Treatment-resistant schizophrenia: definitions and implications of the concept of Treatment-Resistant Schizophrenia

Pizarro-Galleguillos Benjamín 1, Óscar Waissbluth2, Álvaro Cavieres3, Pablo R Moya4,5, M. Leonor Bustamante6,7

Schizophrenia (SZ) is a highly heterogeneous clinical entity. It causes a severe disruption in quality of life, and it imposes a significant burden to society. Antipsychotics are the first line treatment; however, up to 30% of the patients will present resistance to treatment. Treatment-resistant schizophrenia (TRS) could be a disorder neurobiologically distinct and not merely an extremely severe form of SZ. However, there is no consensus in the literature as to the definition of TRS. In the present work we review different definitions of TRS, mainly from clinical guidelines. Furthermore, we discuss therapeutic alternatives for TRS and suggest future perspectives regarding the identification of response predictors and understanding the neurobiology of TRS.

Keywords: Treatment-resistant, Clozapine, Antipsychotics.

Introduction

Schizophrenia is a highly heterogeneous clinical entity, and a better characterization of this heterogeneity is needed to make progress in the research of its causal mechanisms and potential treatments [1]. One of the variables that shows important distinctions among patients is their response to treatment. The mechanisms as to why some patients present symptoms that do not improve with habitual treatment are not clear, but several lines of evidence suggest that they could represent a distinct neurobiological subgroup of the illness [1], [2]. While the majority of schizophrenic patients respond to treatment with first or second generation anti-psychotics (APs), up to a third of them do not, and are characterized as treatment-resistant with a reported range of 13- to 45% [3]-[5]. There is an important limitation to the interpretation of this data, as there is no consensus about the definition of treatment-resistant schizophrenia (TRS). Thus, there are many definitions [6]-[8]. Next, we will present a review of different proposed definitions of TR schizophrenia, discussing their implications in clinical decision-making and

The author does not have any conflict of interests to disclose - There was no financing of any kind.

Accepted: 07/01/2020
Received: 14/08/2019

1 Medical Resident, School of Medicine, Universidad de Chile
2 Clínica Los Tiempos
3 Department of Psychiatry, School of Medicine, Universidad de Valparaíso
4 Physiology Institute, School of Science, Universidad de Valparaíso
5 Interdisciplinary Center of Neuroscience of Valparaíso (CINV), Universidad de Valparaíso
6 Department of Psychiatry and Mental Health North, School of Medicine, Universidad de Chile
7 Human Genetics Program, Institute of Biomedical Science, School of Medicine, Universidad de Chile.

research about the neurobiology of the illness.

Treatment-resistant schizophrenia

One of the first operational definitions of treatment-resistant schizophrenia was proposed in 1988, when John Kane et al, demonstrated the efficacy of Clozapine in cases of TRS that did not respond to conventional treatment, which they defined as the absence of a satisfactory answer according to the scores on scales such as BPRS — Brief Psychiatric Rating Scale — and CGI — Clinical Global Impression Scale — after three therapeutic trials, understood as three full dosages of antipsychotics, and taking as reference 400-600 mg of chlorpromazine [9]. Generally, different subsequent definitions have been posed based on three principal variables: indicators of improvement per clinical scales, number of drug tests and dosage, and duration of the treatment [6]–[8], [10]. Table 1 shows a summary of various proposals, detailing the assigned criteria for each variable.

After three decades of discussion about TRS, significant controversies persist among the different proposals revised by Suzuki [7]. First, they have not shown consistency concerning dosage and duration of tests with APs, which vary between four to six weeks and dosages between 400 to 1000 mg of Chlorpromazine per day. Secondly, they are based on the measurement of positive symptoms without incorporating functional or cognitive variables in an operationalized form.

