Criteri di scelta dei farmaci nei pazienti con disturbi psichiatrici gravi in corso di terapia integrata. Implicazioni per la cognitività e il mantenimento della risposta

Andrea de Bartolomeis
Sezione di Psichiatria
Unità di Farmacoresistenze e Laboratorio di Psichiatria Traslazionale e Molecolare
Università di Napoli Federico II

Roma 19 giugno 2017
Prologue
A triple link in psychosis: glutamate, inflammation, brain aging


GWA PsyGenCons 2016: convergenza di pathway della densità postsinaptica, del sistema immunologico, ed epigenetici (istoni)
Overview

1. Factors that may influence the choice of antipsychotics treatment in severe psychotic disorders: the efficacy/adverse conondrum
2. Receptor profile as guided criteria for choosing antipsychotics in complex conditions: the typicals/ atypicals dilemma
3. Treatment resistant as landmark of severe and complex disorder
4. Long term treatment choosing to block or not to block the dopamine D2R
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Clinical issues in Choosing beyond CPR in severe psychotic disorder

1. Physical health comorbidities
2. Polipharmacy for non psychiatry and psychiatry disorders
3. Pharmacokinetics issues (...PK-PD conundrum)
4. Feasibility after acute treatment (...adherence)
5. Age
6. Integrated treatment evaluation
7. Long term effect on brain function and cognitivity
Sixty Years of Placebo-Controlled Antipsychotic Drug Trials in Acute Schizophrenia: Systematic Review, Bayesian Meta-Analysis, and Meta-Regression of Efficacy Predictors

Leucht et al., 2017, American J Psychiatry
As adjunctive treatment, aripiprazole quetiapine and ziprasidone reduced the overall risk of relapses.

- Only quetiapine as adjunctive therapy reduced both manic as well as depressive relapses.
- No long-term randomized studies beyond 2 years follow-up have been published.
- Almost all studies included patients with bipolar I disorder only, with patients already stabilized during an acute phase.
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May receptor profile inform the choice of antipsychotics in complex disorders? The typicals/atypicals dilemma

### Extrapyramidal symptoms

<table>
<thead>
<tr>
<th>Drug</th>
<th>Odds ratio (95% CrI)</th>
<th>Effect size of antipsychotic compared with placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quetiapine</td>
<td>1.01 (0.68, 1.44)</td>
<td></td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>1.20 (0.73, 1.85)</td>
<td></td>
</tr>
<tr>
<td>Risperidone</td>
<td>2.09 (1.54, 2.78)</td>
<td></td>
</tr>
<tr>
<td>Lurasidone</td>
<td>2.46 (1.55, 3.72)</td>
<td></td>
</tr>
</tbody>
</table>

### Sedation

<table>
<thead>
<tr>
<th>Drug</th>
<th>Odds ratio (95% CrI)</th>
<th>Effect size of antipsychotic compared with placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>1.84 (1.05, 3.05)</td>
<td></td>
</tr>
<tr>
<td>Lurasidone</td>
<td>2.45 (1.31, 4.24)</td>
<td></td>
</tr>
<tr>
<td>Risperidone</td>
<td>2.45 (1.76, 3.35)</td>
<td></td>
</tr>
<tr>
<td>Quetiapine</td>
<td>3.76 (2.68, 5.19)</td>
<td></td>
</tr>
</tbody>
</table>

### Weight gain

<table>
<thead>
<tr>
<th>Drug</th>
<th>SMD (95% CrI)</th>
<th>Effect size of antipsychotic compared with placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lurasidone</td>
<td>0.10 (-0.02, 0.21)</td>
<td></td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>0.17 (0.05, 0.28)</td>
<td></td>
</tr>
<tr>
<td>Risperidone</td>
<td>0.42 (0.33, 0.50)</td>
<td></td>
</tr>
<tr>
<td>Quetiapine</td>
<td>0.43 (0.34, 0.53)</td>
<td></td>
</tr>
</tbody>
</table>

EPS were assessed through the use of antiparkinson medication; CrI=credible interval; SMD=standardised mean difference

Antipsychotics’ pharmacodynamics dogma

• All antipsychotics block dopamine D2 receptor to achieve the anti-psychotic effect: no D2R blockade no effect, therefore alla antipsychotica are dopamine antagonist.

  ➢ Antipsychotics such as aripiprazole are partial agonist and do not block D2R in the canonical fashion but occupy D2R.

