

Refractory schizophrenia

Esquizofrenia refratária

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Abstract

Objective: The aim of the present paper is to review the various aspects of refractory schizophrenia regarding issues such as definitions, clinical aspects, psychobiological correlates, pharmacological and non-pharmacological treatment options and predictors of treatment response. **Method:** Medline search as well as articles of the authors. **Results and Conclusions:** Refractory schizophrenia affects at least one third of patients with schizophrenia and the best evidence shows that is monotherapy with clozapine remains the mainstay for the treatment of such condition. Antipsychotic polypharmacy is not supported by current evidence and recent clinical trials have shown that clozapine augmentation with antipsychotics has no benefit over placebo.

Descriptors: Schizophrenia/therapy; Drug utilization review; Clinical protocols; Pharmacologic actions; Treatment outcome

Resumo

Objetivo: O propósito deste artigo é o de revisar vários aspectos da esquizofrenia refratária levando em conta questões relacionadas a definição, aspectos clínicos, correlatos psicobiológicos, tratamentos farmacológicos e não farmacológicos, assim como preditores de resposta terapêutica. **Método:** Pesquisa no Medline, assim como artigos dos autores. **Resultados e Conclusões:** Pelo menos um terço dos pacientes com esquizofrenia são refratários a tratamento com antipsicóticos e as evidências apontam a clozapina em monoterapia como a principal opção nesses casos. A politerapia com antipsicóticos não tem apoio em evidências. Ensaios clínicos recentes mostraram que a potencialização da clozapina com outros antipsicóticos não é superior ao placebo.

Descritores: Esquizofrenia/terapia; Revisão do uso de medicamentos; Protocolos clínicos; Ações farmacológicas; Resultado de tratamento

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Introduction

What is refractory schizophrenia? In so far as schizophrenia is, by definition, a chronic disease in which 80-90% of patients manifest social or occupational dysfunction compared to what might have been expected of them from their premorbid or familial level of function, it is difficult to draw the line between treatment responsive and treatment refractory schizophrenia.¹ Chronicity is frequently taken as a synonym of refractoriness but that does not help to illuminate the concept. There is clear distinction between chronicity and refractoriness in other areas of medicine since there are various chronic diseases, as for example diabetes or hypertension which, despite their chronicity, do, in fact, respond to treatment, with patients achieving stability, by taking hypoglycemic agents or antihypertensives throughout their lives.

Sometimes the term refractory schizophrenia (RS) or "treatment-resistant schizophrenia (TRS)" is incorrectly applied to patients who are symptomatic because of lack of compliance. This is better thought of as the patient is resisting treatment rather than that the illness itself is resistant to the expected response to treatment.

1. Clinical aspects of RS

Various cohort studies indicate that 20-30% of patients with schizophrenia meet criteria for RS. Although higher rates have been reported, it is likely that this represents an usual clustering of refractory cases or inadequate treatment strategies with regard to dose or duration of treatment.²

Meltzer et al., comparing TRS-patients versus non-RS patients reported that the RS patients had, on average, a 2-year earlier age of onset, and were more likely to be males.³ Similarly, Henna and Elkis observed that, in terms of gender distribution, patients with RS were predominantly male, experienced a higher number of hospitalizations, and had an age of onset of around 17 years for the disorder, as compared to those without RS (around 20 years).⁴ Other features reported to be associated with RS are a greater number of episodes of illness and hospitalizations, and a history of substance abuse. Because they are refractory to ordinary doses of typical neuroleptic drugs, RS patients will often have been treated with much higher than normal doses of medication and polypharmacy.

In terms of the psychopathology, Lindenmayer et al., using the Positive and Negative Syndrome Scale (PANSS), evaluated 157 patients with RS and found that the factor structure was no different from non RS patients, i.e. positive, negative, excitement, cognitive and depressive clusters.⁵ The same type of results were obtained with the Brief Psychiatric Rating Scale (BPRS), where McMahon et al. compared the structure of the scale in 1,074 patients with schizophrenia intolerant to antipsychotics, of whom 197 met criteria for observed through Confirmatory Factor Analysis that 13 of the 18 items of the BPRS loaded into four factors: reality distortion, disorganization, negative, anxiety/depression in both groups.⁶

Similarly, we analyzed data from an homogenous population of 96 patients narrowly defined as having RS and assessed by an anchored version of the BPRS and found also four dimensions: negative/disorganization, excitement, positive and depression.⁷

2. Current definitions of RS

For most investigators, persistent moderate to severe positive symptoms is the core feature of RS.⁸ Some believe that other

dimensions of schizophrenia should be included, such as negative and cognitive symptoms, as well as the inability to return to the best premorbid level of functioning.²