Table 1. Summary of proposed definitions of treatment-resistant schizophrenia

Reference	Number, Type and Dosage	Time	Resistance Clinical Criteria	Management	Type of Study
Kane [9]	3 drugs in 5 years, > 1000 mg chlorpromazine	Six weeks each test	Clinical functioning, BPRS >= 45, CGI minimum of 4; score of 4 in two BPRS domains: behavioral disorganization, paranoid delirium, hallucinatory behavior, unusual thought	Clozapine up to 900 mg/day	Study no. 1
The Schizophrenia Patients Outcomes Research Team] Team Recommendations (PORT) [11]	2 drugs, adequate use		Persistence of clinically significant positive symptoms	Clozapine at least eight week, 300-800/day	Clinical guideline-Systemic Review

American Psychiatric Association (APA) [12]	At least 2, dosage in therapeutic range	6 weeks	Little or no clinical response	Clozapine	Clinical guideline-Systemic Review
European Medicine Agency (EMEA) [13]	At least 2, including an atypical, in adequate dosage; one of the tests must be prospective	Adequate duration	Unsatisfactory improvement, having discarded substance abuse	Clozapine	Clinical guideline-European Research Protocol
Suzuki [7], [10]	2 AP, dosage equivalent >600 mg chlorpromazine	6 weeks	CGI >=4, GAF >50; FACT-Sz <=50	Not specified	Review
The World Federation of Socities of Biological Psychiatry (WFSBP) [14], [15]	2 drugs of different chemical classes, at least one atypical in the past five years, in the recommended dosage for each drug	2-8 weeks	Persistence of objective symptomatology; having discarded other causes for failure such as comorbidity, substance abuse, low treatment compliance, polypharmacy.	Begin Clozapine, average dosage 400 mg/day	Clinical guideline- Systemic Review
Scottish Intercollegiate Guidelines Network (SIGN) [16]	Two types of drugs, at least one a second-generation drug	Adequate duration	Lack of response	Clozapine	National Clinical guideline- Systemic Review
The National Institute for Health and Care Excellence (NICE) [17]	At least two drugs including an atypical	Adequate duration		Begin Clozapine	National Clinical guideline- Systemic Review

Treatment response and resistance in Psychosis Group () [8]	> = 2 drugs > = 1 prior treatment with long term injectable AP	6 weeks orally or >4 months parenteral	Symptom reduction <20%; functional disturbance according to validated scale; with compliance confirmed by serum levels of the drug	Not specified	Clinical guideline- Systemic Review
Ministry of Health (MINSAL) [18]	At least 2 antipsychotic drugs, including at least one atypical AP, in adequate dosages	6 weeks	There is no satisfactory clinical improvement, having discarded non-compliance, comorbidity, drug interaction, and substance abuse. Non-pharmacological therapy must be optimized.	Begin Clozapine and Electro-convulsive therapy as alternative to antipsychotic drugs of habitual use.	Clinical guideline- Systemic Review

Treatment of treatment-resistant schizophrenia with Clozapine.

Despite different criteria in the definitions of TRS the majority of major clinical guidelines concur about the use of Clozapine as the first line of treatment for TRS ([12], [13], [15]–[19]. Clozapine (3-cloro-6-(4-methylpiperazine-1-yl)-11H-benzo[b][1,4] benzodiazepine)) belong to the class of tricyclic dibenzodiazepines. Clozapine is an inverse agonist of serotonin receptor type 2 (5-HT2A y 5-HT2C) [20] and antagonist of dopamine receptors type 2 (D2, although with weak effect), adrenergics 1 and 2, and histaminergic H1. Clozapine's actions beyond its effect on dopamine and serotonin receptor may explain its other therapeutic and secondary effects: its antagonism of muscarinic receptors M1-5 may explain its anticholinergic effects. The somnolence observed with clozapine may be explained by its antagonism over histamine receptors H1, and its antagonism of adrenergic receptors a1 would explain the orthostatic hypotension observed with Clozapine.[21]. In contract with other neuroleptics, Clozapine would have fewer extra-pyramidal effects [9]. Nevertheless, since its implementation, significant hematological disturbances have been described, such as agranulocytosis [22], [23]. For this reason, beginning in 1975, it was withdrawn from several countries. It was left out of the market and lacked financing for clinical research for over a decade. Later, its use was permitted only in carefully selected cases, including TRS or severe extra-pyramidal symptoms[24]. When a vigilance protocol was associated to the hematological effects, the frequency of agranulocytosis and mortality caused by it were significantly reduced[9].

