# Determination of combination therapy prescribing patterns for the treatment of acute agitation in psychiatric patients: A regression model of patient diagnoses and demographics

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## Abstract

**Introduction:** Guidelines for the treatment of acute agitation typically recommend monotherapy with an antipsychotic or a benzodiazepine, but combination therapy is frequently used in practice. We created a regression model to identify which factors lead to the prescribing of combination therapy for acute agitation on a psychiatry unit.

**Methods:** We collected retrospective data from hospitalized patients in the psychiatry unit. An a priori alpha of 0.05 was used for binary logistic regression models to determine if and how the number of prescribed medications for acute agitation was influenced by: age, sex, race, cardiovascular comorbidities, and psychiatric diagnoses.

**Results:** We identified 1998 encounters from 1200 patients. Patients are significantly more likely to be prescribed combination therapy if they are young, male, and of non-white race or have a diagnosis of central nervous system stimulant use, hallucinogen use, depression, bipolar, cluster B personality, or psychosis. Patients are significantly more likely to be prescribed monotherapy if they have cardiovascular comorbidity or have neurocognitive disorder.

**Discussion:** Several demographic or diagnostic factors predict combination therapy prescribing. Acute agitation guidelines should be reviewed to include more clear instructions on combination therapy use.

**Keywords:** agitation, prescribing, regression, combination, adjunct

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## Background

Acute agitation is a serious medical complication with many possible etiologies.[1,2] Whether patients present in the emergency department, psychiatric unit, or other medical units, rapid treatment is required to prevent harm to the patient or others. According to the National Emergency Department Safety Study, about one quarter of all emergency department practitioners felt safe at work *sometimes*, *rarely*, or *never*.[3] Additionally, 10% to 25% of all emergency psychiatric presentations include acute agitation.[2] Because of its prevalence, acute agitation is a significant impediment toward safe, high-

quality provision of patient care.[3] Initial treatment should be non-pharmacologic, but pharmacotherapy may be required if behavioral de-escalation techniques are unsuccessful.[1] Commonly used medications for acute agitation include first or second generation antipsychotics, benzodiazepines, and anticholinergics.[1,4-6]

The consensus statement developed by the American Association of Emergency Psychiatry recommends pharmacologic class selection based on patient comorbidities and agitation etiology.[1] Antipsychotics are recommended for central nervous system (CNS) depressant intoxication, delirium that is not secondary to ethanol withdrawal, or psychosis.[1] Benzodiazepines are recommended for CNS stimulant intoxication, alcohol withdrawal, or idiopathic agitation without psychosis. Combination treatment with an antipsychotic medication and a benzodiazepine is only recommended in refractory psychosis due to a known psychiatric disorder.

Combination therapy for acute agitation may also include an antihistamine or anticholinergic medication, despite guideline recommendations.[1] A survey of psychiatry practitioners indicated that antihistamines are often used together with haloperidol and lorazepam in acute agitation.[7] The use of antihistamines with anticholinergic activity has been shown to reduce antipsychotic-induced dystonia and improve agitation when used together with haloperidol compared to haloperidol monotherapy.[8] However, risk of adverse effects (eg, excessive sedation) are more pronounced when all three medications – an antipsychotic, a benzodiazepine, and an antihistamine – are prescribed concurrently.

Despite guideline recommendations, combination therapy is prevalent in practice and some studies claim efficacy.[7,9,10] One study[9] reported that the combination of a benzodiazepine and a first-generation antipsychotic is non-inferior to high-dose monotherapy of olanzapine when used for acute agitation. A systematic literature review[10] found that the combination of an antipsychotic with a benzodiazepine or an antipsychotic alone had superior safety and efficacy compared to monotherapy with a benzodiazepine. Overall, studies and guidelines are mixed regarding the use of combination therapy.[1,8-10]

Previous retrospective studies[11,12] have been completed that assess the prescribing patterns of physicians in the emergency department when treating acute agitation. However, there is insufficient data on the prescribing patterns regarding combination therapy in psychiatric units specifically, and prediction models are lacking. Regression models may be useful in formulary development decisions or in the development of order sets.[13] In this study, we created a regression model to identify which factors lead to the prescribing of combination therapy for patients with acute agitation on a psychiatry unit.

