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**Should Antipsychotic Medications For Schizophrenia**

**Be Given For a Lifetime? A Naturalistic Follow Up Study**

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**Abstract**

Introduction

Schizophrenia remains a major health problem despite antipsychotic medications that for most patients, can decrease acute symptoms, decrease relapses, and contribute to partial and sometimes strong positive response in chronic patients. What has not been clear – since a double-blind, randomized, placebo controlled trial is not feasible or ethical, is how many years after the initial episode, or onset of antipsychotic treatment to continue medication to achieve the best global outcome. We designed a small, clinical study to retrospectively do a detailed follow-up to examine antipsychotic medication as it relates to both global outcome and to life satisfaction.

Methods

This is a naturalistic study of 35 patients with chronic schizophrenia examining antipsychotic medication adherence from 8-50 (average 21) years after onset of antipsychotic treatment. The sample was derived from all patients treated over many years in one physician’s academic clinic. Most were treated by community physicians prior to referral to the academic clinic. Information was gathered on 1) medication adherence, 2) long-term global outcomes (based on both the patient ratings as well as a blind-clinician’s assessment (blind to medication data) on both a Global Outcome Scale and the Global Assessment of Function scale) and 3) a patient-rated Satisfaction with Life Scale. Spearman’s rank order correlations were used to relate medication adherence to global outcomes and life satisfaction, as were linear regression models adjusted for demographic and clinical characteristics.

Results

A total of 35 patients, mean age 45, and mean 21 years of possible medication since onset of treatment were assessed. Medication adherence was a statistically significant predictor of better long-term global outcomes and life satisfaction, both in Spearman’s rank order correlations and in covariate-adjusted linear regressions (all p-values <0.01). Poor medication adherence was associated with poor outcomes, often disastrous, with low life satisfaction. Other variables such as presence of substance use disorders or family support did not explain the difference between those who adhered and those who didn’t.

Conclusion
In this naturalistic study, patients who adhered to antipsychotic medication had better long-term global outcomes than those that had poor adherence. Study limitations include the potential for residual confounding. This sample provides data consistent with the recommendation for long-term, continuous antipsychotic treatment for chronic schizophrenia.

Schizophrenia remains a major health problem despite effective medications that, for most patients, can decrease acute symptoms, decrease relapses, and contribute to a partial, and sometimes strong, response in chronic patients.1

Our responsibility as physicians is to plan a long-term course of treatment – possibly for life – for patients with chronic symptoms based on their life circumstances. At some point during the medication treatment, we need to ask whether to continue, and if so, for how long. Most of the current evidence shows a positive correlation between taking medication for at least one-to-two years and good health outcomes. Some studies report outcomes correlated with medication continuation as long as six years1 but other clinicians argue against lifelong medication.

The best way to answer the question of efficacy would be a controlled, random-assignment study following the first episode, in which one group of patients with schizophrenia continues adequate (i.e., dose and duration) antipsychotic treatment over their lifetime and the other group is discontinued after acute treatment and stabilization. That study will never be done for ethical, practical, and financial reasons.

A review of the literature revealed four long-term follow up studies completed before modern antipsychotic treatment 3,4,5,6. However, no data could be found on patients with a clinic or a physician, who implemented both brief supportive psychotherapeutic and adequate medication treatment in carefully diagnosed patients with schizophrenia over many years. Since the advent of modern antipsychotics in the 1950s, there has been no report of medication and outcome over the long-term course, i.e., 6 or more years after initial medication treatment in well-managed patients – including some of whom stayed in treatment and some who dropped out. Despite what has been reported in the literature, the question is, “is a dismal long-term outcome the destiny for most patients with schizophrenia?”

**Methods**

Overall Design

This was a retrospective, naturalistic, 8-45 year follow up of a consecutive series of patients with chronic schizophrenia treated usually after the acute episode by one clinician in an academic clinic for 17 years from 1993-2010, and later on for 5 years in a private practice setting. Most of the patients were treated by other clinics prior to referral to Stanford. Data was collected on lifetime medication adherence, subsequent long-term global outcome, life satisfaction, plus demographic and clinical characteristics. Data collection consisted of “clinician’s notes/memory,” supplemented by chart review, followed by direct phone or in-person interviews with patients and/or their families/significant others – all in 2015, at least 8 years since initial diagnosis and onset of antipsychotic treatment -- usually 20-30 years since symptoms started.