• All antipsychotics need to block at least 60-70% striatal dopamine D2 receptors to develop the anti-psychotic effect.

  ➢ Clozapine blocks striatal D2R to much less extent even at therapeutics dose.

deb Bartolomeis et al., 2014, 2015
TYPICAL AND ATYPICAL DISSECTION OF ATYPICALITY: why the present classification does not tell the truth?

• 5HT2a/D2 RECEPTORS AFFINITY RATIO

  ➢ *Chlorproamazine the first APS is a 5Ht2aR antagonist*

• PLEIOTROPIC MECCANISM OF ACTION

  ➢ *New Benzamides such as amisulpride are mainly D2/D3 antagonist*

• FAST DISSOCIATION

  ➢ *Should be applied for clozapine and quetiapine only?*

*de Bartolomeis et al., Current Pharmaceutical Design 2005, 11, 27, 35-61*
Pharmacokinetics and time-course of D₂-receptor occupancy induced by atypical antipsychotics in stabilized schizophrenia patients

Comparison of steady state plasma concentration and corresponding D₂ RO_{Sim}, against time after dose intake

Curves represent mean (continuous line) and percentiles 5 and 95 (dashed lines) for a single representative dose for each antipsychotic

Reproduced with permission
Dose and D1R/D2R ratio dependent Homer topography

Increased expression vs SAL
Increased expression vs all
Decreased expression

* ANOVA and Tukey post hoc test p<0.05

deb Bartolomeis et al. 2015. European Neuropsychopharmacology
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Early Response to Antipsychotic Drug Therapy as a Clinical Marker of Subsequent Response Schizophrenia treatment

**ER : early responder (n=144)** patients who respond after two week of treatment (▲)

**ER: early not responder (n=378)** patients who do not respond after two week of treatment (◊ Risperidone or ■ olanzapine)

Kinon et al., 2010 Neuropsychopharmacology 35, 581–590
Initial treatment with High D2R affinity APS at high doses: potential effect on the trajectory of schizophrenia.

A prolonged treatment with high doses of D2R high affinity antipsychotics may change the trajectory of treatment response over time.

Indeed after a period of initial adequate response to the antipsychotic treatment a more severe form of psychosis may emerge (supersensitivity psychosis?)

Relationship with tardive motor side effects?

Yin et al., Curr Neuropsy. 2016 Jun 5. [Epub ahead of print]

Modified from Seeman et al., Synapse, 2006; 60, 319
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Treatment-Resistant Schizophrenia: Treatment Response and Resistance in Psychosis (TRRIP) Working Group Consensus Guidelines on Diagnosis and Terminology


Objective: Research and clinical translation in schizophrenia is limited by inconsistent definitions of treatment resistance and response. To address this issue, the authors evaluated current approaches and then developed consensus criteria and guidelines.

Method: A systematic review of randomized antipsychotic clinical trials in treatment-resistant schizophrenia was performed, and definitions of treatment resistance were extracted. Subsequently, consensus operationalized criteria were developed through 1) a multiphase, mixed methods approach, 2) identification of key criteria via an online survey, and 3) meetings to achieve consensus.

Results: Of 2,808 studies identified, 42 met inclusion criteria. Of these, 21 studies (50%) did not provide operationalized criteria. In the remaining studies, criteria varied considerably, particularly regarding symptom severity, prior treatment identified minimum and optimal criteria, employing the following principles: 1) current symptoms of a minimum duration and severity determined by a standardized rating scale; 2) moderate or worse functional impairment; 3) prior treatment consisting of at least two different antipsychotic trials, each for a minimum duration and dosage; 4) systematic monitoring of adherence and meeting of minimum adherence criteria; 5) ideally at least one prospective treatment trial; and 6) criteria that clearly separate responsive from treatment-resistant patients.

Conclusions: There is considerable variation in current approaches to defining treatment resistance in schizophrenia. The authors present consensus guidelines that operationalize criteria for determining and reporting treatment resistance, adequate treatment, and treatment response, providing a benchmark for research and clinical translation.
• Approximately 30% of schizophrenia patients do not respond or respond poorly to APS.

• Treatment resistant schizophrenia (TRS), schizophrenia (responsive to antipsychotics), bipolar disorder, and anxiety/depressive diseases. Also, we investigated the predictors of community functioning outcomes across several domains.

