International Journal of Science and Research (IJSR)
ISSN (Online): 2319-7064
Index Copernicus Value (2013): 6.14 | Impact Factor (2014): 5.611

Treatment Response In Schizophrenia

Irena Thoma[1], Anastas Suli[2]

Psychiatric Service, University Hospital Centre ―Mother Theresa" Tirana, Albania

Abstract: ***Schizophrenia is characterized by a differential response to antipsychotic treatment based on stage of illness, with evidence that shorter duration of untreated psychosis isassociated with greater antipsychotic response.The aim of the study was to assess the clinical response to clozapine.The patients included in this study were those participating in a prospectively designed clozapine monitoring program (n = 202 subjects) who completed at least 52 weeks of treatment and had complete data records at Psychiatric Hospital, University Hospital Centre "Mother Theresa" in Tirana, Albania over the period 2013 -2014. In the study participated 102 subjects with a mean age 44.2 (±10.7) years with a range 22-74 years old.Thirty five (34.3%) were women and 67 (65.7%) men meeting both DSM-IV criteria for schizophrenia and Kane's criteria for drug-resistance.27 (26.8%) patients were classified as responders, 45 (44%) being refractory (Clozapine responders) and 30 (29.2%) super-refractory. The super-refractory group had the highest scores for totals of BPRS (p<0.01) in all visits.Treatment resistant schizophrenia remains a major personal tragedy and a publichealth problem.***

Keywords: schizophrenia, clozapine, super refractory, response,

1. Introduction

Clozapine is an early atypical antipsychotic, first synthesizedin 1958. Although it was formulated as part ofan effort to develop new antidepressants, preclinical workestablished its similarities to chlorpromazine, and it wasultimately evaluated for its potential antipsychotic properties(1). Even then, clozapine established itself as unique,as its low liability for extrapyramidal symptoms challengeda widely held notion at the time that clinical response wasintegrally linked to induction of extrapyramidal symptoms (2).Shortly after its release in the early 1970s, clozapine waslinked to a risk, albeit a low one, of agranulocytosis (1). Asa result, its use was markedly curtailed and a requirementfor mandatory blood monitoring was established in mostcountries. A seminal study in the late 1980s demonstratingclozapine's clinical superiority in refractory schizophrenia(3) established its position in North America as a treatmentof ―last resort," permitted only after the failure of otherantipsychotics and only in conjunction with routine hematologicalmonitoring.Despite the introduction of a number of newer atypicalantipsychotics over the past two decades, clozapineremains the treatment of choice in refractory schizophrenia,a position endorsed by various guidelines (4–7). As arule, clozapine is recommended only after incompleteresponse to two adequate antipsychotic trials, which isreflected in some product monographs. For example, inCanada clozapine can be prescribed only as a third-linetreatment (8), although in the United States it is permitted(although not recommended) as a second-line treatment (9).The criteria that define treatment resistance have beenmodified to reflect changes in recommended antipsychoticdosing guidelines that now advocate somewhat lowerdosages (10). Also, treatment criteria have been proposedfor ―ultra resistant schizophrenia," applicable to patients whodemonstrate a suboptimal response to clozapine (11).It is noteworthy that there remains hesitancy in prescribingclozapine for individuals with refractory schizophrenia.For example, a review of the Veterans Affairsdatabases for 1999–2006 indicated that while the atypicalantipsychotics were rapidly supplanting their conventionalcounterparts, clozapine use remained flat at 2%–3% (12).Other researchers have reported an average delay of 5 years inmoving to clozapine in the face of treatment resistance (13).Schizophrenia is characterized by a differential responseto antipsychotic treatment based on stage of illness, withevidence that shorter duration of untreated psychosis isassociated with greater antipsychotic response (14). Notwithstandingthe different trial designs and thresholds thatdefine clinical response, as well as nonpharmacologicalvariables such as adherence problems, studies of patientswith first-episode schizophrenia report response rates in the range of 40%–90% (15), although time toresponse increases and likelihood of response declinessubstantially in subsequent trials (16).

