Atypical NMS and Third-Generation Antipsychotic Medications: A Systematic Literature Review and Comparison with International Expert Consensus NMS Diagnostic Criteria

- **Gregory Nikogosyan, DO**, University of New Mexico School of Medicine
- **Julio Nunes, MD**, Yale University School of Medicine
- **Gabriel P. A. Costa**, University of Ribeirão Preto Brazil, Faculty of Medicine
- **M. Andres Caro, MD**, Yale University School of Medicine

**Acknowledgements:**
- **Orrin Myers, PhD**, University of New Mexico School of Medicine
- **Davin Quinn, MD**, University of New Mexico School of Medicine
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Disclosure: All contributors

With respect to the following presentation, in the 24 months prior to this declaration there has been no financial relationship of any kind between the author party listed on the prior slide and any ACCME-defined ineligible company which could be considered a conflict of interest.
Background

• Neuroleptic Malignant Syndrome (NMS) is a rare and potentially fatal syndrome. There has been limited research on atypical NMS case presentations, with the absence of absence of fever or rigidity, despite increasing acceptance of such cases occurring.
  • Levenson 1985

• The defined International Expert Consensus NMS Diagnostic Criteria has not been well defined for atypical NMS case presentations

• Hypothesis:
  • Expert consensus criteria at the validation study cut-off score does not adequately capture atypical NMS case presentations
  • 3rd generation antipsychotics will have significant differences from 1st and/or 2nd generation antipsychotics for atypical NMS case presentations.
Background

• In our experience, several cases with NMS presented as atypical NMS with some cases even requiring ECT.

• Many of our clinically observed cases with third-generation antipsychotics presented with low-grade hyperthermia but not fever, thus prompting us to do a systematic case literature review.
• DSM IV-TR research criteria required Rigidity, Increased Temperature, and 2 other minor criterion

• Caroff and Mann Criterion: Treatment with neuroleptic within 7 days, Hyperthermia (>38 Celsius), and Muscle Rigidity

• *In our study all cases had dopamine antagonist exposure and we defined atypical NMS as absence of rigidity and/or fever.*
International Consensus Study of NMS Diagnostic Criteria – Delphi Method

- Validation Study:
  - Cut-off score of 74
  - 69.6% sensitivity, 90.7% specificity
    - Gurrera et al 2017

### Table 1. Neuroleptic Malignant Syndrome Diagnostic Criteria: Expert Panel Consensus

<table>
<thead>
<tr>
<th>Diagnostic Criterion</th>
<th>Priority Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposure to dopamine antagonist, or dopamine agonist withdrawal, within past 72 hours</td>
<td>20</td>
</tr>
<tr>
<td>Hyperthermia (&gt;100.4°F or &gt;38.0°C on at least 2 occasions, measured orally)</td>
<td>18</td>
</tr>
<tr>
<td>Rigidity</td>
<td>17</td>
</tr>
<tr>
<td>Mental status alteration (reduced or fluctuating level of consciousness)</td>
<td>13</td>
</tr>
<tr>
<td>Creatine kinase elevation (at least 4 times the upper limit of normal)</td>
<td>10</td>
</tr>
<tr>
<td>Sympathetic nervous system lability, defined as at least 2 of the following:</td>
<td>10</td>
</tr>
<tr>
<td>Blood pressure elevation (systolic or diastolic ≥25% above baseline)</td>
<td></td>
</tr>
<tr>
<td>Blood pressure fluctuation (≥20 mm Hg diastolic change or ≥25 mm Hg systolic change within 24 hours)</td>
<td></td>
</tr>
<tr>
<td>Diaphoresis</td>
<td></td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td></td>
</tr>
<tr>
<td>Hypermetabolism, defined as heart-rate increase (≥25% above baseline) AND respiratory-rate increase (≥50% above baseline)</td>
<td>5</td>
</tr>
<tr>
<td>Negative work-up for infectious, toxic, metabolic, or neurologic causes</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
</tr>
</tbody>
</table>

- Gurrera et al 2011
Methods

• A literature search of PUBMED, OVID, PSYCHINFO, and EMBASE utilizing search terms “neuroleptic malignant syndrome” AND respective antipsychotics following the 2020 PRISMA guidelines.

• Article requirements: available online, case reports involving NMS of antipsychotic etiology, exposure to dopamine antagonist within 72 hours, and data regarding rigidity and fever being present.

• No language limitations applied

• Two independent reviewers searched all four databases and removed duplicate articles.
  • Further exclusion criteria
    • No concurrent or immediately recent additional antipsychotics
    • Absent documentation of fever, rigidity, or exposure to dopamine

• Independent reviewers then compared search results and analyzed inconsistencies for correction.
Methods

• Data was then separated into cases meeting all Delphi Criteria score components and those with missing criterion domains.
  • Cases were excluded if missing criteria scores would lead to the Delphi criterion score crossing over the validation cutoff score of 74.
  • Antipsychotics with less than 5 cases for “meeting all Delphi Criteria score” were removed from statistical analysis.