The evidence that supports the use of Clozapine as the drug of choice in TRS dates back to the classic study by Kane in 1988[5]. In this double-blind study, Chlorpromazine and

Clozapine were compared in a multicentric clinical trial based in 16 different centers, and included 268 patients who had not responded to three different types of neuroleptic[9]. The study showed that 30% of the patients with TRS responded to Clozapine versus only 4% who responded to chlorpromazine, using BPRS (Brief Psychiatric Rating Scale), CGI (Clinical Global Impression Scale) and NOBS (Nurse observations calefor inpatient evolution), and including positive and negative symptoms[9]. This study had as background previous works that showed Clozapine had a superior effect than other antipsychotics, particularly in patients whose condition had a more severe course[25], [26], but the importance of Kane was such that it helped Clozapine obtain authorization from the FDA to enter the market again in 1988, with the indication to be used for patients with TRS[24]. More recently, other protocols have substantiated these observations, among them, CATIE, INTERSEP and CUTLASS 2, being the CATIE study the second pivotal study to endorse the use of Clozapine, after Kane's [24], [27].

In 1999, the National Institute of Mental Health in USA, upon noticing that a significant number of studies about new antipsychotics came from trials financed by the pharmaceutical industry, contacted Dr. Jeffrey Lieberman to perform a multicentric trial to evaluate the efficacy and tolerance of these pharmaceuticals in more representative therapeutic conditions [24]. The first phase of the CATIE study was designed to compare Perphenazine against new antipsychotics in a randomized, double-blind manner. Subsequently, in the second phase, resistant patients where randomized with Clozapine as alternative in an open label study, versus double-blind study with Olanzapine, Quetiapine, or Risperidone[28]. Among various findings, one of them confirmed Clozapine was the most effective drug for individuals with poor responses to previous trials with other antipsychotics, despite being associated with serious adverse effects, such as weight gain and metabolic complications, and even decreasing measured symptoms via PANSS were modest [28]. On the other hand, with respect to other functional domains, the data in this study shows that none of the treatments produces a significant improvement in cognitive symptoms or quality of life [29], [30].

Despite the robust evidence of major observational studies and open label studies that have supported the used of Clozapine as the Gold Standard in TRS, currently there is certain controversy concerning its effectiveness due to two works published in 2016 that showed contradicting evidence[31]. On one hand, a Network Metanalysis published by Samara et al, 2016[32], only revealed modest benefits for Clozapine, Olanzapine, and Risperidone in general TRS symptoms, without a clear benefit of Clozapine over other APs. On the other hand, a second meta-analysis published by Siskind et al, 2016[33], showed the superiority of Clozapine versus the rest of APs of first and second generation in reducing short and long term positive symptoms in TRS. Also, it was shown that a greater onset severity was correlated with better a response to Clozapine. Without prejudice to the latter, as Taylor 2017 [31] points out, even with these contradicting results, thirty years of cumulative evidence, the use of Clozapine as the Gold Standard in TRS is still substantiated. Interestingly, Taylor notes, that the differences obtained in these meta-analyses could correspond to methodological differences, particularly due to the heterogeneity in the definitions of TRS used, thus highlighting the importance of adopting similar criteria for its definition.

Resistance and prognosis.