2. Material and Methods

The patients included in this study were those participating in a prospectively designed clozapine monitoring program (n = 202 subjects) who completed at least 52 weeks of treatment and had complete data records at PysychiatricHospital, University Hospital Centre ―Mother Theresa" in Tirana, Albania over the period 2013 -2014. In an effort to have consistent baseline conditions, before entering into the study, all the patients' psychoactive drugs except for typical antipsychotics were tapered and discontinued. After patients had been taken on this drug regimen for at least 2 weeks, baseline assessment was completed. Then, clozapine treatment was started with dose increments of 25–50 mg every 2 days to bring patients to the dose of 400 mg/day by the end of the week 2. Patients were taken at this dose regimen up to the end of week 4, when a second clinical assessment was performed. Those subjects meeting the response criteria (see below) were maintained on the 400 mg/day dose regimen up to the end of the study, whereas the remaining patients received further dose increments of 50 mg every 2 days to reach the maximum established dose of 600 mg/day by the end of week 6, and then were kept on this dose regimen up to week 52. Typical antipsychotics were rapidly tapered and discontinued during the first week of clozapine treatment. Clozapine was administered in 2–3 divided (and approximately equal) doses, with the last dose of the day given between 7:00 P.M. and 8:00 P.M. Patients were hospitalized up to the achievement of their maximum clozapine daily dose; then,

they were discharged and clozapine was administered at home by staff nurses, who carefully checked patients' compliance up to the end of the study.Psychopathological assessment was performed by means of the Expanded Brief Psychiatric Rating Scale (BPRS: 24 items and a scoring from 1 to 7) both before starting clozapine (baseline) and every 2 weeks up to week 52. Patients were a priori defined responders as they attained a 20% decrease in the BPRS total score plus a post-treatment BPRS score of 47 or less. These criteria had to be met at two consecutive rating points; responders were classified as such when they first met a priori criteria.The aim of the study was to assess the clinical response to clozapine.Results were expressed as mean ± SD and statistically assessed by analysis of variance (ANOVA) with or without repeated measures, post-hoc Tukey's test and $\chi 2$ (Chi-square) test with Yate's correction, where appropriate.

3. Results and Discussion

In the study participated 102 subjects with a mean age 44.2 (±10.7) years with a range 22-74 years old. Thirty five (34.3%) were women and 67 (65.7%) men meeting both DSM-IV criteria for schizophrenia and Kane's criteria for drug-resistance except one patient who did not met the Kane's criterion of duration of illness of at least 5 years. The mean duration of their illness was 23.4 years.Of the 102patients, 27 (26.8%) were classified as responders, 45 (44%) being refractory (Clozapine responders) and 30 (29.2%) super-refractory (fig. 1).The super-refractory group had the highest scores for totals of BPRS ($p<0.01$) in all visits (table 1).To date, only a few studies have addressed the characteristics of patients with super-refractory schizophrenia.An incomplete response to clozapine is the persistence ofpsychotic symptoms despite a trial of clozapine with adequatedoses (i.e. 300-900 mg/day) during a minimum of 8 weeksup to 6 months. Thus, the improvement of psychotic symptomsis considered the main treatment target and, as an apparentlogical consequence, it has been proposed the addiction ofhigh potency antipsychotics to clozapine for the treatment ofthese symptoms.It is estimated that approximately 30% of patients treatedwith clozapine do not respond adequately, remaining withpersistent psychotic symptomatology, despite having receivedadequate treatment for sufficient periods. Such patients arecalled ~~–~~partial responders to clozapine", ~~–~~clozapine resistant"or even ~~–~~super-refractory", and represent a challenge for thetreatment of RS, as well as a great economic burden (17).The treatment of these patients is problematic andpharmacological and non-pharmacological augmentationstrategies remain the only options for this population, despitethe lack of adequate evidence for efficacy (18). Many reviewshave been published describing in detail such strategiesthat will be summarized.Various antipsychotics were used supposedly to augmentthe antipsychotic properties of clozapine: amisulpride, aripiprazole, haloperidol, loxapine, olanzapine, pimozide, andziprasidone. The benefits of these augmentation strategiesremain inconclusive since they were tested in case series orcase reports, which have a low strength of evidence, ascompared with controlled trials (19). More robust evidence is derived from four placebo controlledtrials, one with sulpiride and three with risperidone and,due to their importance, they are summarized below (20). A study showed a significant improvement on positive andnegative symptoms in the group that received sulpiride addedto clozapine when compared with placebo group, and it waspproposed that this effect could be explained by the selectiveenhancement of D2 blockage by sulpiride (21). However, it is well known that risperidone has a strongaffinity for D2 receptors and the hypothesis that blocking thesereceptors would improve persistent positive symptoms in patientsresistant to clozapine was only supported by some studies which found no differences between risperidoneor placebo groups (22). Therefore, the hypothesis that adding a more potentantipsychotic to enhance or optimize D2 affinity, and thusimproving psychotic symptoms in poor clozapine responders,was not supported by the previous studies, and it is alsointeresting to point out that in the studythe placebo group showed a greater reduction in the PANSSpositive scores than the risperidone group (23).Finally, when clozapine augmentation with antipsychoticsfails, it has been proposed to switch to another antipsychotic.This strategy is considered to have a weak level of evidenceand olanzapine was the antipsychotic most frequently testedin some open trials