In this concept, RS is multidimensional which implies that a simple dichotomous (yes or no) definition is inadequate. Some authors tried to construct one-dimensional definitions based upon global symptom reduction⁹ or bi-dimensional, taking into account social adaptation, as well as symptom reduction¹⁰ Brenner et al. conceived RS as a continuum of resistance to refractoriness and developed a scale for measurement based on psychopathology and social adaptation.¹¹

The operational criterion most widely used for the definition of RS in clinical studies is that of Kane and Meltzer used for the study that introduced clozapine to the therapeutic armamentarium for schizophrenia.¹² Kane and Meltzer criteria are three-dimensional: 1) *Historic*: a history of total or partial lack of response to previous treatment using two antipsychotics at adequate doses and periods; 2) *Actual* (Severity of Symptoms): the patient must present a certain level of psychopathologic severity as assessed by the BPRS and the Global Clinical Impression (GCI) and 3) *Confirmatory*, i.e. following treatment with one or more antipsychotic drug, the patient must show minimal improvement in symptomatology (BPRS and CGI) as compared to pretreatment levels of psychopathology.

3. Definitions of RS based on algorithms

Guidelines for the treatment of schizophrenia such as the American Psychiatric Association¹³ or algorithms such as the Texas Medication Algorithm Project (TMAP)¹⁴ have established that after the failure of two or three treatments on atypical antipsychotics, the patient should be considered as having RS. This has been considered to make the patient a good candidate for treatment with clozapine, the only drug approved for RS.

The most recent algorithm, the Schizophrenia Algorithm of the International Psychopharmacology Algorithm Project (IPAP) (www.ipap.org) defines that a patient is considered to be refractory if he or she failed to respond to two trials of 4 to 6 weeks of duration of monotherapy with two different SGA (or two trials with a FGA, if SGAs are not available). In this case the patient is considered to have RS and is eligible for treatment with clozapine, at doses ranging from 300 mg/day up to 900 mg/day (see Figure 1). Patients who are so intolerant of treatment with any antipsychotic drug available that they cannot have an adequate trial of any drug of this class would be considered antipsychotic intolerant, not RS.

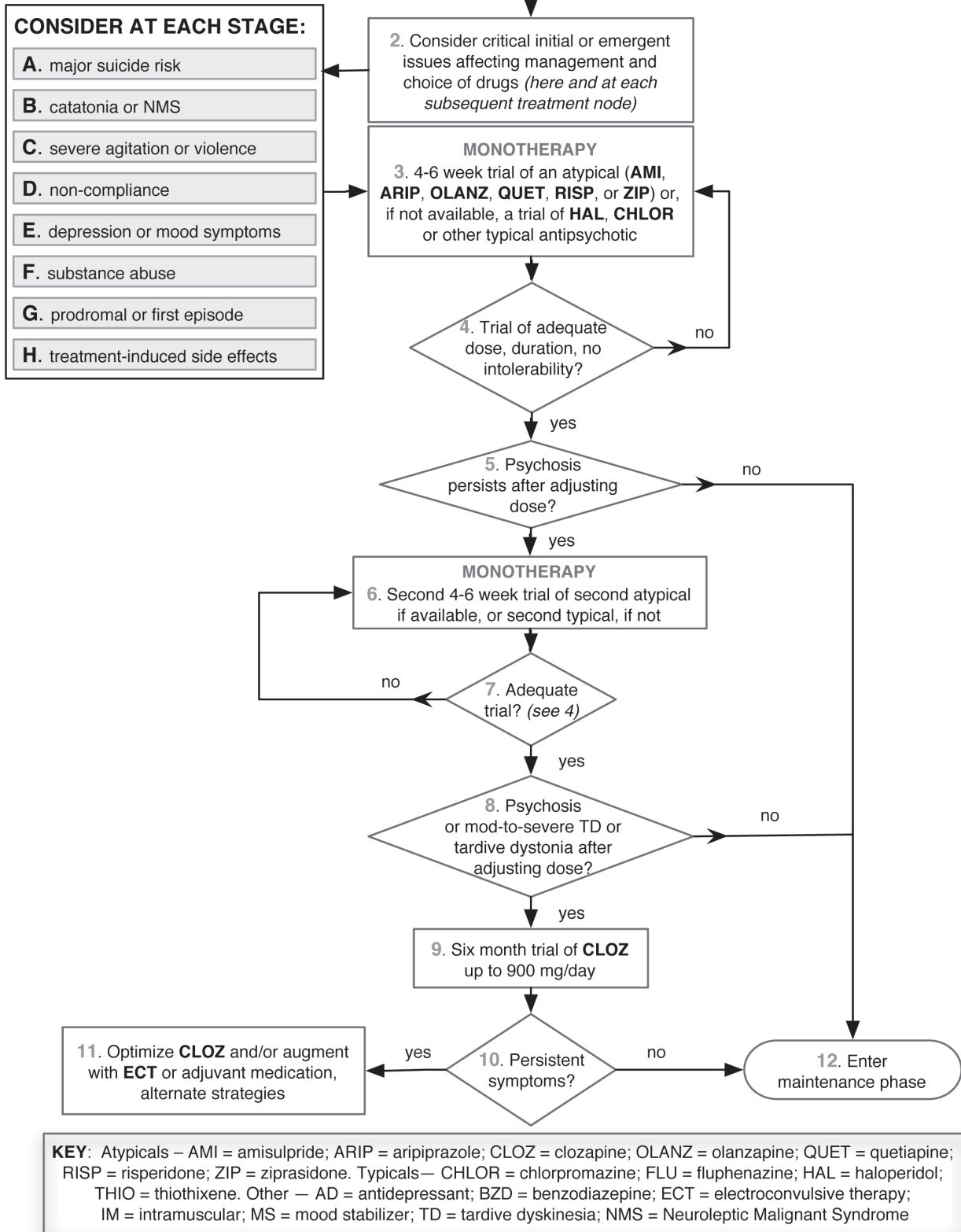
4. Clinical and psychobiological correlates of RS