• TRS was found to have more severe psychopathology, more impaired cognitive functioning, and poorer psychosocial adjustment compared to all the other groups. In the whole sample, the main predictors of community functioning
Clinical Study

Patients with Poor Response to Antipsychotics Have a More Severe Pattern of Frontal Atrophy: A Voxel-Based Morphometry Study of Treatment Resistance in Schizophrenia

Mario Quarantelli,1 Olga Palladino,2 Anna Prinster,1 Vittorio Schiavone,3 Barbara Carotenuto,4 Arturo Brunetti,4 Angela Marsili,5 Margherita Casiello,2 Giovanni Muscettola,2 Marco Salvatore,4 and Andrea de Bartolomeis2

BioMed Research International
Differential cognitive performances between schizophrenic responders and non-responders to antipsychotics: Correlation with course of the illness, psychopathology, attitude to the treatment and antipsychotics doses

Tukey's post-hoc test: p<0.05 vs. responders and controls.

*Tukey's post-hoc test: p<0.05 vs. responders and controls.

Cognitive dysfunction in MMD: the challenge

BOX 1-1
Statement of Task

An ad hoc committee will plan and conduct a 1-day workshop to explore opportunities and challenges related to discovery, development, and translation of treatments for cognitive dysfunction in depression. The workshop will bring together key stakeholders to explore the discovery, development and regulatory path for new treatments addressing this aspect of depression.

Presentations and discussion will be designed to:

- Examine opportunities to facilitate new target and validation strategies aimed at reinvigorating the development of treatments that address cognition, an undertreated aspect of depression.
- Discuss how lessons from the translational aspects of cognitive dysfunction in other disorders could apply to depression.
- Highlight gaps and limitations of current tools for assessing cognitive dysfunction in depression in clinical trials, and consider how improvements in cognition could relate to functional outcomes.
- Explore potential regulatory challenges, such as recognition of cognitive dysfunction in depression as a public health need, and opportunities for treatments.
Efficacy of 42 Pharmacologic Cotreatment Strategies Added to Antipsychotic Monotherapy

**Figure 1. Meta-analysis—Based Effect Sizes of Psychopharmacologic Augmentation of any Antipsychotic Drug for Total Psychopathology**