4. Conclusion

TRS remains a major personal tragedy and a publichealth problem. However, because so little is knownabout TRS and because the results of treatment are sovariable, it is essential to weight carefully the risk-benefitratio.Although atypical novel antipsychotics are bettertolerated than older drugs and may be more effective insome but not most TRS patients, no proven treatment exists for TRS. It is essential that, instead of increasing thedose and relentlessly adding and changing medications,or embarking upon unproven interventions, psychiatristsacknowledge to themselves and explain to frustratedpatients and family members, the limits of pharmacologicaltreatment. Otherwise, we run the risk of making abad situation worse by adding the suffering of adverseeffects to that of the illness.

References

[1] Kane J, Honigfeld G, Singer J, Meltzer H: Clozapine for the treatment-resistant schizophrenic: a double-blind comparison with chlorpromazine. Arch Gen Psychiatry 1988; 45:789–796
[2] Schizophrenia NICE: Core Interventions in the Treatment and Management of Schizophrenia in Adults in Primary and Secondary Care. NICE clinical guideline 82. London: National Institutefor Health and Clinical Excellence, 2009.
[3] American Psychiatric Association: Practice guideline for the treatment of patients with schizophrenia, second edition. Am J Psychiatry 2004; 161(Feb Suppl)
[4] Canadian Psychiatric Association: Clinical practice guidelines: treatment of schizophrenia. Can J Psychiatry 2005; 50(Suppl 1)
[5] Canadian Pharmacists Association: Compendium of Pharmaceuticals and Specialities (CPS). Ottawa, Canadian Pharmacists Association, 2012
[6] Physicians Desk Reference, 66th ed. Montvale, NJ, Thomson PDR, 2012