Sheitman and Lieberman¹⁵ hypothesize that the evolution of RS occurs in three stages: 1) cortical pathology and deficient neuromodulatory capacity; 2) neurochemical sensitization; and 3) neurotoxicity. RS have been related to neurodevelopmental brain abnormalities such as the presence of ventricular enlargement, which have a negative correlation with treatment response with antipsychotics. Reviews of retrospective studies suggest that ventricular enlargement is related to poor outcome, whereas in prospective studies such abnormality is associated with response to conventional antipsychotics, while cortical atrophy possibly mediates the effects of atypical neuroleptics.¹⁶

There are few other neurobiological correlates of RS such as plasma homovanillic acid, which is decreased in first

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IPAP Schizophrenia Algorithm



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Figure 1 - IPAP Schizophrenia Algorithm

episode patients or altered T- cell functions, as well as alterations of inflammatory process mediated by interleukins that do not respond to treatment.¹⁷ The importance of genetic factors that govern response to treatment will be discussed subsequently.

5. Treatment of RS

1) Clozapine

Meta-analyses of controlled trials and systematic reviews involving patients with RS are consistent in showing that clozapine, when compared to other SGA, is the treatment of choice for RS.¹⁸⁻²¹

There are three meta-analyses of the clozapine vs FGA¹⁸ and FGA vs SGA.^{19,20} One of the studies which favorably compared clozapine to FGA and found an effect size of 0.44 in favor of clozapine, nevertheless pointed out that many other studies that found these same results suffered from methodological bias, including the heterogeneity and duration of the studies, the initial psychopathology of patients, the year of publication and sponsorship.²⁰

The meta-analysis of the Cochrane Center included only eight studies that compared Clozapine with SGA. Clozapine showed a trend to be more effective in terms of improving positive symptoms but not negative symptoms, while other outcome variables such as relapse rates or global improvement showed no differences.²¹

2) Predictors of treatment response with clozapine

Since clozapine is the mainstay for the treatment of RS, we will summarize its main predictors of response. The reader is also referred to an excellent review published by Chung and Remington on this subject.²²

A number of authors investigated the factors associated with response to clozapine in cohort studies and found that high levels of psychopathology, female gender, age at early onset of the disorder and years of schooling, all to be predicted good response.²³ Other authors however, have obtained opposite results finding that patients who displayed low levels of psychopathologic at baseline, as well as less severe negative and extra-pyramidal symptoms, were the best responders.²⁴

Doses of 300-600 mg/day are generally needed to achieve the plasma threshold for response.²² Although studies are not unanimous, plasma levels equal to or greater than 350 ng/ml reaching 500 ng/ml tend to be associated with a satisfactory clinical response. Caution is in order since these levels are lowered by nicotine.²² However, Potkin et al. observed that around 30% of non-responders achieved plasma levels above the supposed adequate threshold.²⁵

Genetic variants due to polymorphisms of dopaminergic receptors D2, D3 and D4 have been described which influence the response to clozapine, with the same occurring for genetic variants of serotonergic receptors 5HT2a, 5HT2c and 5HT6.²⁶ Glutamate and norepinephrine receptors were also investigated,²² and recently the metabolic activity of the prefrontal cortex of patients responsive to clozapine has been shown to be associated with alleles of the D1 receptor.²⁷ Nevertheless, as reviewed by Chung and Remington, the available data on the genetic predictors of treatment response to clozapine are presently inconsistent.²²

