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IS NON-PHARMACOLOGICAL TREATMENT AN OPTION FOR CERTAIN SCHIZOPHRENIA PATIENTS?

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SUMMARY

Background: *Schizophrenia treatment has been debated at length and presently pharmacological treatment is being advocated as the most beneficial for patients. However, research has shown contradictory results regarding the suitability of pharmacological treatment for certain groups of schizophrenia patients.*

Methods: *The present review discusses results from the literature indicating good outcomes only for patients who adhered to prescribed pharmacological treatments. It also describes studies favoring non-drug treatments in certain schizophrenic patients.*

Results*: The authors described two groups of patients where the long-term use of neuroleptics may be useless, if not harmful. The first group comprised schizophrenic people with a single psychotic episode and therefore very good prognosis. In their case, the prolonged use of antipsychotics would not be beneficial due to pharmacological and social (stigma) side effects. Further research is warranted to identify and investigate biological, environmental, and psychological factors associated with single-episode schizophrenia. The second group comprised ultra-resistant schizophrenic patients. In their case, in the absence of a therapeutic response in acute episodes or aggressive behavior, clinicians should use short episodes of treatment with benzodiazepines or other sedative medications such as mood stabilizers.*

Conclusions: *The present paper attempted to answer the important question as to whether all schizophrenic people should be treated with antipsychotics for the same good prognosis. The authors have provided solutions for better outcomes in a greater number of patients using alternative treatment after identifying schizophrenic patients who should not receive neuroleptic treatment. Suggestions for future research are also discussed.*

Key words: *schizophrenia – neuroleptics - non-pharmacological treatment*

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INTRODUCTION

The first descriptions of symptoms resembling what is presently known as schizophrenia date back to approximately 2000 BC in the Book of Hearts, part of the ancient Egyptian Ebers Papyrus. During ancient Greek and Roman times, there appears to have been some awareness of psychotic conditions (Evans et al. 2003). Over time treatments varied and included exorcism, shamanism, and other remedies mentioned in Hippocrates and Galen recorded history. Regardless of the debate throughout the centuries on the nature of schizophrenia (evil/divine, disease/damnation) there has been a continuous search for therapy. Common cures of the times included caustics rubbed into open sores daily for months, bleeding leading to unconsciousness, liberal use of purges, simulated drowning, and near-starvation diets. More specific therapies such as drilling holes in the skull, the "swinging chair" (Irwin 2004), as well as cold baths, dialysis, lobotomies, and cingulotomy were also attempted. As bizarre as these treatments might seem today, at the time they all had their solid pathophysiological rationale, and benefited some, but obviously not the majority of the patients. The certainty of various therapists throughout times that the best treatment was being delivered to their patients, no matter how worthlessness, dangerous, or painful such treatment may be, represents an important lesson for today's clinicians, and a call for modesty.

The modern era of schizophrenia treatment began in 1952 with the discovery that chlorpromazine, an antihistamine drug used in anesthesia, had psychiatric clinical effects (Delay et al. 1952, López-Muñoz et al. 2005). Since then, the wide availability of chlorpromazine benefited many schizophrenia patients and being able to treat patients with psychotropic agents reunited psychiatrists with the rest of the medical profession (Cancro 2000). What followed was a plethora of new drugs designed to treat schizophrenia, broadly called antipsychotics or neuroleptics. These drugs ameliorated both acute symptoms and reduced the risk of the exacerbation of new ones (Davis & Casper 1977, Kane & Marder 1993, Janicak et al. 2001).

Since then, psychiatric textbooks and various guidelines (e.g., NICE guidelines) considered the treatment of schizophrenia with neuroleptics, the standard treatment for schizophrenia. Irrespective of whether the setting was in a hospital, in an outpatient clinic, or a community setting, antipsychotic medicines remained the primary treatment for schizophrenia. Some studies (McGorry et al. 2002) even advocate using them in youngsters who are at ultra-risk of developing schizophrenia; however, other studies do not (McDonald et al. 2004).