## Methods

We conducted a retrospective database analysis of patient encounters from a psychiatry unit at a Midwest academic hospital that had no active order set for acute agitation during the study period. An encounter was defined as a single psychiatry admission. Patients were identified and their information was collected using Healthcare Enterprise Repository for Ontological Narration (HERON), a searchable clinical database of patient records.[14] Patient data was retrieved using HERON without review of individual patient charts and included all items shown on Table 1.

Patients were included if they were at least 18 years of age, had a psychiatry admission between September 1, 2014 and September 1, 2017, and were prescribed either a parenteral or oral antipsychotic, benzodiazepine, or diphenhydramine. Actual medication administration was not assessed. Of the benzodiazepines, only lorazepam was included as it is the only parenteral benzodiazepine available on the psychiatry unit. We assumed other benzodiazepines were used for anxiety. Patients were included only if one of the above medications were prescribed with an as needed dosing interval of less than or equal to 8 hours. Any instances of diphenhydramine prescribed alone were excluded. Demographic information, psychiatric diagnoses, and concurrent cardiovascular medications were retrieved. Any psychiatric diagnoses listed as a billing diagnosis or active problem were included in the analysis. An *active problem* included any problem documented by a prescriber or nurse for a specific admission.

Encounters were assessed for concurrent prescribing of the selected medications. Encounters were reported as one of the following scenarios: concurrent antipsychotic with lorazepam, concurrent antipsychotic with diphenhydramine, concurrent lorazepam with diphenhydramine, or a combination of the 3 medications (triple therapy). Concurrent prescribing was defined as an order of multiple as-needed medications within 1 hour, regardless of whether the medications were prescribed upon admission or reactively following an acute agitation event.

Data analysis was conducted using SPSS v.23 (IBM Corp, Armonk, NY). Descriptive statistics were analyzed to determine patient demographics and billing diagnoses. We conducted 3 separate binary logistic regressions to determine if and how the number of prescribed medications for acute agitation was influenced by the following factors: age, sex, race, cardiovascular comorbidity, and

**TABLE 1:** Characteristics of patient population[a]

| No. of Encounters | 1998 |
|---|---|
| Age, y | |
|   Mean | 42.4 ± 14.3 |
|   Median (range) | 41 (18-84) |
|   Female (%) | 892 (44.6) |
| Race (%) | |
|   White | 1343 (67.2) |
|   Non-white | 655 (32.8) |
|   Prescribed ≥3 cardiovascular medications | 311 (15.6) |
| Diagnosis (%) | |
|   CNS stimulant use disorders | 306 (15.3) |
|   CNS depressant use disorders | 865 (43.3) |
|   Hallucinogen use disorders | 39 (2.0) |
|   Depression disorders | 1049 (52.5) |
|   Bipolar disorders | 399 (20.0) |
|   Cluster B personality disorders | 299 (15.0) |
|   Anxiety, posttraumatic, and obsessive-compulsive disorders | 809 (40.5) |
|   Neurocognitive disorders | 58 (2.9) |
|   Psychotic disorders | 764 (38.2) |
|   Neurodevelopmental disorders | 226 (11.3) |
| Therapy regimen (%) | |
|   Monotherapy prescribed | 1177 (58.9) |
|   Antipsychotic monotherapy prescribed | 612 (30.6) |
|     1st generation antipsychotic monotherapy prescribed | 430 (21.5) |
|     2nd generation antipsychotic monotherapy prescribed | 182 (9.1) |
|   Lorazepam monotherapy prescribed | 565 (28.3) |
|   Dual therapy prescribed | 742 (37.1) |
|     Antipsychotic and lorazepam prescribed | 515 (25.8) |
|     Antipsychotic and diphenhydramine prescribed | 123 (6.2) |
|     Lorazepam and diphenhydramine prescribed | 104 (5.2) |
|   Triple therapy - antipsychotic, lorazepam, and diphenhydramine prescribed | 79 (4.0) |

CNS = central nervous system.