[7] Conley RR, Kelly DL: Management of treatment resistance in schizophrenia. Biol Psychiatry 2001; 50:898–911
[8] Mouaffak F, Tranulis C, Gourevitch R, Poirier MF, Douki S, Olié JP, Lôo H, Gourion D: Augmentation strategies of clozapine with antipsychotics in the treatment of ultraresistant schizophrenia. ClinNeuropharmacol 2006; 29:28–33
[9] Sernyak MJ, Rosenheck RA: Antipsychotic use in the treatment of outpatients with schizophrenia in the VA from fiscal years 1999 to 2006. PsychiatrServ 2008; 59:567–569
[10] Taylor DM, Young C, Paton C: Prior antipsychotic prescribing in patients currently receiving clozapine: a case note review. J Clin Psychiatry 2003; 64:30–34
[11] Perkins DO, Gu H, Boteva K, Lieberman JA: Relationship between duration of untreated psychosis and outcome in firstepisode schizophrenia: a critical review and meta-analysis. Am JPsychiatry 2005; 162:1785–1804
[12] Agid O, Arenovich T, Sajeev G, Zipursky RB, Kapur S, Foussias G, Remington G: An algorithm-based approach to first-episode schizophrenia: response rates over 3 prospective antipsychotic trials with a retrospective data analysis. J Clin Psychiatry 2011; 72: 1439–1444
[13] Boter H, Peuskens J, Libiger J, Fleischhacker WW, Davidson M, Galderisi S, Kahn RS; EUFEST study group: Effectiveness of antipsychotics in first-episode schizophrenia and schizophreniform disorder on response and remission: an open randomized clinical trial (EUFEST). Schizophr Res 2009; 115: 97–103
[14] Derks EM, Fleischhacker WW, Boter H, Peuskens J, Kahn RS; EUFEST Study Group: Antipsychotic drug treatment in first-episode psychosis: should patients be switched to a different antipsychotic drug after 2, 4, or 6 weeks of nonresponse? J Clin Psychopharmacol2010; 30:176–180
[15] Emsley R, Oosthuizen PP, Kidd M, Koen L, Niehaus DJ, Turner HJ: Remission in first-episode psychosis: predictor variables and symptom improvement patterns. J Clin Psychiatry 2006; 67:1707–1712
[16] Emsley R, Rabinowitz J, Medori R: Time course for antipsychotic treatment response in first-episode schizophrenia. Am J Psychiatry 2006; 163:743–745
[17] Schennach-Wolff R, Seemüller FH, Mayr A, Maier W, Klingberg S, Heuser I, Klosterkötter J, Gastpar M, Häfner H, Sauer H, Schneider F, Gaebel W, Jäger M, Möller HJ, Riedel M: An early improvement threshold to predict response and remission in first-episode schizophrenia. Br J Psychiatry 2010; 196:460–466
[18] Stauffer VL, Case M, Kinon BJ, Conley R, Ascher-Svanum H, Kollack-Walker S, Kane J, McEvoy J, Lieberman J: Early response to antipsychotic therapy as a clinical marker of subsequent response in the treatment of patients with first-episode psychosis. Psychiatry Res 2011; 187:42–48
[19] Girgis RR, Phillips MR, Li X, Li K, Jiang H, Wu C, Duan N, Niu Y,Lieberman JA: Clozapine v. chlorpromazine in treatment-naive,first-episode schizophrenia: 9-year outcomes of a randomized clinical trial. Br J Psychiatry 2011; 199:281–288
[20] Rosenheck RA, Davis S, Covell N, Essock S, Swartz M, Stroup S,McEvoy J, Lieberman J: Does switching to a new antipsychoticimprove outcomes? Data from the CATIE Trial. Schizophr Res2009; 107:22–29
[21] Howes OD, Vergunst F, Gee S, McGuire P, Kapur S, Taylor D: Adherence to treatment guidelines in clinical practice: study of antipsychotic treatment prior to clozapine initiation. Br J Psychiatry 2012, 201(6):481–485.
[22] Guyatt GH, Oxman AD, Kunz R, Brozek J, Alonso-Coello P, Rind D, Devereaux PJ, Montori VM, Freyschuss B, Vist G, Jaeschke R, Williams JW, Murad MH, Sinclair D, Falck-Ytter Y, Meerpohl J, Whittington C, Thorlund K, Andrews J, Schünemann HJ: GRADE guidelines 6. Rating the quality of evidence—imprecision. J ClinEpidemiol 2011, 64(12):1283–1293.
[23] Gallego JA, Bonetti J, Zhang J, Kane JM, Correll CU: Prevalence and correlates of antipsychotic polypharmacy: a systematic review and meta-regression of global and regional trends from the 1970s to 2009. Schizophr Res 2012, 138(1):18–28.

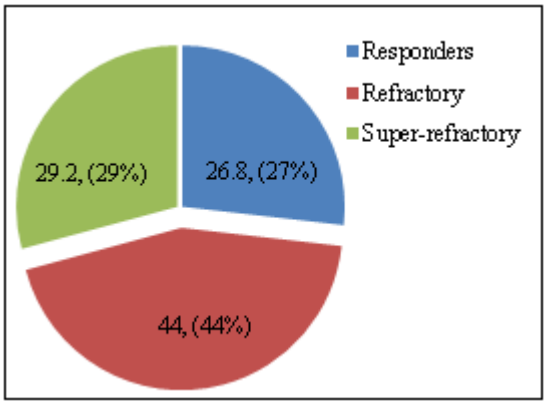

Figure 1: The response to treatment

Table 1: Mean BPRS score at baseline and at 1 year

	Baseline	Week 4	Week 8	Week 12	Week 24	Week 52
BPRS Total Score						
All responders	70.1 ± 13.1	54.2 ± 10.2	50.4 ± 9.9	42.3 ± 9.2	36.0 ± 6.9	35.1 ± 8.7
New responders at week 4	63.0 ± 4.7	40.5 ± 5.5	40.5 ± 8.3	35.5 ± 7.8	33.0 ± 7.9	33.0 ± 6.6
New responders at week 8	69.2 ± 10.8	52.1 ± 4.6	43.2 ± 2.3	38.6 ± 6.7	35.1 ± 9.1	31.0 ± 6.9
New responders at week 12	66.6 ± 5.1	58.1 ± 7.3	54.6 ± 5.1	39.2 ± 7.2	36.0 ± 7.2	34.4 ± 10.3
New responders at week 24	79.6 ± 19.7	62.1 ± 12.7	61.4 ± 13.4	54.4 ± 10.1	39.4 ± 7.6	41.3 ± 7.2
Super refractory	77.4 ± 18.5	68.6 ± 10.8	67.6 ± 12.5	61.6 ± 12.3	54.6 ± 4.8	60.0 ± 11.3