Neuroleptics cannot by any means be considered a "cure" for schizophrenia. More than half the treated patients (Klein & Davis 1969, Kane 1996) continue to show moderate to severe psychotic symptoms and about one third are persistently psychotic. The risk-benefit ratio is heavily affected by common adverse effects such as sedation, lethargy, movement disorders, weight gain, sexual dysfunction, and emotional-blunting. The risk-benefit ratio is further affected by less common but serious adverse conditions such as diabetes mellitus, blood dyscrasia, and lethal arrhythmias (Casey et al. 2004, Montout et al. 2002, Morgan et al. 2003). Moreover, the CATIE study revealed that a significant number of patients do not respond to treatment despite switching between drugs (Lieberman et al. 2005, Swartz et al. 2008). In the long-term, the best predictors of functionality in schizophrenia are cognitive functioning and negative symptoms (Green 1996) but not positive symptoms. Our present armamentarium for the treatment of schizophrenia, comprising either classical neuroleptics or atypical neuroleptics (Manschreck & Boshes 2007), is of limited importance in treating negative and cognitive symptoms, despite the initial enthusiasm about the superiority of atypical antipsychotics in treating negative and cognitive functioning.

Knowing the dimension of neuroleptic side effects, it becomes of great importance to identify schizophrenia patients who would benefit from non-neuroleptic treatment, regardless of how small this group may be.

Data suggesting better evolution of schizophrenic patients without antipsychotic agents

Murphy and Raman (1971) investigated 90 first-episode schizophrenic patients diagnosed with schizophrenia 12 years earlier (98% of people were available at follow-up; Murphy & Raman 1971). According to the investigators, 64% of the patients were asymptomatic and of these 92% had only a single psychotic episode. Moreover, patients who were employed at follow-up had a higher mean occupational status than that prior to their initial hospitalization. Importantly, none of these patients were treated with neuroleptics. The data above are consistent with some other studies regarding the long-term evolution of schizophrenia (Hopper & Wanderling 2000, Gupta et al. 2010).

In addition, in the largest randomized, double-blind study of chlorpromazine ever performed (344 patients; Schooler et al. 1967), when the patients were interviewed one year later, the authors found that placebo patients had better outcomes and significantly reduced rates of rehospitalisation. In a more recent study (Kua et al. 2003), the authors analyzed data for 402 people for a period of 20 years. Forty-eight percent were not receiving any treatment and those considered to have the best outcomes belonged to this group.

Letemendia and Harris (1967) randomized 28 people diagnosed with chronic schizophrenia (patients without any prior history of neuroleptic treatment) to chlorpromazine or placebo in a double-blind crossover design (Letemendia & Harris 1967). The duration of the study was 2.5 years and at the end of study, there were no statistically significant differences on any outcome measure, but trends consistently favored the placebo.

In another review of literature, Irwin (2004) compared the psychosocial interventions with neuroleptic treatment and concluded that, "long-term outcomes were statistically equivalent or superior in the nondrug group in all six studies, as well as those where the quality of the psychosocial treatment was questionable" (Irwin 2004).

In another study (Messier et al. 1969), 41 chronic schizophrenic patients who received medication showed better short-term outcomes while in the hospital, but 5 years later there were no statistically significant differences on any measures, with the trends favoring psychotherapy.

The Soteria project (Bola 2003, Mosher 1999) was one of the most interesting ventures designed specifically for minimizing medication-induced toxicities. The theoretical backgrounds of the authors of the Soteria project were the "recognition of significant rates of recovery without drug treatment in early episode psychosis, the observation that many patients do not benefit from medications (through drug treatment resistance and non-compliance), and a valuing of interpersonal care and treatment of mentally ill patients." The hypothesis that support the authors' theoretical backbone was constructed on the basis of studies indicating a placebo response rate for patients with acute schizophrenia ranging from 10% to 40% with a median of 25% (Dixon 1995), the long-term follow-up studies conducted prior to the widespread use of antipsychotic drugs reporting functional recovery rates greater than 50% (Ciompi 1980), and the fact that treatment resistance to antipsychotic agents is estimated to be 20% to 40% (Hellewell 1999). The Soteria project employed "predominantly extramedical treatment," which provided a "developmental crisis approach to recovery from psychosis." The treatment used "a small, home-like, intensive, interpersonally focused therapeutic milieu with non-professional staff that expected recovery and related with clients," and 76% (62 out of 82) received no antipsychotic medications during the initial 45-day period. Control facilities were well-staffed general hospital psychiatric units, where virtually all subjects (94%, 85 out of 90) were treated with continuous courses of antipsychotic medication. At the end of the study (two-year follow-up period), beneficial effects of the Soteria treatment were still evident.