The prefrontal region has been shown to have an important role in the mediation of treatment response to atypical antipsychotics. It is noteworthy that in the case of clozapine, 3 CT studies²⁸⁻³⁰ all found that an increased prefrontal sulcal prominence was associated with a lesser response. However,

another CT study³¹ and an MRI study³² found no relationship between prefrontal atrophy and treatment response to clozapine. One of the most consistent findings was the reduction of the caudate in patients taking clozapine when compared with patients who received FGA.³³

Functional studies using Single Photon Emission Tomography (SPECT)³⁴ have observed an association between reduction of metabolic activity in prefrontal regions and clozapine response. However, a study by Chen et al. showed results in the opposite direction, i.e. increase prefrontal activity and clozapine response.³⁵ As previously mentioned, a later study of the same author found an association between reduction of metabolism in various brain areas and response to clozapine in patients homozygotes for 2.2 DRD1 gene, while no such reduction was found in non-responders homozygotes for 1.2 DRD1.²⁷

3) Treatment with non-clozapine antipsychotics

With advent of clozapine in 1988,¹² which became the gold standard for the treatment of RS, other SGA (mainly risperidone, olanzapine, quetiapine, ziprasidone) were tested for RS through various clinical trials.²

Two famous meta-analyses showed opposite results in terms of the efficacy of SGA over FGA. In one of these studies, Geddes et al. found that the superiority of FGA is related to the dose of the comparator, i.e. when the dose was ≤ 12 mg of haloperidol SGA had no superiority over FGA in terms of efficacy and tolerability.³⁶ Some of the studies of this meta-analysis involved controlled trials with RS patients treated with clozapine, but no specific conclusion on this item was reported.

Davis et al. challenged these results with another meta-analysis³⁷ where clozapine showed almost twice the effect size (0.49) in comparison with some others SGA (amisulpride = 0.29, risperidone = 0.25, olanzapine = 0.21). The effect size obtained for clozapine is due to studies involving RS populations but also in this meta-analysis the authors haven't acknowledged this issue.

Differently from randomized controlled trials, pragmatic or practical trials are designed to measure effectiveness in a real-world setting and population in order to provide the more complete information for practice physician. A recent important pragmatic trial supports the evidence of the effectiveness of clozapine over SGA for the treatment of schizophrenia. As part of phase 2 of the CATIE study³⁸ – which involved about 1400 patients – Mc Evoy et al.³⁹ studied 99 patients who haven't responded to atypical antipsychotics in previous phases of the CATIE due to lack of efficacy.⁴⁰ Patients were then assigned randomly to open label clozapine (n = 49) or blinded treatment with another SGA (olanzapine n = 19; quetiapine n = 15; risperidone n = 16). As results were compared to others SGA, clozapine showed to have greater reductions in the PANSS total score, as well as the lowest discontinuation rates, i.e. the use of clozapine proved to be more effective than switching to another SGA in patients who have previously not responded to another SGA.

4) Polypharmacy with SGA

Polypharmacy in schizophrenia is widespread all over the world⁴¹ despite the fact that there is no evidence of the superiority of this empiricist therapeutic habit over monotherapy. Some consider that combinations of SGA are well tolerated and may be effective for the treatment of RS, while other authors remain more cautious due a lack of well-controlled studies⁴² or evidence of harm as, for example, increased mortality.⁴³ In a naturalistic study in seven psychiatric hospitals, Janssen et al.⁴⁴ found that patients discharged with more than

one antipsychotic had significantly poorer outcomes with respect to both mental state and social functioning, while Suzuki et al.⁴¹ observed an improvement when patients under antipsychotic polytherapy were switched to monotherapy.

5) Clozapine polypharmacy

An incomplete response to clozapine is the persistence of psychotic symptoms despite a trial of clozapine with adequate doses (i.e. 300-900 mg/day) during a minimum of 8 weeks up to 6 months. Thus, the improvement of psychotic symptoms is considered the main treatment target and, as an apparent logical consequence, it has been proposed the addition of high potency antipsychotics to clozapine for the treatment of these symptoms.

It is estimated that approximately 30% of patients treated with clozapine do not respond adequately, remaining with persistent psychotic symptomatology, despite having received adequate treatment for sufficient periods. Such patients are called "partial responders to clozapine", "clozapine resistant" or even "super-refractory", and represent a challenge for the treatment of RS, as well as a great economic burden.⁴⁴

The treatment of these patients is problematic and pharmacological and non-pharmacological augmentation strategies remain the only options for this population, despite the lack of adequate evidence for efficacy.^{45,46} Many reviews have been published describing in detail such strategies^{45,47} that will be summarized.