TRS is a chronic illness, where up to 80% to 90% of the patients will show some type of persistent social or labor dysfunction[34]. In that sense, TRS present an episodic course with relapses that may have a variable severity. Without prejudice to the latter, TRS is a chronic illness, where up to 80% to 90% of the patients will show some type of persistent social or labor dysfunction[34]. Considering this, some authors have used its chronicity as a marker of resistance, defined as the number of hospitalizations or the existence of prolonged hospitalizations[4]. In regard to relapses, a recent study of Kesserwani kadra et. al[35] which included 3651 individuals found an association with the use of Clozapine and the decrease of hospitalization compared to those who used

APs in monotherapy. This was sustained even in gravelly ill patients who were treated with Clozapine, who had a more deficient functional state and a graver psychopathology at the beginning of the prescription. Considering the rate of relapse has an economic impact, as Kennedy et al[36] observed, who showed that the cost of TRS in the US was of US$34 billion per year in medical costs, considering an annual cost of US$15,500 and US$22,300 per patient, which is triples in patients with TRS[37].

Discussion

Research about the effectiveness of anti-psychotics in TRS have defined resistance to treatment heterogeneously, which limits the validity of the guidelines based on the evidence. Nevertheless, it is possible to find some common elements in all these definitions. First, almost all these studies compare the response only in terms of positive symptoms. The central role of the positive symptoms is said to be related to the effects of these drugs, which is clearly superior in this symptomatic domain with respect to others, as well as the relevance of them for the disability of the patients[2]. Although there is growing evidence that the cognitive and negative symptoms may have a role in the long-term prognosis, until now there is no evidence that antipsychotics may have a decisive role in alleviating them. This appears to be the cause why even contemporary studies, performed during a period of greater consciousness concerning the impact of these other symptomatic domains, continue to focus almost exclusively in positive symptoms. Nevertheless, given the impact of cognitive symptoms in the functionality of the patients, it is necessary that clinicians and researchers consider their significance in the search of future interventions.

A second aspect that emerges with clarity is that guidelines decidedly recommend Clozapine in the management of TRS. Although the terms to define its onset are variable, these fluctuate around 6 weeks. In contrast to this recommendation, the studies in the literature show that, in practice, there is a significant delay in the implementation of this antipsychotic, which averages four years[38]. This figure surpasses any of the recommendations, and relates to the use, on average, of five APs prior to the implementation of Clozapine, reaching also higher dosages than the ones recommended in clinical guidelines[38]. This major delay was also found in other studies such as Wheeler's in New Zealand, where the time prior to the commencement of the administration averages ten years[39]. Certain barriers that involve both the prescribing physician as well as the institutions have been identified in the delay in the implementation of Clozapine. Farooq et al., in a systematic review from 1972 to March 2018, selected 15 articles related to the barriers for the use of Clozapine in patients with TRS, and found that the main causes were related to mandatory blood extractions, fear to serious secondary effects, lack of familiarity with the use of the drug, lack of clarity in the diagnosis, difficulty on identifying/selecting adequate patients, service fragmentation (conducting the exam, delivery of results, prescription and delivery of the drug), and insufficient training of healthcare staff[40]. The resistance of the treatment to indicate Clozapine is not funded in reality, as concluded a study that analyzed the mortality of more than 14,000 subjects with severe mental disorders, and which identified a strong association between having received Clozapine and a reduction in mortality[41]. The authors show that the dimension of this protective effect cannot be explained only by the fact of receiving a hematological monitoring, and that it would be explained by a reduction in the risk of suicide as a reduction in mortality for medical causes.

The severe dysfunction associated to psychosis, along with the well-established benefit of Clozapine, make patent the need for identifying predictors for the response that may be measured early in the course of the treatment with antipsychotics. Given that the identification of treatment-resistant patients requires a period of observation of many week with full dosages of APs prior to defining an adequate treatment to the specific characteristics of these patients, they live with psychotic symptoms that may lead to a severe deterioration of their quality of life, including the risk of suicide. Along with this, they are exposed to the potential side effects

caused by high dosages of pharmaceuticals. There are known environmental factors that may contribute to TRS, such as the duration of psychosis without treatment or substance abuse. A significant role of genetic factors has also been identified[42], [43]. Nevertheless, biological bases are not exactly known and there are no biomarkers nor clear clinical predictors to identify early on which patients will require Clozapine. Interestingly, a review in 2018 that compiled 92 pharmacogenetic studies about the variation in the effectiveness of APs reveals only 19 individuals of Hispanic decent from a total of 9,600 patients[44]. Given that an association between ancestry and pharmacokinetics parameters has been demonstrated, this lack puts emphasis in the necessity to develop studies in our Chilean population that contribute to relevant decision-making for individuals and the population.