It is of note that many of the studies presented above are older ones and may well be plagued by differences in schizophrenia definition or methodological issues. However, the conclusion of Harrow after a 15-year long study (Harrow et al. 2008) was that "patients with schizophrenia not on antipsychotic medication for a long period of time have significant better global functioning than those on antipsychotics."

Data suggesting superiority of neuroleptic treatment for schizophrenia patients

There is no doubt that the data are overwhelmingly in favor of continuous treatment with neuroleptics for schizophrenia and therefore we will not focus on this topic too much.

Hegarty (1994) and Davis (2003) reviewed the literature on maintenance treatment with conventional antipsychotic agents and found that the average relapse rate during the first year after hospitalization was 41% with active medication compared to 68% with a placebo.

The majority of studies comparing neuroleptics with a placebo for the treatment of schizophrenia are of short duration. Recent meta-analyses (Leucht et al. 2012a, Leucht et al. 2012b) clearly indicated that long-term treatment with neuroleptics is associated with improved quality of life, decreased hospitalization, decreased aggressive behaviors, and relapse prevention.

Patients not taking any antipsychotics apparently also have increased mortality (Tiihonen et al. 2009, Suvisaari et al. 2013) but not in all studies (Weinmann et al. 2009) and this fact may represent a very powerful argument for using long-term neuroleptic treatment in schizophrenia patients.

Putative sub-groups of schizophrenia patients who do not need long-term antipsychotic treatment

Despite various attempts (Rappaport 1978, Bola 2002), it is difficult to predict from the beginning of the disease the group of patients who will not benefit from treatment with neuroleptics. Nonetheless, the data above clearly shows some evidence of non-neuroleptic treatment in schizophrenia being associated with acceptable long-term outcomes. Thus, we can infer that there is also a place for non-neuroleptic treatment in schizophrenia, but this remains to be identified.

Referring again to Harrow's study, the main predictors of good evolution of untreated schizophrenic patients are a low vulnerability to anxiety, better cognitive functioning, good pre-morbid development, and some attitudinal variables. However, for the moment, due to the fact that these factors are too common, we cannot predict on their basis which patients do or do not need long-term neuroleptic treatment.

DISCUSSION

We will adopt therefore a more conservative approach and assume that there are two groups of patients where continuous neuroleptics treatment use may be useless if not harmful. The first group comprises single-episode schizophrenic people with very good prognosis. The second group comprises ultra-resistant schizophrenic patients.

I

Roughly 20% of patients with schizophrenia will experience only a single psychotic episode during their lifetime (Alvarez-Jimenez et al. 2011, Linszen et al. 2001, an der Heiden et al. 2000, Wiersma et al. 1998) and therefore life-long antipsychotic treatment would not be necessary. However, the predictors of single psychotic episode are too general (short duration of untreated psychosis, more rapid response to anti-psychotic treatment, and no parent loss) for making reliable predictions.

When compared with "usual" schizophrenia patients (with multiple psychotic relapses), this group of patients seems to have greater resiliency, better pre-morbid development, less vulnerability to anxiety, and better neurocognitive skills (Harrow et al. 2012, Dell'osso 2013). However, as observed, these factors are virtually identical with good prognosis factors identified in non-treated schizophrenic patients.

In our opinion, the identification of first-episode schizophrenic patients at minimal risk of psychotic relapse and therefore not needing long-term neuroleptic treatment, is of paramount importance both from a theo-retical (pathophysiology of schizophrenia) and practical (such as non-exposure to deleterious side effects of neuroleptics, economical, and ethical reasons) point of view.

Further research is warranted to identify and investigate biological, environmental, and psychological factors associated with single-episode schizophrenia. Thereby, the advantages would be the proper identification of schizophrenic patients with a unique psychotic episode and also the development of methods (both medication and psychological) for improving the clinical evolution of multiple-episode schizophrenia patients.

II

Another potential group who may benefit from non-pharmacological treatment for their schizophrenia are those with resistant/ultra-resistant schizophrenia. Usually, persistent moderate to severe positive symptoms are the core feature of resistant schizophrenia (Peuskens 1999). Other authors believe that different characteristic dimensions of schizophrenia, such as negative and cognitive symptoms, as well as the inability to return to the best pre-morbid level of functioning should be included (Meltzer & Kostacoglu 2001). According to various criteria, 30-60% of patients with schizophrenia are defined as having treatment resistant schizophrenia.