<table>
<thead>
<tr>
<th>Drug Added to AP (Source)</th>
<th>Type of Agent</th>
<th>Statistics for Each Study</th>
<th>Favors Combination Treatment</th>
<th>Favors Monotherapy</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNRIs (Galling et al.10)</td>
<td>Antidepressants</td>
<td>-1.27 -2.35 -0.19 1/40 3</td>
<td>-</td>
<td>-</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Serotonin 3 rec ant (Kishi et al.,2014)</td>
<td>Miscellaneous</td>
<td>-1.03 1.70 -0.26 5/261 3</td>
<td>-</td>
<td>-</td>
<td>.01</td>
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<tr>
<td>Lamotrigine (Premkumar and Pick, 2006)</td>
<td>Mood stabilizers</td>
<td>-0.73 -1.26 -0.20 3/98 2</td>
<td>-</td>
<td>-</td>
<td>.01</td>
</tr>
<tr>
<td>NsaMA (Galling et al.)</td>
<td>Antidepressants</td>
<td>-0.73 -2.46 -0.30 6/177 2</td>
<td>-</td>
<td>-</td>
<td>.01</td>
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<tr>
<td>Exogenous action (Bharat et al.,2015)</td>
<td>Miscellaneous</td>
<td>-0.52 -0.50 -0.26 1/254 1</td>
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<td>-</td>
<td>.01</td>
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<tr>
<td>Lithiums (Leach et al., 2015)</td>
<td>Mood stabilizers</td>
<td>-0.63 -0.94 -0.46 6/299 3</td>
<td>-</td>
<td>-</td>
<td>.01</td>
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<tr>
<td>Mirtocline (Sofini et al.,2016)</td>
<td>Antioxidants</td>
<td>-0.59 -1.15 -0.03 5/299 3</td>
<td>-</td>
<td>-</td>
<td>.04</td>
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<td>Topiramate (Zhang et al.)</td>
<td>Miscellaneous</td>
<td>-0.58 -0.81 -0.35 13/651 4</td>
<td>-</td>
<td>-</td>
<td>&lt;.01</td>
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<tr>
<td>Adenosine modulators (Nitta et al.)</td>
<td>Miscellaneous</td>
<td>-0.49 -0.82 -0.16 7/484 2</td>
<td>-</td>
<td>-</td>
<td>.01</td>
</tr>
<tr>
<td>Arazotrim (Kishi et al.,2013)</td>
<td>Miscellaneous</td>
<td>-0.46 -0.79 -0.13 4/153 2</td>
<td>-</td>
<td>-</td>
<td>.01</td>
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<tr>
<td>N-acetylcysteine (Sommer et al.,2014)</td>
<td>Antioxidants</td>
<td>-0.45 -0.78 -0.12 1/140 3</td>
<td>-</td>
<td>-</td>
<td>.01</td>
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<tr>
<td>Any antidepressant (Galling et al.)</td>
<td>Antidepressants</td>
<td>-0.73 -0.44 -0.38 7/139 3</td>
<td>-</td>
<td>-</td>
<td>.01</td>
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<tr>
<td>NSADs (Nitta et al.,2012)</td>
<td>Antioxidants</td>
<td>-0.24 -0.47 -0.01 8/774 3</td>
<td>-</td>
<td>-</td>
<td>.04</td>
</tr>
<tr>
<td>Modafinil/amodafinil (Andrade et al.,2015)</td>
<td>Stimulants</td>
<td>-0.23 -0.44 -0.02 8/342 4</td>
<td>-</td>
<td>-</td>
<td>.04</td>
</tr>
<tr>
<td>TCA (Galling et al.)</td>
<td>Antidepressants</td>
<td>-0.71 -1.80 -0.28 1/34 3</td>
<td>-</td>
<td>-</td>
<td>.20</td>
</tr>
<tr>
<td>Testosterone (Haringa et al.,2015)</td>
<td>Hormones</td>
<td>-0.51 -1.19 -0.17 1/39 3</td>
<td>-</td>
<td>-</td>
<td>.14</td>
</tr>
<tr>
<td>NMDA rec ant (Matsuda et al.,2013)</td>
<td>Miscellaneous</td>
<td>-0.48 -1.02 0.06 7/387 4</td>
<td>-</td>
<td>-</td>
<td>.08</td>
</tr>
<tr>
<td>Oxytocin (Oya et al.,2016)</td>
<td>Miscellaneous</td>
<td>-0.46 -1.22 -0.13 1/122 3</td>
<td>-</td>
<td>-</td>
<td>.22</td>
</tr>
<tr>
<td>Antipsychotics (Galling et al.)</td>
<td>Antipsychotics</td>
<td>-0.30 -0.78 -0.18 4/278 4</td>
<td>-</td>
<td>-</td>
<td>.22</td>
</tr>
<tr>
<td>Pregnanolone (Grinberg et al.,2015)</td>
<td>Hormones</td>
<td>-0.27 -0.65 -0.11 4/232 3</td>
<td>-</td>
<td>-</td>
<td>.16</td>
</tr>
<tr>
<td>SSRIs (Galling et al.)</td>
<td>Antidepressants</td>
<td>-0.26 -0.54 -0.02 2/177 3</td>
<td>-</td>
<td>-</td>
<td>.07</td>
</tr>
<tr>
<td>SARI (Galling et al.)</td>
<td>Antidepressants</td>
<td>-0.19 -0.59 -0.05 2/876 3</td>
<td>-</td>
<td>-</td>
<td>.20</td>
</tr>
<tr>
<td>Achlorophylle Inhib (Singh et al.,2012)</td>
<td>Miscellaneous</td>
<td>-0.17 -0.72 -0.28 2/31 4</td>
<td>-</td>
<td>-</td>
<td>.54</td>
</tr>
<tr>
<td>NRIIs (Galling et al.)</td>
<td>Antidepressants</td>
<td>-0.14 -0.91 -0.63 2/97 3</td>
<td>-</td>
<td>-</td>
<td>.72</td>
</tr>
<tr>
<td>Histamine 2 blockers (Kishi et al.,2014)</td>
<td>Miscellaneous</td>
<td>-0.14 -0.44 -0.16 7/386 4</td>
<td>-</td>
<td>-</td>
<td>.54</td>
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<tr>
<td>Valproic acid (Schweizer et al.,2008)</td>
<td>Mood stabilizers</td>
<td>-0.44 -0.02 -0.26 5/261 3</td>
<td>-</td>
<td>-</td>
<td>.61</td>
</tr>
<tr>
<td>PEAs (Sommer et al.,2014)</td>
<td>Antidepressants</td>
<td>-0.10 -0.34 -0.16 7/387 4</td>
<td>-</td>
<td>-</td>
<td>.49</td>
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<td>MAO-B inhibitors (Galling et al.)</td>
<td>Antidepressants</td>
<td>-0.07 -0.06 -0.22 2/876 3</td>
<td>-</td>
<td>-</td>
<td>.86</td>
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<tr>
<td>Carbamazepine (Leach et al.,2014)</td>
<td>Mood stabilizers</td>
<td>-0.06 -1.15 -0.13 3/79 3</td>
<td>-</td>
<td>-</td>
<td>.91</td>
</tr>
<tr>
<td>DLHA (Haringa et al.,2014)</td>
<td>Miscellaneous</td>
<td>-0.24 -0.32 -0.14 1/480 3</td>
<td>-</td>
<td>-</td>
<td>.28</td>
</tr>
<tr>
<td>Varenicline (Kishi and Iwata,2015)</td>
<td>Miscellaneous</td>
<td>-0.06 -0.21 -0.33 4/264 3</td>
<td>-</td>
<td>-</td>
<td>.28</td>
</tr>
<tr>
<td>Damuventide (Sommer et al.,2014)</td>
<td>Miscellaneous</td>
<td>-0.23 -0.18 -0.64 2/85 3</td>
<td>-</td>
<td>-</td>
<td>.28</td>
</tr>
</tbody>
</table>