Moreover, new perspectives concerning the classification of TRS have been proposed. Recently, Kinnon et al. [45] poses the possibility of dividing patients with TRS between primary and secondary types, i.e., between those whose resistance manifests before five years of treatment and after five years of treatment. Additionally, Kinon poses the category of ultra-resistance to treatment, defined as those patients with TRS who do not respond to Clozapine. Under the same logic, the group of Lee et al. proposes the distinction between "responding to APs", "responding to Clozapine", and "resistant to Clozapine"[2]. Again, both proposals open the discussion about whether this group corresponds to a severity spectrum or, rather, to a categorically different TRS group of different neurobiology and genetic architecture. In this way, the goals of these proposals are in line with the intention of the Research Domain Criteria (RDoc) of modifying the nosology of the psychiatric illnesses using neurobiological variables[46].

In sum, although there are no unified criteria concerning the definition of TRS, this is a clinical problem that may be tackled by different strategies. This is why a critical approach to this definition and its implications will allow clinicians to optimize the treatment in this group of patients, improving their prognosis and reducing costs. At the same times, it will allow researchers to deepen and widen the spectrum of their research in regard to the cause and treatment of schizophrenia.

Bibliography

[1] A. L. Gillespie, R. Samanaite, J. Mill, A. Egerton, and J. H. MacCabe, "Is treatment-resistant schizophrenia categorically distinct from treatment-responsive schizophrenia? A systematic review," BMC Psychiatry, 2017.

[2] J. Lee et al., "Subtyping schizophrenia by treatment response: Antipsychotic development and the central role of positive symptoms," Canadian Journal of Psychiatry. 2015.

[3] L. B. Dixon, A. F. Lehman, and J. Levine, "Conventional antipsychotic medications for schizophrenia.," Schizophr. Bull., vol. 21, no. 4, pp. 567–77, 1995.

[4] H. Elkis, "Treatment-Resistant Schizophrenia," Psychiatr. Clin. North Am., vol. 30, no. 3, pp. 511–533, 2007.

[5] M. Herrera-Estrella and K. Luna, "Clozapina: una revisión," Psiquiatr. Biol., vol. 23, no. 3, pp. 87–92, 2016.

[6] A. Barquero-Madrigal, "Esquizofrenia resistente al tratamiento: ¿hemos tomado una decisión? Treatment-resistant schizophrenia: have we made a decision?," vol. 55, no. 2, pp. 85–92, 2017.

[7] T. Suzuki et al., "Defining treatment-resistant schizophrenia and response to antipsychotics: A review and recommendation," Psychiatry Res., vol. 197, no. 1–2, pp. 1–6, 2012.

[8] O. Agid, A. Board, C. J. Johnson, E. Lilly, U. S. Company, and E. L. Canada, "Treatment resistant schizophrenia : Treatment Response and Resistance in Psychosis (TRRIP) working group consensus guidelines on diagnosis and terminology," vol. 174, no. 666, pp. 216–229, 2018.

[9] J. Kane, "Clozapine for the Treatment-

Resistant Schizophrenic," Arch. Gen. Psychiatry, vol. 45, no. 9, p. 789, 1988.

[10] T. Suzuki et al., "Treatment resistant schizophrenia and response to antipsychotics: A review," Schizophr. Res., vol. 133, no. 1–3, pp. 54–62, 2011.

[11] J. Kreyenbuhl, R. W. Buchanan, F. B. Dickerson, and L. B. Dixon, "The schizophrenia patient outcomes research team (PORT): Updated treatment recommendations 2009," Schizophrenia Bulletin. 2010.

