antipsychotics, and haloperidol represented the majority of typical antipsychotic use. Among admissions with any antipsychotic exposure, 16% received at least one daily dose in excess of the recommended daily dose; 12% of those with atypical antipsychotic exposure, and 21% of those with typical antipsychotic exposure. Among admissions age 65 and up (n = 8,822), the prevalence of potentially excessive use was somewhat lower - 8% received at least one daily dose in excess of the recommended daily dose; 6% of those with atypical antipsychotic exposure, and 13% of those with typical antipsychotic exposure.

Reasons for Initiation

In our subgroup analysis of 100 admissions with antipsychotic initiation, the most common reasons for initiation were delirium (53%), probable delirium (12%), nausea (13%), anxiety (8%), and insomnia (7%). See Table 3 for full list of reasons for initiation.

Characteristics Associated with Initiation and Subsequent Continuation on Discharge

Among admissions without preadmission exposure to antipsychotics, characteristics associated with antipsychotic initiation included: age 75 years (RR 1.4 [1.2–1.7]); male sex (RR 1.2 [1.1–1.4]); black race vs. white (RR 0.8 [0.6–0.96]); delirium (RR 4.8, [4.2–5.7]); dementia (RR 2.1 [1.7–2.6]); admission to a medical service (RR 1.2 [1.1–1.4]); intensive care unit stay (RR 2.1 [1.8–2.4]); and mechanical ventilation (RR 2.0 [1.7–2.4]). Characteristics associated with discharge on antipsychotics among initiators included: age 75 years (RR 0.6 [0.4–0.7]); discharge to any location other than home (RR 2.5 [1.8–3.3]) and class of in-hospital antipsychotic exposure (RR 1.6 [1.1–2.3] for atypical vs. typical; RR 2.7 [1.9–3.8] for both vs. typical; see Table 4).

DISCUSSION

In this cohort of non-psychiatric admissions to a large academic medical center, we found that antipsychotic medications were used in 9% of admissions, more than half of which were initiated in the hospital, with atypical antipsychotics representing the majority of use. In the charts we reviewed, treatment of delirium was the most commonly documented reason for initiating an antipsychotic. We found potentially excessive daily doses based on CMS recommendations for long-term care facilities occurring in 16% of admissions with any antipsychotic exposure. More than 25% of patients initiated on antipsychotics during hospitalization were subsequently discharged on an antipsychotic. We identified several predictors of initiation and discharge on these medications, suggesting potential targets for enhanced prescribing guidance and medication reconciliation practices.

Prior studies examining antipsychotic prescribing have focused almost exclusively on the long-term care setting. We are aware of only 1 prior study, published as a research letter, examining antipsychotic prescribing in the acute-care hospital setting. In their analysis, Loh et al. focused exclusively on hospitalized patients over the age of 65, and found an identical 9% incidence of antipsychotic use.[19] They similarly found that delirium was the most common reason for use. Their analysis was limited to descriptive statistics, and to our knowledge, ours is the first to investigate dosage patterns or predictors of use in the hospital setting.

Off-label and inappropriate use of antipsychotics is common in multiple settings.[20] Studies in the long-term care setting have demonstrated that 25–30% of such patients receive antipsychotics,[21–23] and despite guidelines and regulations designed to achieve more oversight of prescribing, the majority of use is inappropriate with respect to either indication or dosage in excess of recommended daily dosing levels.[21] Due to the lack of regulatory oversight of prescribing of these medications in the hospital setting, we hypothesized that use of dosages in excess of the CMS guidelines would be common. Despite this, we found relatively low rates of potentially excessive dosing overall, with even lower rates of excessive dosing in older adults. This may reflect a successful computerized decision support prompt at our medical center, reminding clinicians of recommended (lower) psychotropic medication doses in older patients, and dosages may therefore be higher in hospitals without such decision support.[24, 25] Our findings should be validated at other institutions.