Various antipsychotics were used supposedly to augment the antipsychotic properties of clozapine: amisulpride, aripiprazole, haloperidol, loxapine, olanzapine, pimozide, and ziprasidone. The benefits of these augmentation strategies remain inconclusive since they were tested in case series or case reports, which have a low strength of evidence, as compared with controlled trials.⁴⁷

More robust evidence is derived from four placebo controlled trials, one with sulpiride⁴⁸ and three with risperidone⁴⁹⁻⁵¹ and, due to their importance, they are summarized below. Shiloh et al. showed a significant improvement on positive and negative symptoms in the group that received sulpiride added to clozapine when compared with placebo group, and it was proposed that this effect could be explained by the selective enhancement of D2 blockage by sulpiride.⁴⁸

However, it is well known that risperidone has a strong affinity for D2 receptors and the hypothesis that blocking these receptors would improve persistent positive symptoms in patients resistant to clozapine was only supported by the Josiassen et al.'s study,⁴⁹ but not by Anil Yagcioglu or Honer's studies, since both studies found no differences between risperidone or placebo groups.^{50,51}

Therefore, the hypothesis that adding a more potent antipsychotic to enhance or optimize D2 affinity, and thus improving psychotic symptoms in poor clozapine responders, was not supported by the previous studies, and it is also interesting to point out that in the Anil Yagcioglu et al.'s study the placebo group showed a greater reduction in the PANSS positive scores than the risperidone group.⁵⁰

Finally, when clozapine augmentation with antipsychotics fails, it has been proposed to switch to another antipsychotic. This strategy is considered to have a weak level of evidence⁴⁶ and olanzapine was the antipsychotic most frequently tested in some open trials.⁵²

Other medications were tested in controlled trials for augmenting clozapine efficacy in negative or cognitive symptoms, such as serine, cycloserine, glycine, fluoxetine,

mirtazapine, carbamazepine, topiramate, Benzodiazepines, valproic acid.⁴⁷

6) Suicide

Considering that suicide may represent an important outcome dimension of RS, it is important to mention the results of the International Suicide Prevention Trial (InterSePT)⁵³ of 2-year duration where 980 patients with schizophrenia (about 260 with RS), recruited from 67 medical centers in 11 countries, were randomized either for clozapine or olanzapine. Results showed that compared to olanzapine, patients taking clozapine had significantly reduced rates of suicidal behavior or suicide attempts, while the rates of deaths due to suicide were not statistically different between groups. A Number Needed to Treat (NNT) equals 13 was obtained, showing that for every 13 high-risk patients treated, one less patient will have suicide events if they were treated with clozapine rather than olanzapine.

6. Non-pharmacological treatments

1) ECT and TMS

Despite the fact that ECT is recommended as an augmentation strategy for clozapine non-responders in some guidelines¹³ or algorithms such as the TMAP¹⁴ or the IPAP (www.ipap.org), there only few studies providing evidence of efficacy for this intervention.⁵⁴

Despite the fact that Transmagnetic Cranial Stimulation (TMS) has been used for the treatment of medication-resistant auditory hallucinations in controlled studies, only recently Rosa et al. tested TMS in the first controlled study for clozapine non-responders as compared with placebo ("sham") and found that TMS can be administered safely for patients taking clozapine, although the authors couldn't find a significant difference between the groups due to the lack of power of the study (active TMS = 6 patients; Sham: 5 patients).⁵⁵

2) Cognitive behavior therapy

Cognitive behavioral therapy (CBT) has been extensively used in patients refractory to antipsychotics, but only few studies included patients resistant to clozapine,⁵⁶ showing that this technique can help them to control their symptoms, especially hallucinations. We presented preliminary data showing that CBT in severe patients resistant to clozapine can also improve general psychopathology and quality of life.⁵⁷

References

1. Meltzer HY. Defining treatment refractoriness in schizophrenia. *Schizophr Bull.* 1990;16(4):563-5.
2. Meltzer H, Kostacoglu A. Treatment-resistant schizophrenia. In: Lieberman J, Murray R, editors. *Comprehensive care of schizophrenia: a textbook of clinical management.* London: Martin Dunitz; 2001. p. 181-203.
3. Meltzer HY, Rabinowitz J, Lee MA, Cola PA, Ranjan R, Findling RL, Thompson PA. Age at onset and gender of schizophrenic patients in relation to neuroleptic resistance. *Am J Psychiatry.* 1997;154(4):475-82.
4. Henna J, Oliveira , Mello M, Alves TM, Eizenman IB, Elkis H. Predictors of response and outcome in treatment resistant versus non treatment resistant schizophrenics patients. *Schizopr Res.* 1999;36(1-3):281-2.
5. Lindenmayer JP, Czobor P, Volavka J, Lieberman JA, Citrome L, Sheitman B, McEvoy JP, Cooper TB, Chakos M. Effects of atypical antipsychotics on the syndromal profile in treatment-resistant schizophrenia. *J Clin Psychiatry.* 2004;65(4):551-6.