[a]All percentages are shown as the portion out of the total number of encounters (n = 1998).

psychiatric diagnoses. Cardiovascular comorbidity was defined as concurrent use of ≥3 cardiovascular medications based on studies finding patients with significant cardiovascular comorbidities (eg, coronary artery disease) are prescribed at least 3 cardiovascular medications.[15]

Regression was conducted using a non-stepwise, standard entry method, and an alpha of 0.05 was set a priori. A binary logistic regression model was determined to have optimal goodness-of-fit and was deemed the most applicable compared to other regression models tested. We categorized psychiatric diagnoses into 10 groups according to the *Diagnostic and Statistical Manual of Mental Disorders,* 5th edition.[16] Separate models were developed for prescribing of monotherapy, dual therapy, or triple therapy, where the prescribing regimen was used as a binary variable in each model (eg, the monotherapy model predicted if a patient had been prescribed only 1 class of medication or multiple classes). Only the initial prescribing of medication in an encounter was included in the analysis. This study was approved by the institutional review board.

## Results

We identified 1998 encounters from 1200 patients. Patient characteristics are summarized in Table 1. Three separate binary regression models were conducted. The monotherapy binary regression model had an overall correct percentage of 66.8 for the prediction of therapy regimens. Similarly, the dual therapy binary regression model had an overall correct percentage of 66.9. The triple therapy binary regression model had an overall correct percentage of 96.0. However, the triple therapy model did not correctly predict any affirmative cases where triple therapy was used.

The results of the binary logistic regression for the prediction of monotherapy are summarized in Table 2. For the monotherapy model, negative B values are indicative of an association with monotherapy prescribing, while positive B values are indicative of an association with combination therapy prescribing (either dual or triple therapy). The exception to this is age, which was entered as a continuous variable, and a positive B value demonstrates an association with monotherapy prescribing. A summary of significant factors is included in Table 3. No evidence of multicollinearity was detected for any factors in the regression model.

The dual therapy model yielded similar results and is summarized in Table 4. All significant associations (P ≤ .050) were the same as the monotherapy model with the following exceptions: patients are more likely to be prescribed combination therapy if they have a neurodevelopmental disorder (P = .012) and there was no significant association between prescribing regimen and bipolar disorders (P = .186) or hallucinogen use disorder (P = .140). Results for the triple therapy model were discarded because of the 0.0% prediction for triple therapy.

## Discussion

To our knowledge, this is the first study to create a statistical model that connects demographics and diag-

**TABLE 2:** Binary logistic regression output: Monotherapy model[a]

| Covariate or Factor | B | Exp(B) | 95% Confidence Interval for Exp(B) | | SE | P Value[b] |
|---|---|---|---|---|---|---|
| | | | Lower | Upper | | |
| Age | 0.014 | 1.015 | 1.007 | 1.022 | 0.004 | **<.001** |
| Female sex | −0.327 | 0.721 | 0.589 | 0.882 | 0.103 | **.002** |
| Non-white race | 0.474 | 1.606 | 1.302 | 1.980 | 0.107 | **<.001** |
| Prescribed ≥3 cardiovascular medications | −0.526 | 0.591 | 0.439 | 0.796 | 0.152 | **.001** |
| Diagnoses | . . . | . . . | . . . | . . . | . . . | . . . |
| CNS stimulant use disorders | 0.478 | 1.612 | 1.229 | 2.115 | 0.138 | **.001** |
| CNS depressant use disorders | −0.043 | 0.958 | 0.775 | 1.185 | 0.108 | .694 |
| Hallucinogen use disorders | 0.745 | 2.107 | 1.001 | 4.433 | 0.380 | **.050** |
| Depression disorders | 0.266 | 1.304 | 1.052 | 1.618 | 0.110 | **.015** |
| Bipolar disorders | 0.248 | 1.281 | 1.001 | 1.640 | 0.126 | **.049** |
| Cluster B personality disorders | 0.407 | 1.502 | 1.143 | 1.973 | 0.139 | **.004** |
| Anxiety, posttraumatic, and obsessive-compulsive disorders | 0.041 | 1.042 | 0.848 | 1.281 | 0.105 | .697 |
| Neurocognitive disorders | −0.844 | 0.430 | 0.207 | 0.893 | 0.373 | **.024** |
| Psychotic disorders | 0.947 | 2.579 | 2.085 | 3.190 | 0.109 | **<.001** |
| Neurodevelopmental disorders | 0.244 | 1.277 | 0.942 | 1.731 | 0.155 | .116 |

CNS = central nervous system.