Some of the associations we observed with respect to age and race were unexpected. First, we found that while patients age 75 and older were significantly more likely to receive antipsychotic medications during hospitalization, they were significantly less likely to be discharged on them. That the oldest patients are most likely to receive these medications probably partly reflects the higher rates of delirium/dementia in this age group.[26] However, given that age is a risk factor for delirium persistence,[27, 28] the reason for the reduced use on discharge in the oldest age group is not readily apparent. One potential explanation is that older adults are much more likely to be discharged to post-acute facilities, however we did not find evidence for effect modification by disposition location, so this does not explain the observed association. We also found that non-white patients were less likely to receive antipsychotics than white patients, and although this relationship was significant only for black patients, statistical power was limited by small sample size for the other racial groups. Both of these findings warrant further investigation.

Our finding that 26% of patients initiated on antipsychotics during hospitalization had them continued at discharge, and that discharge to a facility was strongly associated with continuation suggests that hospitalization may be responsible for many patients receiving these medications at long-term care facilities. The direction of the relationship between use of these medications and discharge to a facility is not clear, however. For example, it may be that the decision to discharge a patient to another monitored setting makes a physician more likely to continue these medications regardless of underlying necessity. Alternatively, continuation of these medications after discharge could reflect an ongoing need (such as persistent delirium), which could in part drive the necessity for discharge to a facility. In either case, the continued need for these medications, particularly in patients recently discharged from the hospital, should be re-evaluated soon after discharge by the physicians caring for patients in the long term care facility. Moreover, it should be clearly documented in the hospital discharge paperwork that the antipsychotic was initiated in the hospital and that long term use is not anticipated.

We found that the majority of antipsychotic use in this non-psychiatric patient population was for delirium or probable delirium – both off-label indications – and delirium was the strongest predictor of initiation, even after controlling for other patient and hospitalization characteristics. In recent years, use of both typical and atypical antipsychotics has come under increased scrutiny owing to studies demonstrating increased risk of death among current users,[11, 12, 29] prompting a Food and Drug Administration black box warning against use in elderly patients with dementia-related psychosis. Concern over these risks and the findings of our study are compounded by lack of evidence for efficacy of these medications in prevention or treatment of delirium.[5] A recent systematic review noted that the only placebo-controlled randomized trial on the topic did not show significant differences in mean delirium severity, and that due to severe methodological limitations of the remaining studies, the evidence does not currently support their use in treatment of delirium.[4] However, lack of studies on the topic does not necessarily imply lack of effect, and there is clearly a perception of effectiveness on the part of clinicians who continue to use these drugs for this purpose. Furthermore, while non-pharmacologic approaches to prevention and treatment of delirium in the hospital are highly effective,[30, 31] they are unfortunately time and resource intensive, particularly in the setting of acute agitation. The clinician caring for

a hospitalized patient with agitated delirium is therefore faced with a difficult therapeutic challenge. A need exists for increased recognition by hospital leadership that investment in additional resources for the care of patients with delirium is a worthwhile endeavor. Additionally, efforts to hasten the dissemination of delirium prevention programs, along with development of new, targeted approaches for prevention and management, are crucial for reducing morbidity associated with this common hospital complication.

Despite very similar characteristics of patients receiving the two classes of antipsychotics, we found that atypical antipsychotics were used more than twice as frequently as typical antipsychotics in our cohort. Additionally, physicians were more likely to continue atypical antipsychotics on discharge than typical antipsychotics, even after controlling for patient and hospitalization characteristics, including delirium and dementia. We are not able to determine the reasons for this from our study, but the findings could suggest a higher level of comfort with atypical antipsychotics on the part of physicians, and/or a perception of lower risk for adverse outcomes associated with atypical compared to typical antipsychotics. This is concerning, as several rigorous analyses have found similar risk of adverse events, including pneumonia, sudden cardiac death, and overall mortality, among users of atypical compared to typical antipsychotics.[9–11, 32] Studies investigating factors driving physician decision making in their choice of antipsychotics would be useful in designing targeted educational and decision support interventions.