[12] L. B. Dixon and D. O. Perkins, "Treatment of Patients With Schizophrenia Second Edition," Am. Psychiatr. Assoc., no. February, pp. 1–184, 2010.

[13] European Medicines Agency, "Guideline on clinical investigation of medicinal products, including depot preparations in the treatment of schizophrenia," vol. 44, no. September, pp. 1–24, 2012.

[14] A. Hasan et al., "World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Schizophrenia, Part 2: Update 2012 on the long-term treatment of schizophrenia and management of antipsychotic-induced side effects," World J. Biol. Psychiatry, vol. 14, no. 1, pp. 2–44, 2013.

[15] A. Hasan et al., "World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Schizophrenia, Part 1: Update 2012 on the acute treatment of schizophrenia and the management of treatment resistance," World J. Biol. Psychiatry, vol. 13, no. 5, pp. 318–378, 2012.

[16] Healthcare Improvement Scotland, "Management of schizophrenia: A key to Evidence Statements and grades of recommendations.," Sign, no. March, pp. 1–71, 2013.

[17] National Institute of Health and Clinical Excellence, "Psychosis and schizophrenia in adults," NICE Guidel. treament Manag., no. February, pp. 74–80, 2014.

[18] Ministerio de Salud Subsecretaria de Salud, "Guía Clínica para el tratamiento de personas desde primer episodio de Esquizofrenia," Guías Clínicas MINSAL, pp. 1–99, 2009.

[19] D. Addington, S. Abidi, I. Garcia-Ortega, W. G. Honer, and Z. Ismail, "Canadian Guidelines for the Assessment and Diagnosis of Patients with Schizophrenia Spectrum and Other Psychotic Disorders," Can. J. Psychiatry, vol. 62, no. 9, pp. 594–603, 2017.

[20] L. C. Sullivan, W. P. Clarke, and K. A. Berg, "Atypical antipsychotics and inverse agonism at 5-HT2 receptors.," Curr. Pharm. Des., vol. 21, no. 26, pp. 3732–8, 2015.

[21] "National Center for Biotechnology Information. PubChem Database. Clozapine, CID=135398737," p. CID=135398737.

[22] R. W. Griffith and K. Saameli, "Clozapine and Agranulocytosis," Lancet, vol. 306, no. 7936, p. 657, Oct. 1975.

[23] A. de la Chapelle, C. Kari, M. Nurminen, and S. Hernberg, "Clozapine-induced agranulocytosis - A genetic and epidemiologic study," Hum. Genet., 1977.

[24] O. Freudenreich, H. E. Brown, and D. J. Holt, 28 - Psicosis y esquizofrenia, Second Edi. Elsevier Espa8#241;a, S.L.U., 2018.

[25] J. Claghorn et al., "The risks and benefits of clozapine versus chlorpromazine.," J. Clin. Psychopharmacol., vol. 7, no. 6, pp. 377–84, Dec. 1987.

[26] K. A. Fischer-Cornelssen and U. J. Ferner, "An example of European multicenter trials: multispectral analysis of clozapine.," Psychopharmacol. Bull., vol. 12, no. 2, pp. 34–9, Apr. 1976.

[27] J. A. Inchauspe Aróstegui and M. Á.

Valverde Eizaguirre, "Creer en la clozapina: fe y evidencias," Rev. la Asoc. Española Neuropsiquiatría, vol. 38, no. 133, pp. 239–262, 2018.

[28] M. S. Swartz et al., "Special Section on Implications of CATIE: What CATIE Found: Results From the Schizophrenia Trial," Psychiatr. Serv., vol. 59, no. 5, pp. 500–506, 2008.

[29] M. D. Marvin S. Swartz et al., "Effects of antipsychotic medications on psychosocial functioning in patients with chronic schizophrenia: findings from the NIMH CATIE study," Am. J. Psychiatry, 2007.