Compelling evidence (Taylor & Duncan-Mcconnell 2000, Chakos et al. 2001) has established clozapine as the drug of choice for resistant schizophrenia. Despite this, between 30% and 70% (Kane et al. 1988, Lieberman et al. 1994) of patients with the resistant form of schizophrenia will not respond in any clinically significant manner to the drug, and these patients are labeled as ultra-resistant patients or patients having Super Refractory Schizophrenia (Williams et al. 2002,

Buckley et al. 2001). Various treatment strategies in these populations have been employed such as clozapine combined with various antipsychotics, either typicals (Friedman et al. 1997, Mowerman & Siris 1996) or atypicals (Morera et al. 1999, Raskin et al. 2000), anticonvulsants (Kerwin & Bolonna 2005), lithium (Small et al. 1975), or benzodiazepines (Wolkowitz & Pickar 1991). However, in general the results are not very encouraging. Evidence for specific augmentation strategies are currently very limited, particularly in the form of controlled studies, but also uncontrolled studies. Furthermore, the number of treated individuals is routinely small (Remington 2005).

Moreover, such associations have the potential for extra-burden side effects for these patients. For this reason, these patients should be treated as vulnerable to a non-healthy ageing (Riga et al. 2012). In this particular group of chronic ultra-resistant schizophrenia patients plagued with significant side effects from the medication, it would be interesting to compare drug treatment with palliative care. This group of patients is very often treated with complicated regimens, usually with several neuroleptics in high doses, plus other medications, with limited benefit and the entire grim cohort of side effects. In the absence of a therapeutic response, clinicians may be tempted to increase the dose of neuroleptics or add new medications (sometimes a second or third neuroleptic). In view of this, it is possible that in these cases, neuroleptics simply do not work. For this group of patients, it would be worthwhile implementing some principles stemming from palliative care. The WHO definition of palliative care is, "active total care of patients whose disease is not responsive to curative treatment." Control of pain, other symptoms, and psychological, social, and spiritual problems is paramount. "The goal of palliative care is the achievement of the best quality of life for patients and their families" (WHO definition of palliative care 2002). Psychiatrists, particularly those working in hospitals, have a frequent need for interventions to calm and control behavior for the safety of the patient and/or the public. For many decades, prior to the discovery of neuroleptics, sedation was the standard method for calming and controlling psychiatric patients. For the above group of patients, part of their palliative care would be to use short episodes of treatment with benzodiazepines or other sedatives medications such as mood stabilizers only in cases of acute episodes or severe behavioral misconduct. There are some indications that benzodiazepine alone might be useful for acute psychosis in non-resistant schizophrenia patients (Carpenter 1999), suggesting that this could also be a potential strategy (among others) to use for patients with ultra-resistant schizophrenia, in case of acute psychosis. We are unaware of the existence of a good quality study assessing this issue but the therapeutic benefits of sedation should not be underestimated, partially because sedation can usually be achieved safely and without the severe side effects of neuroleptics, which are of no use in this group of patients anyway. Moreover, improving the quality of sleep would make patients feel and function better. Identifying patients with resistant schizophrenia and resistance to neuroleptics and using palliative care approaches for them could represent an important step in improving their treatment. Despite the difficulties of designing and implementing a study that would investigate alternative treatments for the population of patients described above, we strongly believe that such a study would be of great importance in improving the quality of life of patients with ultra-resistant schizophrenia.

CONCLUSIONS

Our paper raised the important question about which schizophrenic patients would not need neuroleptic treatment. The answer to this question is more complex than simply identifying schizophrenic patients where neuroleptics would be appropriate. Time factors should also be considered as some patients do not need neuroleptics at all, some patients need short-term neuroleptic treatment, and there will be situations where the decision to treat or not to treat a patient with neuroleptics will not be clear at all. Thus, the prevailing uncertainties in this area suggest the need for further research in order to enable psychiatrists to treat their patients with higher chances of achieving recovery.