• Data was analyzed by independent T-test of the Delphi Criteria Score for the typicality of each antipsychotic.

• Equal variance was not assumed, and additional bootstrap analysis was performed.

• A univariate general linear model was utilized to compare antipsychotics with multiple comparisons correction
### Literature Search Through March 2023

<table>
<thead>
<tr>
<th>Antipsychotic</th>
<th>OVID</th>
<th>EMBASE</th>
<th>PUBMED</th>
<th>APA Psychinfo</th>
<th>Total</th>
<th>Cases Meeting Inclusion Criteria</th>
<th>Cases with Data for All Delphi Criteria</th>
<th>Typical</th>
<th>Atypical</th>
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</thead>
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<td>Haloperidol</td>
<td>372</td>
<td>2024</td>
<td>379</td>
<td>178</td>
<td>2953</td>
<td>148</td>
<td>94</td>
<td>80</td>
<td>14</td>
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<tr>
<td>Risperidone</td>
<td>179</td>
<td>1253</td>
<td>182</td>
<td>132</td>
<td>1746</td>
<td>33</td>
<td>14</td>
<td>9</td>
<td>5</td>
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<tr>
<td>Paliperidone</td>
<td>26</td>
<td>175</td>
<td>26</td>
<td>16</td>
<td>243</td>
<td>8</td>
<td>4</td>
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<td>Lurasidone</td>
<td>2</td>
<td>51</td>
<td>3</td>
<td>2</td>
<td>58</td>
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<td>1</td>
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<td>Ziprasidone</td>
<td>29</td>
<td>422</td>
<td>29</td>
<td>16</td>
<td>496</td>
<td>11</td>
<td>8</td>
<td>6</td>
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<td>47</td>
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<td>51</td>
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<td>1</td>
<td>0</td>
<td>1</td>
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<tr>
<td>Olanzapine</td>
<td>189</td>
<td>1161</td>
<td>193</td>
<td>117</td>
<td>1660</td>
<td>40</td>
<td>11</td>
<td>7</td>
<td>4</td>
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<td>229</td>
<td>1104</td>
<td>236</td>
<td>176</td>
<td>1745</td>
<td>15</td>
<td>11</td>
<td>8</td>
<td>3</td>
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<td>Asenapine</td>
<td>4</td>
<td>73</td>
<td>4</td>
<td>73</td>
<td>154</td>
<td>2</td>
<td>0</td>
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<td>Quetiapine</td>
<td>104</td>
<td>873</td>
<td>105</td>
<td>81</td>
<td>1163</td>
<td>29</td>
<td>23</td>
<td>17</td>
<td>6</td>
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<td>Brexpiprazole</td>
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<td>16</td>
<td>1</td>
<td>7</td>
<td>25</td>
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<td>18</td>
<td>2</td>
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<td>Aripiprazole</td>
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<td>520</td>
<td>62</td>
<td>396</td>
<td>1040</td>
<td>25</td>
<td>9</td>
<td>5</td>
<td>4</td>
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<tr>
<td>Pimavanserin</td>
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<td>7</td>
<td>1</td>
<td>9</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>0</td>
</tr>
</tbody>
</table>
Demographics of Data

- Mean age: 41.37
- Standard deviation: 20.465
- Sample size: N = 309

- Male: 64%
- Female: 36%
- Unknown: 1%
Demographics of Data

- Unknown: 79%
- Black: 4%
- White: 14%
- Asian: 3%
- Hispanic: 1%

Legend:
- Black
- Unknown
- White
- Asian
- NA/PI
- Hispanic
- Multiple
Percent of NMS Cases vs Treatments Utilized

- IV fluid/supportive: 43.5%
- Dopamine agonist: 37.7%
- Dantrolene: 30.4%
- Amantadine: 4.5%
- Anticholinergics: 15.0%
- Benzodiazepine: 29.4%
- ECT: 3.8%
- Multiple Tx: 38.7%
Findings