[30] R. S. E. Keefe et al., "Neurocognitive effects of antipsychotic medications in patients with chronic schizophrenia in the CATIE trial," Arch. Gen. Psychiatry, 2007.

[31] D. M. Taylor, "Clozapine for Treatment-Resistant Schizophrenia: Still the Gold Standard?," CNS Drugs, vol. 31, no. 3, pp. 177–180, 2017.

[32] M. T. Samara et al., "Efficacy, acceptability, and tolerability of antipsychotics in treatment-resistant schizophrenia: A network meta-analysis," JAMA Psychiatry, vol. 73, no. 3, pp. 199–210, 2016.

[33] D. Siskind, L. McCartney, R. Goldschlager, and S. Kisely, "Clozapine v. first- and second-generation antipsychotics in treatment-refractory schizophrenia: Systematic review and meta-analysis," Br. J. Psychiatry, vol. 209, no. 5, pp. 385–392, 2016.

[34] H. Y. Meltzer, "Commentary: Defining Treatment Refractoriness in Schizophrenia," Schizophr. Bull., vol. 16, no. 4, pp. 563–565, Jan. 1990.

[35] J. Kesserwani et al., "Risk of readmission in patients with schizophrenia and schizoaffective disorder newly prescribed clozapine.," J. Psychopharmacol., vol. 33, no. 4, pp. 449–458, Apr. 2019.

[36] J. L. Kennedy, C. A. Altar, D. L. Taylor, I. Degtiar, and J. C. Hornberger, "The social and economic burden of treatment-resistant schizophrenia: a systematic literature review.," Int. Clin. Psychopharmacol., vol. 29, no. 2, pp. 63–76, Mar. 2014.

[37] J. L. Gören, A. J. Rose, E. G. Smith, and J. P. Ney, "The Business Case for Expanded Clozapine Utilization," Psychiatr. Serv., vol. 67, no. 11, pp. 1197–1205, Nov. 2016.

[38] O. D. Howes, F. Vergunst, S. Gee, P. McGuire, S. Kapur, and D. Taylor, "Adherence to treatment guidelines in clinical practice: study of antipsychotic treatment prior to clozapine initiation.," Br. J. Psychiatry, vol. 201, no. 6, pp. 481–5, Dec. 2012.

[39] A. J. Wheeler, "Treatment pathway and patterns of clozapine prescribing for schizophrenia in New Zealand.," Ann. Pharmacother., vol. 42, no. 6, pp. 852–60, Jun. 2008.

[40] S. Farooq, A. Choudry, D. Cohen, F. Naeem, and M. Ayub, "Barriers to using clozapine in treatment-resistant schizophrenia: systematic review," BJPsych Bull., 2019.

[41] R. D. Hayes et al., "The effect of clozapine on premature mortality: an assessment of clinical monitoring and other potential confounders.," Schizophr. Bull., vol. 41, no. 3, pp. 644–55, May 2015.

[42] M. J. Arranz and J. de Leon, "Pharmacogenetics and pharmacogenomics of schizophrenia: a review of last decade of research.," Mol. Psychiatry, vol. 12, no. 8, pp. 707–47, Aug. 2007.

[43] D. J. Müller et al., "Familial occurrence of tardive dyskinesia," Acta Psychiatr. Scand., vol. 104, no. 5, pp. 375–379, Jul. 2008.

[44] K. Yoshida and D. J. Müller, "Pharmacogenetics of Antipsychotic Drug Treatment: Update and Clinical Implications," 2018.

[45] B. J. Kinon, "The group of treatment

resistant schizophrenias. Heterogeneity in treatment resistant schizophrenia (TRS)," Front. Psychiatry, vol. 10, no. JAN, pp. 1–6, 2019.

[46] D. C. Javitt, "Biotypes in Psychosis: Has the RDoC Era Arrived?," Am. J. Psychiatry, vol. 173, no. 4, pp. 313–4, Apr. 2016.

Mailing:
María Leonor Bustamante
Avenida la Paz 1103, Recoleta,
mbustamante@med.uchile.cl
22978601