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References

1. *Alvarez-Jimenez M, Gleeson JF, Henry LP, et al.: Prediction of a single psychotic episode: a 7.5-year, prospective study in first-episode psychosis. Schizophr Res 2011; 125:236–246.*
2. *an der Heiden W, Hafner H: The epidemiology of onset and course of schizophrenia. Eur Arch Psychiatry Clin Neurosci 2000; 250:292–303.*
3. *Bola JR & Mosher LR: At Issue: Predicting Drug-Free Treatment Response in Acute Psychosis From the Soteria Project. Schizophr Bull 2002; 28:559-575.*
4. *Bola JR & Mosher LR: Treatment of acute psychosis without neuroleptics: Two-year outcomes from the Soteria project. J Nerv Ment Dis 2003; 191:219-229.*
5. *Buckley P, Miller A, Olsen J, et al.: When symptoms persist: clozapine augmentation strategies. Schizophr Bull 2001; 27:615-28.*
6. *Cancro R: The introduction of neuroleptics: a psychiatric revolution. Psychiatr Serv 2000; 51:333-335.*
7. *Carpenter WRJ, Buchanan RW, Kirkpatrick B, et al.: Diazepam treatment of early signs of exacerbation in schizophrenia. Am J Psychiatry 1999; 156:299–303.*
8. *Casey DE, Haupt DW, Newcomer JW: Antipsychotic induced weight gain and metabolic abnormalities.*

Implications for increased mortality in patients with schizophrenia. J Clin Psychiatry 2004; 65(suppl 7):4-18.