• All NMS cases (n = 313)
  • NMS cases that documented improvement (n = 295)
• Atypical NMS cases with all Delphi criterion domains described (n = 58)
  • 44 cases at or below 74 validation cutoff score
  • 43 with the absence of only fever criteria
  • 13 with the absence of only rigidity criteria
  • 2 cases with the absence of both rigidity and fever
<table>
<thead>
<tr>
<th>Antipsychotics</th>
<th>NMS</th>
<th>Mean</th>
<th>Std. Error</th>
<th>Confidence Interval</th>
<th>Significance two tailed p equal variance not assumed</th>
<th>Levene’s Test Sig.</th>
<th>Bootstrap Analysis tailed</th>
<th>two</th>
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</thead>
<tbody>
<tr>
<td>Haloperidol</td>
<td>Typical</td>
<td>93.01</td>
<td>0.92</td>
<td>[91.14 : 94.77]</td>
<td>&lt;0.001</td>
<td>0.319</td>
<td>&lt;0.001</td>
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<td></td>
<td>Atypical</td>
<td>71.86</td>
<td>3.13</td>
<td>[65.25 : 77.77]</td>
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<tr>
<td>Risperidone</td>
<td>Typical</td>
<td>85</td>
<td>2.32</td>
<td>[80.25 : 89.30]</td>
<td>0.003</td>
<td>0.834</td>
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<td>Atypical</td>
<td>67.4</td>
<td>3.36</td>
<td>[60.50 : 73.76]</td>
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<tr>
<td>Ziprasidone</td>
<td>Typical</td>
<td>97.67</td>
<td>1.34</td>
<td>[94.76 : 100]</td>
<td>&lt;0.001</td>
<td>0.027</td>
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<tr>
<td></td>
<td>Atypical</td>
<td>69.5</td>
<td>0.38</td>
<td>[69 : 70]</td>
<td></td>
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<td>Olanzapine</td>
<td>Typical</td>
<td>91.14</td>
<td>1.61</td>
<td>[87.89 : 94.37]</td>
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<td>0.787</td>
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<td>2.74</td>
<td>[65.65 : 75.86]</td>
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<td>Clozapine</td>
<td>Typical</td>
<td>94.88</td>
<td>2.45</td>
<td>[89.9 : 100]</td>
<td>0.02</td>
<td>0.284</td>
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<td></td>
<td>Atypical</td>
<td>57</td>
<td>6.06</td>
<td>[44 : 67]</td>
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<tr>
<td>Quetiapine</td>
<td>Typical</td>
<td>92.12</td>
<td>1.83</td>
<td>[88.29 : 95.56]</td>
<td>0.008</td>
<td>0.023</td>
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<td>65.5</td>
<td>6.76</td>
<td>[51.20 : 78.5]</td>
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<tr>
<td>Aripiprazole</td>
<td>Typical</td>
<td>89.4</td>
<td>1.76</td>
<td>[85.5 : 93]</td>
<td>0.007</td>
<td>0.446</td>
<td>0.02</td>
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<tr>
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<td>Atypical</td>
<td>72.5</td>
<td>3.04</td>
<td>[78.75 : 67]</td>
<td></td>
<td></td>
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<tr>
<td>All Antipsychotics</td>
<td>Typical</td>
<td>92.44</td>
<td>0.66</td>
<td>[91.12 : 93.65]</td>
<td>&lt;0.001</td>
<td>0.176</td>
<td>&lt;0.001</td>
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</tr>
<tr>
<td></td>
<td>Atypical</td>
<td>68.79</td>
<td>1.82</td>
<td>[64.86 : 72.16]</td>
<td></td>
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</tbody>
</table>
Results
Results – Univariate General Linear Models

P-value with Multiple Comparison/Bonferroni Correction

• Antipsychotic Generation & Typicality of NMS
  • Generation 1*2, Typical p = 6.17, Atypical p = 2.61
  • Generation 2*3, Typical p = 7.06, Atypical p = 4.93
  • Generation 1*3, Typical p = 5.38, Atypical p = 7.99

• Age & Typicality of NMS, p = 6.05
• Age & Antipsychotic, p = 2.91
• Age & Delphi Criterion Score, p = 6.54
• Gender & Typicality of NMS, p = 7.81
• Gender & Antipsychotics, p = 2.76
• Gender & Delphi Criterion Score, p = 6.90

• Peak Temperature & Typicality of NMS, p = 0.02
• Peak Temperature & Antipsychotic, p = 5.120
• Peak Temperature & Delphi Criterion Score, p = 0.136
• Race & Typicality of NMS, p = 6.42
• Race & Antipsychotic, p = 5.36
• Race & Delphi Criterion Score, p = 6.04
• CK Peak Value & Typicality of NMS, p = 0.35
• CK Peak Value & Antipsychotic, p = 5.18
• CK Peak Value & Delphi Criterion Score, p = 0.47
Discussions

• Classical NMS is described as high fever, rigidity, elevated CK, and altered mental status, among many other symptoms.

• The current validation cut-off score is 74 (Gurrera et al 2017), but from our case data review, many cases fall below this score.

• No specific generation and individual antipsychotic differences were observed for Delphi Criterion Score, race, gender, CK peak value, or age. I suspect such differences would require a significantly larger sample size.

• A significant effect between peak temperature and typicality of NMS was found. We assume there is a higher likelihood of having concurrent rigidity with higher temperatures.
Limitations

• Case reports are not from representative population samples and can only signal a possible significant association if a cluster of similar cases exists.

• Publication bias:
  • Nearly all cases in the review showed improvement in NMS.
  • Emphasis on unique and rare cases

• Qualitative descriptions of temperature in case studies.
  • “Fever” included and was assumed to be 38°C and above.
  • Terms: Cases with descriptors such as elevated temperature, hyperthermia, and pyrexia were excluded unless quantitative data on temperature was also shared.
Conclusions

• Patients with atypical NMS have a lower Delphi Criterion Score below the validation cutoff than typical NMS cases.
• Further studies would be warranted to clarify the presentation and identification of atypical NMS.