[a]Monotherapy model information: Correct overall = 66.8%; correct for prediction of monotherapy prescribing = 79.9%; correct for prediction of combination therapy prescribing = 47.9%; Nagelkerke pseudo $R^2$ = 0.165; omnibus test of model coefficient: $\chi^2$ = 261.704, $P \le .001$.

[b]P values in bold are considered statistically significant when using a predetermined alpha of 0.05.

noses to prescribing patterns for acute agitation in practice. Compared to previous studies[11,12] assessing acute agitation treatment in the emergency department, this study showed a higher rate of combination therapy prescribing. Our study found several factors that have a significant association with the prescribing of combination therapy for acute agitation. While the monotherapy and dual therapy models produced were acceptable, the triple therapy model likely failed because of a low number of patients being prescribed that regimen.

The *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition[16] lists many mental health disorders that may contribute to agitation, and we expected them to be connected to combination therapy prescribing. Guidelines list severe agitation secondary to psychosis to be an indication for combination therapy use.[1] Thus, it is

**TABLE 3:** List of patient factors and their relation to prescribing patterns

| More Likely to be Prescribed Monotherapy | More Likely to be Prescribed Combination Therapy | No Significant Association With Prescribing Patterns |
|---|---|---|
| Older age | Younger age | CNS depressant use disorder |
| Female sex | Male sex | Anxiety, posttraumatic, or obsessive-compulsive disorder |
| White race | Non-white race | |
| Cardiovascular comorbidities present | No cardiovascular comorbidities present | Neurodevelopmental disorder[b] |
| Neurocognitive disorder | CNS stimulant use disorder | |
| | Hallucinogen use disorder[a] | |
| | Depressive disorder | |
| | Bipolar disorder[a] | |
| | Cluster B personality disorder | |
| | Psychotic disorder | |

CNS = central nervous system.

[a]Only significant in the monotherapy model.

[b]Significantly associated with combination therapy in the dual therapy model, but not the monotherapy model.

**TABLE 4:** Binary logistic regression output: Dual therapy model[a]

| Covariate or Factor | B | Exp(B) | 95% Confidence Interval for Exp(B) | | SE | P Value[b] |
| --- | --- | --- | --- | --- | --- | --- |
| | | | Lower | Upper | | |
| Age | −0.011 | 0.989 | 0.982 | 0.997 | 0.004 | **.006** |
| Female sex | 0.296 | 1.344 | 1.097 | 1.647 | 0.104 | **.004** |
| Non-white race | −0.447 | 0.639 | 0.518 | 0.789 | 0.107 | **<.001** |
| Prescribed ≥3 cardiovascular medications | 0.461 | 1.585 | 1.173 | 2.142 | 0.154 | **.003** |
| Diagnoses | . . . | . . . | . . . | . . . | . . . | . . . |
| CNS stimulant use disorders | −0.501 | 0.606 | 0.463 | 0.793 | 0.137 | **<.001** |
| CNS depressant use disorders | 0.103 | 1.109 | 0.895 | 1.373 | 0.109 | .344 |
| Hallucinogen use disorders | −0.520 | 0.595 | 0.298 | 1.186 | 0.352 | .140 |
| Depression disorders | −0.304 | 0.738 | 0.595 | 0.916 | 0.110 | **.006** |
| Bipolar disorders | −0.167 | 0.846 | 0.660 | 1.084 | 0.126 | .186 |
| Cluster B personality disorders | −0.446 | 0.640 | 0.488 | 0.841 | 0.139 | **.001** |
| Anxiety, posttraumatic, and obsessive-compulsive disorders | −0.014 | 0.986 | 0.801 | 1.214 | 0.106 | .896 |
| Neurocognitive disorders | 0.841 | 2.319 | 1.093 | 4.918 | 0.384 | **.028** |
| Psychotic disorders | −0.796 | 0.451 | 0.365 | 0.558 | 0.109 | **<.001** |
| Neurodevelopmental disorders | −0.388 | 0.679 | 0.502 | 0.917 | 0.154 | **.012** |

CNS = central nervous system.