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Does long-term of schizophrenia with antipsychotic medications facilitate recovery and functioning?

- Antipsychotic medications are viewed as cornerstones for both the short-term and long-term treatment of schizophrenia.
- Double-blind discontinuation studies indicate significantly more relapses in unmedicated schizophrenia patients in the first 6-10 months, but also present some potentially paradoxical features.
- Evidence of antipsychotic efficacy on long-term (10 or more years) is mixed.

Harrow and Jobe *Schizophrenia Bulletin* vol. 39 no. 5 pp. 962–965, 2013
doi:10.1093/schbul/sbt034
Advance Access publication March 19, 2013
Are Brain changes in schizophrenia progressive?
A meta-analysis of structural MRI findings

- Twenty-seven studies were included in the meta-analysis, with 928 patients and 867 control subjects, and 32 different brain regions.

Results support the idea that schizophrenia has a progressive component to its pathophysiology, although this is not necessarily degenerative, and this model and the neurodevelopmental model are not mutually exclusive.

Olabi et al., 2011, Biological Psychiatry, 70:88-96
Patterns of Gray Matter changes in Schizophrenia

• Source-based morphometry (SBM) and voxel-based morphometry (VBM) analyses on GMC images from 784 Schizophrenia pz and 936 controls across 23 scanning sites in Europe and the United States.

• The regions of gray matter loss are organized in networks of *anterior temporal, insular, and medial prefrontal regions*, as well as parts of the *frontal cortex, posterior brain regions, and several separate brainstem and cerebellar networks*.

Thinner cortex in antipsychotics medicated schizophrenia patients: how they perform?

Case control cross sectional study
- First episode patients unmedicated n= 22
- First episode patients medicated (atypicals) n=23
- Normal controls n= 37

- The medicated patient group showed thinner cortex compared with the unmedicated patient group in the dorsolateral prefrontal cortex (DLPFC) (MR, 0.26 mm; $P = .001$) and temporal cortex (MR, 0.33 mm; $P = .047$).

- However, the medicated patient group demonstrated higher DLPFC activation ($P = .02$) and better behavioral performance ($P = .02$) than the unmedicated patient group.

Lesh et al. JAMA Psychiatry. 2015;72(3):226-234
Little evidence was found to support a negative long-term effect of initial or maintenance antipsychotic treatment on outcomes, compared with withholding treatment. Strategies for treatment discontinuation or alternative nonpharmacologic treatment approaches may benefit a subgroup of patients but may be associated with incremental risk of relapse and require further study.
Final remarks

• Multiple variables should be taken into account in severe psychotic disorders both for the acute and long-term treatment.

• Efficacy and adverse events may represent a starting point of the treatment both to be “tuned” by the trajectory of the disease.

• Albeit still a controversial issue, the impact on brain architecture is