6. McMahon RP, Kelly DL, Kreyenbuhl J, Kirkpatrick B, Love RC, Conley RR. Novel factor-based symptom scores in treatment resistant schizophrenia: implications for clinical trials. *Neuropsychopharmacology*. 2002;26(4):537-45.
7. Alves T, Pereira JR, Elkis H. The psychopathological factors of refractory schizophrenia. *Rev Bras Psiquiatr*. 2005;27(2):108-12.
8. Peuskens J. The evolving definition of treatment resistance. *J Clin Psychiatry*. 1999;60(Suppl 12):4-8.
9. Csernansky JG, Yesavage JA, Maloney W, Kaplan J. The treatment response scale: a retrospective method of assessing response to neuroleptics. *Am J Psychiatry*. 1983;140(9):1210-3.
10. May PR, Dencker SJ, Hubbard JW. A systematic approach to treatment resistance in schizophrenic disorders. In: Dencker SJ, Kulhanek F, editors. *Treatment Resistance in Schizophrenia*. Braunschweig/Wiesbaden: Vieweg Verlag; 1988. p. 22-3.
11. Brenner HD, Dencker SJ, Goldstein MJ, Hubbard JW, Keegan DL, Kruger G, Kulhanek F, Liberman RP, Malm U, Midha KK. Defining treatment refractoriness in schizophrenia. *Schizophr Bull*. 1990;16(4):551-61.
12. Kane J, Honigfeld G, Singer J, Meltzer HY. Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. *Arch Gen Psychiatry*. 1988;45(9):789-96.
13. Lehman AF, Lieberman JA, Dixon LB, McGlashan TH, Miller AL, Perkins DO, Kreyenbuhl J; American Psychiatry Association; Steering Committee on Practice Guidelines. Practice guideline for the treatment of patients with schizophrenia, second edition. *Am J Psychiatry*. 2004;161(2 Suppl):1-56.
14. Miller AL, Hall CS, Buchanan RW, Buckley PF, Chiles JA, Conley RR, Crismon ML, Ereshefsky L, Essock SM, Finnerty M, Marder SR, Miller DD, McEvoy JP, Rush AJ, Saeed SA, Schooler NR, Shon SP, Stroup S, Tarin-Godoy B. The Texas Medication Algorithm Project antipsychotic algorithm for schizophrenia: 2003 update. *J Clin Psychiatry*. 2004;65(4):500-8.
15. Sheitman B, Lieberman J. The natural history and pathophysiology of treatment resistant schizophrenia. *J Psychiatr Res*. 1988;32(3-4):143-50.
16. Crosthwaite CG, Reveley MA. Structural imaging and treatment response in schizophrenia. In: Reveley MA, William Deakin JF, editors. *The Psychopharmacology of Schizophrenia*. London: Arnold; 2000. p. 89-108.
17. Lieberman J, Alvir J, Koreen A, Geisler S, Chakos M, Woerner M. Psychobiological correlates of treatment response in schizophrenia. *Neuropsychopharmacology*. 1996;14(3S):13s-21s.
18. Wahlbeck K, Cheine M, Essali A, Adams C. Evidence of clozapine's effectiveness in schizophrenia: a systematic review and meta-analysis of randomized trials. *Am J Psychiatry*. 1999;156(7):990-9.
19. Chakos M, Lieberman J, Hoffman E, Bradford D, Sheitman B. Effectiveness of second-generation antipsychotics in patients with treatment-resistant schizophrenia: a review and meta-analysis of randomized trials. *Am J Psychiatry*. 2001;158(4):518-26.
20. Moncrieff J. Clozapine v. conventional antipsychotic drugs for treatment-resistant schizophrenia: a re-examination. *Br J Psychiatry*. 2003;183:161-6.
21. Tuunainen A, Wahlbeck K, Gilbody S. Newer atypical antipsychotic medication in comparison to clozapine: a systematic review of randomized trials. *Schizophr Res*. 2002;56(1-2):1-10.
22. Chung C, Remington G. Predictors and markers of clozapine response. *Psychopharmacology (Berl)*. 2005;179(2):317-35.
23. Ciapparelli A, Ducci F, Carmassi C, Carlini M, Paggini R, Catena M, Bottai M, Dell'Osso L. Predictors of response in a sample of treatment-resistant psychotic patients on clozapine. *Eur Arch Psychiatry Clin Neurosci*. 2004;254(5):343-6.
24. Umbricht DS, Wirshing WC, Wirshing DA, McMeniman M, Schooler NR, Marder SR, Kane JM. Clinical predictors of response to clozapine treatment in ambulatory patients with schizophrenia. *J Clin Psychiatry*. 2002;63(5):420-4.
25. Potkin SG, Bera R, Gulasekaram B, Costa J, Hayes S, Jin Y, Richmond G, Carreon D, Sitanggan K, Gerber B. Plasma clozapine concentrations predict clinical response in treatment-resistant schizophrenia. *J Clin Psychiatry*. 1994;55(Suppl B):133-6.
26. Mancama D, Arranz MJ, Kerwin RW. Genetic predictors of therapeutic response to clozapine: current status of research. *CNS Drugs*. 2002;16(5):317-24.