There are several limitations of our analysis. First, although we studied almost 20 thousand admissions at a large academic medical center, the single center nature of our study limits the generalizability of our findings. Additionally, *ICD-9*-based definitions of delirium, while highly specific, have poor sensitivity, and may have resulted in an underrepresentation of delirium in our cohort.[33] However, the specificity of this administrative definition is a strength in that it should lead to unbiased estimates of association in our regression models. Lastly, because guidelines for dosing in the hospital setting do not exist, we could describe only "potentially" excessive dosing in this analysis, extrapolating from the long-term care setting. Use of higher doses in patients admitted to the hospital may be appropriate given potential differences in patient characteristics and indications for use; whether the dosages administered were actually appropriate and/or indicated in any given patient is not established.

In conclusion, we found that 9% of non-psychiatric admissions to a large academic medical center were exposed to antipsychotics during hospitalization, most commonly for treatment of delirium. The majority of use represented initiation in patients without use prior to admission, and more than a quarter were discharged on these medications. The predictors of continuation on discharge identified in our analysis suggest that patients being discharged to facilities and patients on atypical antipsychotics may be appropriate targets for clinical decision support tools prompting physicians to consider ongoing necessity.

Acknowledgments

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APPENDIX

ICD-9-CM codes defining delirium, dementia, and insomnia:

1. Delirium: 29011, 2903, 29041, 2930, 2931, 3483, 34830, 34831, 34839, 34982, 4372, 5722

2. Dementia: 2900, 29010, 29012, 29013, 29020, 29021, 29040, 29042, 29043, 2908, 2909, 2941, 29410, 29411, 29420, 29421, 3310, 3311, 33111, 33119, 3312, 33182, 797

3. Insomnia: 30740, 30741, 30742, 30745, 30749, 78050, 78051, 78052, 78055, 78056

Table 1

Admission Characteristics and Antipsychotic Use (n=17,775).

Characteristic	Overall (n=17,775) %	No Exposure (n=16,238) %	Atypical Exposure[a] (n=1,274) %	Typical Exposure[a] (n=496) %
Age Group				
18–64	50.4	50.8	46.1	41.9
65–74	21.4	21.9	15.7	17.9
75+	28.2	27.3	38.2	40.1
Female	49.0	48.9	50.7	42.5
Race				
Asian	3.0	3.1	2.9	1.8
Black	13.3	13.6	10.4	12.1
Hispanic	4.5	4.6	4.3	3.8
White	60.6	60.2	65.5	61.7
Other	18.5	18.7	16.9	20.6
Diagnoses				
Delirium	8.4	6.3	47.2	30.0
Dementia	4.7	3.5	17.3	18.5
Insomnia	2.8	2.8	2.4	3.0
Mechanical Ventilation	5.4	4.4	15.4	23.8
ICU Stay	23.9	22.5	36.5	54.2
Admitting Service				
Medicine	56.5	55.5	68.4	63.9
Non-Medicine	43.5	44.5	31.5	35.8
Admission Day of the Week				
Weekday	82.2	82.5	79.6	79.0
Weekend	17.8	17.5	20.4	21.0
Discharge Day of the Week				
Weekday	77.8	77.4	82.3	82.7
Weekend	22.2	22.6	17.7	17.3
Discharge Location				
Home	71.9	74.7	42.5	31.1
SNF/Rehab	22.7	20.8	44.4	48.4
Hospice	1.1	0.9	2.7	5.2
Other	4.3	3.7	10.4	15.3

Abbreviations: AIDS = acquired immunodeficiency syndrome; ICU = intensive care unit; SNF = skilled nursing facility

[a] Antipsychotic exposure categories are not mutually exclusive; patients exposed to both are represented in both columns

Table 2

Prevalence of Antipsychotic Use and Percent of Exposed with At Least One Day of Potentially Excessive Dosing.[a]

