INPLASY PROTOCOL

To cite: Iasevoli et al. Dopamine dynamics and neurobiology of non-response to antipsychotics, relevance for Treatment Resistant Schizophrenia. A systematic review and critical appraisal. Inplasy protocol 202320104. doi: 10.37766/inplasy2023.2.0104

Received: 23 February 2023

Published: 23 February 2023

Corresponding author:
Felice Iasevoli

felice.iasevoli@unina.it

Author Affiliation:
Laboratory of Molecular and Translational Psychiatry and Unit of Treatment Resistant Psychosis, Section of 7Psychiatry, Department of Neuroscience, Reproductive Science, and Odontostomatology University of Na- 8ples Federico II. Napoli, Italy.

Support: **No financial support was provided.**

Review Stage at time of this submission: **Completed but not published.**

Dopamine dynamics and neurobiology of non-response to antipsychotics, relevance for Treatment Resistant Schizophrenia. A systematic review and critical appraisal

Iasevoli, F[1]; Avagliano, C[2]; D'Ambrosio, L[3]; Barone, A[4]; Ciccarelli, M[5]; De Simone, G[6]; Mazza, B[7]; Vellucci, L[8]; and de Bartolomeis, A[9].

Review question / Objective: **The aims of this review are: i) to recapitulate and critically apprise relevant literature on dopamine-related mechanisms of TRS; ii) to discuss the methodological limitations of the studies so far conducted and delineate a theoretical framework on dopamine mechanisms of TRS; iii) to highlight future perspectives of research and unmet needs. Dopamine-related neurobiological mechanisms of TRS may be multiple and putatively subdivided in three biological points: 1) D2R-related, including increased D2R levels; increased density of D2Rs in the high-affinity state; aberrant D2R dimer or heteromer formation; imbalance between D2R short and long variants; extrastriatal D2Rs; 2) presynaptic dopamine, including low or normal dopamine synthesis and/or release compared to responder patients; 3) exaggerated post-synaptic D2R-mediated neurotransmission. Future points to be addressed are: i) a more neurobiologically-oriented phenotypic categorization of TRS; ii) implementation of neurobiological studies by directly comparing TRS vs. non-TRS populations; iii) development of a reliable animal model of non-response to antipsychotics.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 23 February 2023 and was last updated on 23 February 2023 (registration number INPLASY202320104).

INTRODUCTION

Review question / Objective: **The aims of this review are: i) to recapitulate and critically apprise relevant literature on dopamine-related mechanisms of TRS; ii) to discuss the methodological limitations of the studies so far conducted and delineate a theoretical framework on dopamine mechanisms of TRS; iii) to highlight future perspectives of research and unmet needs. Dopamine-related neurobiological mechanisms of TRS may be multiple and putatively subdivided in**

three biological points: 1) D2R-related, including increased D2R levels; increased density of D2Rs in the high-affinity state; aberrant D2R dimer or heteromer formation; imbalance between D2R short and long variants; extrastriatal D2Rs; 2) presynaptic dopamine, including low or normal dopamine synthesis and/or release compared to responder patients; 3) exaggerated post-synaptic D2R-mediated neurotransmission. Future points to be addressed are: i) a more neurobiologically-oriented phenotypic categorization of TRS; ii) implementation of neurobiological studies by directly comparing TRS vs. non-TRS populations; iii) development of a reliable animal model of non-response to antipsychotics.

Condition being studied: Treatment Resistant Schizophrenia (TRS) is characterized by a lack or suboptimal response to antipsychotic agents. Biological underpinnings of TRS are still scarcely understood. Since all antipsychotics block dopamine D2 receptors (D2R), dopamine-related mechanisms should be considered as the main candidates in the neurobiology of antipsychotic non-response, although other neurotransmitter systems play a role.

METHODS

Participant or population: The population included TRS and non- TRS patients involving dopamine-related mechanisms; and animal models of schizophrenia with dopamine related neurobiological correlate of response to antipsychotics.

Intervention: We analyze the impact of antipsychotic treatments on dopamine related neurobiological correlate of response and resistance to pharmacological interventions.

Comparator: Healthy control population or individuals treated with placebo and animal models administered with vehicle.

Study designs to be included: We deemed eligible English-written articles, published in peer-reviewed journals related to treatment resistance/unresponsiveness, schizophrenia/psychotic disorders, and dopamine. Reports on dopamine-related molecular mechanisms putatively implicated in the pathophysiology of schizophrenia or in antipsychotic mechanism of action have been included in the manuscript to enlarge the discussion of the purported dopamine basis of resistance to antipsychotic treatment.

Eligibility criteria: No time constraints were applied, and original clinical, and preclinical research studies and reviews were included. Conference abstracts, and commentaries were excluded.

Information sources: A comprehensive review of the literature was carried out through Medline/Pubmed, Embase, and Scopus databases. Keywords were searched in the Title/Abstract fields; no date restriction was set; only publications in the English language were included.

Main outcome(s): The latest update of available literature was conducted on February 17th, 2023. The search returned 4610 articles. After removing duplicates, 2184 papers were retrieved. All publications were screened by title and abstract to remove not pertinent articles. The outcomes at this stage were: i) any type of direct neurobiological comparison between TRS and non-TRS patients involving dopamine-related mechanisms; and ii) any type of dopamine-related neurobiological correlate of response to antipsychotics. After this step, a total of 724 publications were selected and the full paper of all of them was read. Again, not pertinent publications were removed, and the resulting ones formed the literature base for the present work. These latter steps were carried out separately and in blind by two experimenters. In case of lack of agreement (publications removed by one and included by the other), the first Author was in charge to decide. Additional publications were hand-searched based on the references of included publications. At the end of the screening process, a total of 99 articles were included in the qualitative synthesis.

Quality assessment / Risk of bias analysis: Not applicable.

Strategy of data synthesis: Not applicable.

Subgroup analysis: Not applicable.

Sensitivity analysis: Not applicable.

Language restriction: Only publications in the English language were included.

Country(ies) involved: Italy.

Keywords: psychosis; clozapine; refractory; positive symptoms; negative symptoms; glutamate; ultra-resistant.

Contributions of each author:
Author 1 - Felice Iasevoli.
Author 2 - Camilla Avagliano.
Author 3 - Luigi D'Ambrosio.
Author 4 - Annarita Barone.
Author 5 - Mariateresa Ciccarelli.
Author 6 - Giuseppe De Simone.
Author 7 - Benedetta Mazza.
Author 8 - Licia Vellucci.
Author 9 - Andrea de Bartolomeis.

Conflicts of interest: Andrea de Bartolomeis has received unrestricted research support from Janssen, Lundbeck, and Otsuka and lecture honoraria for educational meeting from Chiesi, Lundbeck, Roche, Sunovion, Vitria, Recordati, Angelini, and Takeda; he has served on advisory boards for Eli Lilly, Jansen, Lundbeck, Otsuka, Roche, Vitria, Chiesi, Recordati, Angelini, and Takeda. No activity is related directly or indirectly to the present manuscript content. All the other authors declare no conflict of interest.