27. Potkin SG, Basile VS, Jin Y, Masellis M, Badri F, Keator D, Wu JC, Alva G, Carreon DT, Bunney WE Jr, Fallon JH, Kennedy JL. D1 receptor alleles predict PET metabolic correlates of clinical response to clozapine. *Mol Psychiatry*. 2003;8(1):109-13.
28. Friedman L, Knutson L, Shurell M, Meltzer HY. Prefrontal sulcal prominence is inversely related to response to clozapine in schizophrenia. *Biol Psychiatry*. 1991;29(9):865-77.
29. Honer WG, Smith GN, Lapointe JS, MacEwan GW, Kopala L, Altman S. Regional cortical anatomy and clozapine response in refractory schizophrenia. *Neuropsychopharmacology*. 1995;13(1):85-7.
30. Konicki PE, Kwon KY, Steele V, White J, Fuller M, Jurjus GJ, Jaskiw GE. Prefrontal cortical sulcal widening associated with poor treatment response to clozapine. *Schizophr Res*. 2001;48(2-3):173-6.
31. Bilder RM, Wu H, Chakos MH, Bogerts B, Pollack S, Aronowitz J, Ashtari M, Degreef G, Kane JM, Lieberman JA. Cerebral morphometry and clozapine treatment in schizophrenia. *J Clin Psychiatry*. 1994;55 Suppl B:53-6.
32. Lauriello J, Mathalon DH, Rosenbloom M, Sullivan EV, Faustman WO, Ringo DL, Lim KO, Pfefferbaum A. Association between regional brain volumes and clozapine response in schizophrenia. *Biol Psychiatry*. 1998;43(12):879-86.
33. Chakos MH, Lieberman JA, Alvir J, Bilder R, Ashtari M. Caudate nuclei volumes in schizophrenic patients treated with typical antipsychotics or clozapine. *Lancet*. 1995;345(8947):456-7.
34. Molina V, Reig S, Sarramea F, Sanz J, Artaloytia JF, Luque R, Aragues M, Pascual J, Benito C, Palomo T, Desco M. Anatomical and functional brain variables associated with clozapine response in treatment-resistant schizophrenia. *Psychiatry Res*. 2003;124(3):153-61.
35. Chen RY, Chen E, Ho WY. A five-year longitudinal study of the regional cerebral metabolic changes of a schizophrenic patient from the first episode using Tc-99m HMPAO SPECT. *Eur Arch Psychiatry Clin Neurosci*. 2000;250(2):69-72.
36. Geddes J, Freemantle N, Harrison P, Bebbington P. Atypical antipsychotics in the treatment of schizophrenia: systematic overview and meta-regression analysis. *BMJ*. 2000;321(7273):1371-6.
37. Davis JM, Chen N, Glick ID. A meta-analysis of the efficacy of second-generation antipsychotics. *Arch Gen Psychiatry*. 2003;60(6):553-64.
38. Stroup TS, McEvoy JP, Swartz MS, Byerly MJ, Glick ID, Canive JM, McGee MF, Simpson GM, Stevens MC, Lieberman JA. The National Institute of Mental Health Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) project: schizophrenia trial design and protocol development. *Schizophr Bull*. 2003;29(1):15-31.
39. McEvoy JP, Lieberman JA, Stroup TS, Davis SM, Meltzer HY, Rosenheck RA, Swartz MS, Perkins DO, Keefe RS, Davies CE, Severe J, Hsiao JK: CATIE Investigators. Effectiveness of clozapine versus olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia who did not respond to prior atypical antipsychotic treatment. *Am J Psychiatry*. 2006;163(4):600-10.
40. Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, Keefe RS, Davies SM, Davies CE, Lebowitz BD, Severe J, Hsiao K: Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med*. 2005;353(12):1209-23.
41. Suzuki T, Uchida H, Tanaka KF, Nomura K, Takano H, Tanabe A, et al. Revising polypharmacy to a single antipsychotic regimen for patients with chronic schizophrenia. *Int J Neuropsychopharmacol*. 2004;7(2):133-42.
42. Freudenreich O, Goff D. Antipsychotic combination therapy in schizophrenia. A review of efficacy and risks of current medications. *Acta Psychiatr Scand*. 2002;106(5):323-30.
43. Waddington JL, Youssef HA, Kinsella A. Mortality in schizophrenia. Antipsychotic polypharmacy and absence of adjunctive anticholinergics over the course of a 10-year prospective study. *Br J Psychiatry*. 1998;173:325-9.
44. Janssen B, Weinmann S, Berger M, Gaebel W. Validation of polypharmacy process measures in inpatient schizophrenia care. *Schizophr Bull*. 2004;30(4):1023-33.
45. Buckley P, Miller A, Olsen J, Garver D, Miller DD, Csernansky J. When symptoms persist: clozapine augmentation strategies. *Schizophr Bull*. 2001;27(4):615-28.