Agent[b]	Overall Prevalence n = 17,775	% of Exposed with Potentially Excessive Dosing[a]		
		Within 100% of Recommended DD[a]	101–150% of Recommended DD[a]	> 150% of Recommended DD[a]
Any Antipsychotic	8.6	84.5	6.5	9.0
Atypical	7.2	87.6	5.3	7.1
Quetiapine (200)	3.3	87.3	5.5	7.2
Olanzapine (10)	3.3	88.7	5.6	5.7
Risperidone (2)	0.6	87.8	4.7	7.5
Other	0.7	95.4	0.0	4.6
Typical	2.8	79.4	9.3	11.3
Haloperidol (4)	2.4	79.6	9.1	11.2
Chlorpromazine (75)	0.3	80.0	9.1	10.9
Other	0.4	99.2	0.4	0.4

Abbreviations: DD = daily dose.

[a] Defined by the Centers for Medicare and Medicaid Services (CMS) guidelines for long term care facilities

[b] Numbers in parentheses represent the recommended daily dose above which use should be justified based on the CMS guidelines for long term care facilities

Table 3

Indications for Antipsychotic Use in 100 Randomly Selected Admissions with In-Hospital Initiation

Documented Indication	%
Delirium	53
Nausea	13
Probable delirium	12
Anxiety	8
Insomnia	7
Hiccups	4
Agitation	3
Other	4

Table 4

Predictors of In-Hospital Exposure and Subsequent Discharge on an Antipsychotic, Among Admissions without Pre-Admission Exposure

Variable	In-Hospital Exposure (n=16,953)			Discharged on an Antipsychotic Among In-Hospital Exposed (n=744)[a]		
	RR[b]	95% CI		RR[b]	95% CI	
Age						
65–74 vs <65	1.0	0.8	1.2	0.9	0.7	1.2
75+ vs <65	1.4	1.2	1.7	0.6	0.4	0.7
Gender						
Male vs Female	1.2	1.1	1.4	1.0	0.8	1.2
Race						
Asian vs White	0.8	0.5	1.2	0.9	0.4	2.1
Black vs White	0.8	0.6	0.96	0.8	0.5	1.2
Hispanic vs White	0.9	0.7	1.3	0.8	0.5	1.4
Other vs White	1.0	0.9	1.2	1.0	0.7	1.3
Diagnoses						
Delirium	4.8	4.2	5.7	1.1	0.9	1.4
Dementia	2.1	1.7	2.6	1.2	0.9	1.6
Insomnia	1.2	0.8	1.7	1.5	0.8	2.8
Admitting Department						
Medicine vs Non-Medicine	1.2	1.1	1.4	1.1	0.8	1.4
Any ICU Stay	2.1	1.8	2.4	0.8	0.6	1.02
Mechanical Ventilation	2.0	1.7	2.4	0.8	0.6	1.1
Admission Day of the Week						
Weekend vs Weekday	0.9	0.8	1.1	N/A	N/A	N/A
Discharge Day of the Week						
Weekend vs Weekday	N/A	N/A	N/A	0.9	0.6	1.2
Disposition Location						
Not Home vs Home	N/A	N/A	N/A	2.5	1.8	3.3
In-Hospital Exposure						
Atypical vs Typical	N/A	N/A	N/A	1.6	1.1	2.3
Both vs Typical	N/A	N/A	N/A	2.7	1.9	3.8

	In-Hospital Exposure (n=16,953)		Discharged on an Antipsychotic Among In-Hospital Exposed (n=744)[a]	
Variable	RR[b]	95% CI	RR[b]	95% CI
As needed only vs scheduled	N/A	N/A N/A	1.0	0.8 1.4

Abbreviations: RR = relative risk; CI = confidence interval; ICU = intensive care unit; N/A = not applicable

[a] Excluding patients who died during hospitalization or left against medical advice.

[b] Derived from a multivariable Poisson model simultaneously including all potential predictors as independent variables.