[a]Dual therapy model information: Correct overall = 66.9%; correct for prediction of monotherapy prescribing: 35.7%; correct for prediction of combination therapy prescribing: 85.3%; Nagelkerke pseudo $R^2$ = 0.134; Omnibus test of model coefficient: $\chi^2$ = 206.935, $P \leq .001$.

[b]P values in bold are considered statistically significant when using a predetermined alpha of 0.05.

unsurprising that psychosis would have a strong connection to combination therapy prescribing in our model. Similarly, stimulant and hallucinogen-induced psychosis requires aggressive treatment and was expected to influence combination therapy prescribing.[16,17] However, it is important to note that combination therapy for substance use disorders is not recommended in guidelines.[1]

Initially, we did not assume a strong association between depression and combination therapy. This diagnosis may have been significantly associated with combination therapy prescribing because each encounter included all billing and active diagnoses rather than only including the primary one. This may have resulted in an excessive percentage of patients having a diagnosis of common psychiatric disorders that may not be directly connected with agitation. We assumed that most patients with a primary diagnosis of depressive disorders would not typically need combination therapy treatment, but many of the patients with a primary diagnosis of psychosis may have had a secondary diagnosis of depression. In this example, our model would have considered both psychosis and depression as being relevant for the prediction of combination therapy.

We suspect that there may be a connection between age, neurocognitive disorder, and cardiovascular comorbidities in these patients, despite the lack of multicollinearity in our model. Elderly patients present with neurocognitive disorders and cardiovascular comorbidities more frequently than younger patients.[16] This may explain why all of these factors were connected to a higher rate of monotherapy prescribing. As clinicians, this is expected as we should avoid the over-sedation of elderly patients.

There have been studies that may support prescribing of combination therapy for acute agitation, including a randomized clinical trial[9] and a comprehensive systematic review.[10] We did not address the reasoning behind combination therapy prescribing for certain patient populations in our study, but development of order sets may help prescribers determine if combination therapy is appropriate. Our study also reinforces the claim that guidelines require more definitive statements on the use of combination therapy.[1] If physicians are to continue using combination therapy with regularity, guidelines should be re-evaluated to elaborate on whether this practice is safe and effective. Future studies should prospectively assess the efficacy and safety of certain drug regimens for the treatment of acute agitation using regression modeling. Such a model would be advantageous for formulary and guideline development. Future models should be stratified to determine if order sets should be based on preexisting diagnoses or demographics.

There are several limitations to this study. A major limitation was that indications were unspecified for as needed prescriptions. Thus, if lorazepam was prescribed, we were unable to determine if it was for acute agitation or anxiety. This limitation may have caused an overestimation of lorazepam monotherapy. Additionally, HERON only reported the initial prescribing of medication. We were unable to address subsequent changes in an acute agitation regimen. Including these cases may have increased the number of encounters where combination therapy was prescribed. Only billing and active diagnoses were included in the regression analysis which may have resulted in over-reporting of certain diagnoses. This study was also only conducted in 1 institution, and our formulary and prescribing practices may differ from other facilities. Additionally, we did not have prescriber data for this study and could not report if prescriber preference would have influenced the regression results. Finally, the retrospective design of this study meant that we were unable to conduct any direct observations and were reliant on consistent documentation in the electronic medical record.

In summary, our regression model shows that young, male, non-white patients without cardiovascular comorbidities and patients with several diagnoses, including psychosis and CNS stimulant use disorder, are more likely to be prescribed combination therapy for acute agitation in a psychiatric, inpatient setting. This model may be helpful in formulary development decisions or in creating opportunities for additional studies.

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