9. *Chakos M, Lieberman J, Hoffman E, et al.: Effectiveness of second-generation antipsychotics in patients with treatment-resistant schizophrenia: a review and meta-analysis of randomized trials. Am J Psychiatry 2001; 158:518-26.*
10. *Ciompi L: Catamnestic long-term study on the course of life and aging of schizophrenics. Schizophr Bull 1980; 6:606–618.*
11. *Davis JM, Chen N, Glick ID: A meta-analysis of the efficacy of second-generation antipsychotics. Arch Gen Psychiatry 2003;60:553–564*
12. *Davis JM & Casper R: Antipsychotic drugs: clinical pharmacology and therapeutic use. Drugs. 1977; 14:260-82.*
13. *Delay J, Deniker P, et al.: Utilisation en therapeutique psychiatrique d'une phenotiazine d'action centrale elective. Ann Med Psychol 1952; 110:112-17.*
14. *Dell'osso B, Glick ID, Baldwin DS, et. al.: Can Long-Term Outcomes Be Improved by Shortening the Duration of Untreated Illness in Psychiatric Disorders A Conceptual Framework. Psychopathology 2013; 46:14–21.*
15. *Dixon LB, Lehman AF, Levine J: Conventional antipsychotic medications for schizophrenia. Schizophr Bull 1995; 21:567–577.*
16. *Evans K, McGrath J, et al.: Searching for schizophrenia in ancient Greek and Roman literature: a systematic review. Acta Psychiatrica Scandinavica 2003; 107:323-330.*
17. *Friedman J, Ault K Powchik P: Pimozide augmentation for the treatment of schizophrenic patients who are partial responders to clozapine. Biol Psychiatry 1997; 42:522-523.*
18. *Green MF: What are the functional consequences of neurocognitive deficits in schizophrenia? Am J Psychiatry 1996; 153:321–330*
19. *Gupta PR, Chakrabarti S and Kulhara P: Lack of association between duration of untreated psychosis and outcome in an Indian cohort. World Psychiatry 2010; 9:124–125.*
20. *Harrow M, Jobe TH, et al.: Recovery in a Subgroup of Patients With Schizophrenia Who Discontinue Antipsychotic Medications: A 15-Year Follow Up. APA Meeting, Washington, DC, 2008.*
21. *Harrow M, Jobe TH, Faull RN: Do all schizophrenia patients need antipsychotic treatment continuously throughout their lifetime? A 20-year longitudinal study. Psychol Med 2012; 42:2145–55.*
22. *Hellewell JS: Treatment-resistant schizophrenia: Reviewing the options and identifying the way forward. J Clin Psychiatry 1999; 60:14–19.*
23. *Hegarty JD, Baldessarini RJ, Tohen M, et al.: One hundred years of schizophrenia: a meta-analysis of the outcome literature. Am J Psychiatry 1994; 151:1409–1416.*
24. *Hopper K & Wanderling J: Revisiting the developed versus developing country distinc tion In course and outcome in schizophrenia: Results from ISoS, the WHO collaborative follow-up project. International Study of Schizophrenia. Schizophr Bull 2000; 264:835-846.*
25. *Irwin M: Reversal of Schizophrenia Without Neuroleptics. Ethical Hum Psychol Psychiatry 2004; 6:53-68*
26. *Irwin M: Treatment of Schizophrenia Without Neuroleptics: Psychosocial Interventions Versus Neuroleptic Treatment. Ethical Hum Psychol Psychiatry 2004; 6:99-110.*
27. *Janicak PG, Davis JM, et al.: Principles and Practice of Psychopharmacotherapy. Third Edition. Lippincot Williams & Wilkins, 2001.*
28. *Kane JM: Factors which can make patients difficult to treat. Br J Psychiatry 1996; 31:10-4.*
29. *Kane JM & Marder SR: Psychopharmacologic treatment of schizophrenia. Schizophr Bull 1993; 19:287-302.*
30. *Kane JM, Honigfeld G, Singer J, et al.: Clozapine for the treatment resistant schizophrenic: a double-blind comparison with chlorpromazine. Arch Gen Psychiatry 1988; 45:789-96.*
31. *Kerwin RW, Bolonna A: Management of clozapine-resistant schizophrenia. Adv Psychiatr Treat 2005; 11:101-106.*
32. *Klein DF & Davis JM: Diagnosis and Drug Treatment of Psychiatric Disorders. Baltimore, Williams & Wilkins, 1969.*
33. *Kua J, Wong KE, et al.: A 20-year follow-up study on schizophrenia in Singapore. Acta Psychiatr Scand 2003; 108:118-125.*
34. *Leucht S, Tardy M, Komossa K, et. al.: Maintenance treatment with antipsychotic drugs for schizophrenia. Cochrane Database Syst Rev 2012; 5:CD008016.*
35. *Leucht S, Tardy M, Komossa K, et al.: Antipsychotic drugs versus placebo for relapse prevention in schizophrenia: a systematic review and meta-analysis. Lancet 2012; 379:2063–2071.*
36. *Letemendia J & Harris AD: Chlorpromazine and the untreated chronic schizophrenic: A long-term trial. Br J Psychiatry 1967; 113:950-958.*
37. *Lieberman LA, McEvoy JP, Stroup S, et al.: Effectiveness of Antipsychotic Drugs in Patients with Chronic Schizophrenia N Engl J Med 2005; 353:1209-122.*
38. *Lieberman JA, Safferman AZ, Pollack S, et al.: Clinical effects of clozapine in chronic schizophrenia: response to treatment and predictors of outcome. Am J Psychiatry 1994; 151:1744-52.*
39. *Linszen D, Dingemans P, Lenior M: Early intervention and a five year follow up in young adults with a short duration of untreated psychosis: ethical implications. Schizophr Res 2001; 51:55–61.*
40. *López-Muñoz F, Alamo C, Cuenca E, Shen WW, Clervoy P, Rubio G: History of the discovery and clinical introduction of chlorpromazine. Annals of Clinical Psychiatry 2005; 17:113–35*
41. *Manschreck TC, Boshes RA: The CATIE schizophrenia trial: results, impact, controversy. Harv Rev Psychiatry 2007; 15:245–258*
42. *McGorry PD, Yung AR, Phillips LJ, et al.: Randomized Controlled Trial of Interventions Designed to Reduce the Risk of Progression to First-Episode Psychosis in a Clinical Sample With Subthreshold Symptoms. Arch Gen Psychiatry 2002; 59:921-928*
43. *McDonald C, Schulze K, Murray RM, et al.: Schizophrenia: Challenging The Orthodox. Taylor and Francis, London, 2004.*
44. *Meltzer H, Kostacoglu A: Treatment-resistant schizophrenia. In Lieberman J, Murray R (eds.): Comprehensive care of schizophrenia: a textbook of clinical management, 181-203. Martin Dunitz, 2001.*
45. *Messier M, Finnerty R, et al.: A follow-up stud y of intensively treated ch ronic schizophrenic patients. Am J Psychiatry 1969; 125:1123-11.*
46. *Montout C, Casadebaig F, Lagnaoui R, et al.: Neuroleptics and mortality in schizophrenia: a prospective*

analysis of deaths in a French cohort of schizophrenic patients. Schizophr Res 2002; 57:147-156.