46. Miller A, McEvoy J, Jeste D, Marder S. Treatment of chronic schizophrenia. In: Lieberman J, Stroup TS, Perkins D, editors. *Textbook of schizophrenia*. Washington DC: The American Psychiatric Publishing; 2006. p. 365-81.
47. Remington G, Saha A, Chong SA, Shammi C. Augmentation strategies in clozapine-resistant schizophrenia. *CNS Drugs*. 2005;19(10):843-72.
48. Shiloh R, Zemishlany Z, Aizenberg D, Radwan M, Schwartz B, Dorfman-Etrog P, Modai I, Khaikin M, Weizman A. Sulpiride augmentation in people with schizophrenia partially responsive to clozapine. A double-blind, placebo-controlled study. *Br J Psychiatry*. 1997;171:569-73.
49. Josiassen RC, Joseph A, Kohegyi E, Stokes S, Dadvand M, Paing WW, Shaughnessy RA. Clozapine augmented with risperidone in the treatment of schizophrenia: a randomized, double-blind, placebo-controlled trial. *Am J Psychiatry*. 2005;162(1):130-6.
50. Anil Yagcioglu AE, Kivircik Akdede BB, Turgut TI, Tumuklu M, Yazici MK, Alptekin K, Ertugrul A, Jayathilake K, Gogus A, Tunca Z, Meltzer HY. A double-blind controlled study of adjunctive treatment with risperidone in schizophrenic patients partially responsive to clozapine: efficacy and safety. *J Clin Psychiatry*. 2005;66(1):63-72.
51. Honer WG, Thornton AE, Chen EY, Chan RC, Wong JO, Bergmann A, Falkai P, Pomarol-Clotet E, McKenna PJ, Stip E, Williams R, MacEwan GW, Wasan K, Procyszyn R; Clozapine and Risperidone Enhancement (CARE) Study Group. Clozapine alone versus clozapine and risperidone with refractory schizophrenia. *N Engl J Med*. 2006;354(5):472-82.
52. Lindenmayer JP, Czobor P, Volavka J, Lieberman JA, Citrome L, Sheitman B, Chakos M, McEvoy JP; Internal Suicide Prevention Trial Study Group (InterSePT). Olanzapine in refractory schizophrenia after failure of typical or atypical antipsychotic treatment: an open-label switch study. *J Clin Psychiatry*. 2002;63(10):931-5.
53. Meltzer HY, Alphs L, Green AI, Altamura AC, Anand R, Bertoldi A, Bourgeois M, Chouinard G, Islam MZ, Kane J, Krishnan R, Lindenmayer JP, Potkin S. Clozapine treatment for suicidality in schizophrenia: International Suicide Prevention Trial (InterSePT). *Arch Gen Psychiatry*. 2003;60(1):82-91.
54. Tang WK, Ungvari GS. Efficacy of electroconvulsive therapy in treatment-resistant schizophrenia: a prospective open trial. *Prog Neuropsychopharmacol Biol Psychiatry*. 2003;27(3):373-9.
55. Rosa M, Gattaz W, Rosa M, Rumi D, Tavares H, Myczkowski M, Sartorelli M, Rigonatti SP, Elkis H, Cabral SB, Teixeira MJ, Marcolin MA et al. Effects of repetitive transcranial magnetic stimulation on auditory hallucinations refractory to clozapine. *J Clin Psychiatry* (accepted for publication).
56. Valmaggia LR, van der Gaag M, Tarrier N, Pijnenborg M, Slooff CJ. Cognitive-behavioural therapy for refractory psychotic symptoms of schizophrenia resistant to atypical antipsychotic medication. Randomised controlled trial. *Br J Psychiatry*. 2005;186:324-30.
57. Barretto E, Avrichir B, Camargo MG, Napolitano IC, Reis AS, Nery F, Banwart S, Elkis H. Randomized controlled trial of cognitive behavioral therapy for partial response to clozapine. *Schizophr Res*. 2006;81(Suppl S):101.