47. *Morera AL, Barreiro P, Cano-Munoz JL: Risperidone and clozapine combination for the treatment of refractory schizophrenia. Acta Psychiatr Scand 1999; 99:305-307.*
48. *Morgan MG, Scully PJ, Youssef HA, et al.: Prospective analysis of premature mortality in schizophrenia in relation to health service engagement: a 7.5 year study within an epidemiologically complete, homogenous population in rural Ireland. Psychiatry Res 2003; 117:127-135.*
49. *Mosher LR: Soteria and other alternatives to acute psychiatric hospitalization. J Ment Nerv Dis 1999; 187:142-149.*
50. *Mowerman S & Siris SG: Adjunctive loxapine in a clozapine-resistant cohort of schizophrenic patients. Ann Clin Psychiatry 1996; 8:193-197*
51. *Murphy BP, Chung YC, et al.: Pharmacological treatment of primary negative symptoms in schizophrenia: a systematic review. Schizophr Res 2006; 88:5-25.*
52. *Murphy H- R & Raman AC: The chronicity of schizophrenia in indigenous tropical peoples: Results of a 12 year follow-up survey in Mauritius. Br J Psychiatry 1971; 118:489-497.*
53. *Peuskens J: The evolving definition of treatment resistance. J Clin Psychiatry 1999; 60(Suppl 12):4-8.*
54. *Rappaport M, Hopkins HK, Hall K et al.: Are there schizophenics for whom drugs may be unnecessary or contraindicated? Int Pharmacopsychiatry 1978; 13:100-111.*
55. *Raskin, S, Katz, G, Zislin, Z, et al.: Clozapine and risperidone combination/ augmentation treatment of refractory schizophrenia: a preliminary observation. Acta Psychiatr Scand 2000; 101:334-336.*
56. *Remington G, Saha A, Chong SA: Augmentation Strategies in Clozapine-Resistant Schizophrenia. CNS Drugs 2006; 19:843-872.*
57. *Riga D, Riga S, Motoc D, Geacar S, Ionescu T: Health-longevity medicine in the global world. In Maddock (ed.): Public Health - Methodology, Environmental and System Issues, 347-366. InTech - Open Access, 2012.*
58. *Schooler NK, Goldberg SC, et al.: One year after discharge: Community adjustment of schizophrenic patients. Am J of Psychiatry 1967; 123:986-996.*
59. *Swartz M, Scott Stroup T, et al.: Special Section on Implications of CATIE: What CATIE Found: Results From the Schizophrenia Trial. Psychiatric Services 2008; 59:500-506.*
60. *Small JG, Kellams JJ, Milstein V, et al.: A placebo-controlled study of lithium combined with neuroleptics in chronic schizophrenic patients. Am J Psychiatry 1975; 132:1315–1317.*
61. *Suvisaari J, Partti K, Perälä J, et al.: Mortality and its determinants in people with psychotic disorder. Psychosom Med 2013; 75:60-7.*
62. *Taylor DM, Duncan-Mcconnell D: Refractory schizophrenia and atypical antipsychotics. J Psychopharmacol 2000; 14:409-18.*
63. *Tiihonen J, Lonnqvist J, Wahlbeck K, et al.: 11-year follow-up of mortality in patients with schizophrenia: a population-based cohort study (FIN11 study). Lancet 2009; 374:620–627.*
64. *Weinmann S, Read J, Aderhold V: Influence of antipsychotics on mortality in schizophrenia: systematic review. Schizophr Res 2009; 113:1-11.*
65. *WHO definition of palliative care. http://www.who.int/cancer/palliative/definition/en/. 2002.*
66. *Wiersma D, Nienhuis FJ, Slooff CJ, Giel R: Natural course of schizophrenic disorders: a 15-year follow up of a Dutch incidence cohort. Schizophr Bull 1998; 24:75–85.*
67. *Williams L, Newton G, Roberts K, et al.: Clozapine-resistant schizophrenia: a positive approach. Br J Psychiatry 2002; 181:184-7.*
68. *Wolkowitz OM & Pickar D: Benzodiazepines in the treatment of schizophrenia: a review and reappraisal. Am J Psychiatry 1991; 148:714–726.*

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