Study Oversight

The primary objective of the present study was to determine if better medication adherence correlated with global outcome and life satisfaction. Other premorbid correlates like “asociality” or other treatments like psychotherapy, were not assessed. This study was designed by the first author and was approved by an independent review board. All patients or family members provided informed, verbal consent for retrospective data collection at the time of the interview in accordance with institutional and federal guidelines.

Setting and Participants

In order to secure as large a sample of patients as possible with a confirmed DSM-TR diagnosis of schizophrenia, all consecutive patients were included from the clinician’s practice from the Stanford Schizophrenia Clinic (one patient from UCSF was included). All patient files in the clinic, not just from one clinician, were examined and individuals were contacted, who met the following criteria:

1) Age 29 or over (since florid symptoms for the disease usually shows in the teens or early 20s, we wanted a sample who had longer than most 2-year follow-ups, in this study at least 8 or more years of possible medication use).

 2) DSM-IV-TR diagnosis of schizophrenia with no secondary diagnosis such as autism, developmental disorder, or childhood schizophrenia, because these would have confounded outcomes. Seven patients had a secondary diagnosis of substance use disorder, including alcohol and/or illegal drugs, were included. Others experimented with alcohol or drugs, mostly early on in their lives, disease or during treatment.

3) At least one year of antipsychotic treatment in adequate doses regardless of whether the patient subsequently adhered to treatment. As such, we did not include acute patients who stopped treatment soon after starting medication.

4) Able to give informed consent. If the patient was deceased or was considered grossly disordered, information from a significant other, typically a family member (well known to the clinician and/or with whom he had worked with in the past), was included.

We were able to interview 33 of the 35 who had been in regular, ongoing treatment at SUSM over seventeen years – one moved with no forwarding address, and another patient had suicided, but we were able to interview his mother (see below, Narrative).

Upon leaving SUSM, 17 chose to continue in private practice with the clinician. Administratively, the other half of patients continued to receive treatment with an experienced psychiatrist at SUSM and received excellent care. No patients, except for the unable-to-reach case, were eliminated from the clinician’s complete files. Thus, 35 patients included in the present study were all the long-term patients treated, contacted, consented, and interviewed by the clinician. The tradeoff for being able to actually collect a large enough sample to do meaningful data analysis, was that this may be a “better prognosis” group.

Measurement Instruments

*Sample Demographics (Table 1)*

* Demographic data – Age, gender, race, and marital status.
* Substance use – Presence of substance use disorder fulfilling DSM-IV-TR criteria.
* Medication history – This focused on the number of years of possible antipsychotic treatment. The clinician’s prescribing practices were aimed at assuring the patients received adequate antipsychotic doses (dose was flexible, but duration was always prescribed as continuous) including patients on clozapine. Psychotherapy was brief, supportive individual therapy with family intervention as indicated.
* Family support – Rated by patient from 1 (no support) to 10 (very supportive over the entire course of treatment).

*Adherence Variable(Table 1)*

* Medication adherence (Table 2) – This is a patient-assessed rating of their adherence to medication as prescribed and checked against patient charts and reports from their significant others. The scale is from 1 (mostly not adherent), 5 (mixed) to 10 (very adherent). We dichotomized adherence (our bias was that antipsychotic treatment must be continuous) as poor-fair, 8 patients scored from 1-8 on the 10 point scale. Twenty-seven patients scored good or excellent (9 or 10 on a 10 point scale).

*Outcome Variables (Table 2)*

Global outcome was assessed on two scales each rated by both the patient and the blind clinician, blind to “patient adherence.”

* Global Outcome Scale (GOS) – This patient-rated scale examined long-term symptoms, relapse, social relationships with friends and family, and work/school performance from the time medication started. The scale is from 1 (severe symptoms, poor functioning and multiple hospitalizations), 5 (mixed), and 10 (excellent with some symptoms, fair functioning, and few/no hospitalizations). The nonblind clinician provided a verbal summary of the patient’s life course and functioning to the blinded clinician who made independent scores. There was a high correlation between the patient and blinded clinician ratings.
* Global Assessment of Functioning (GAF)7,8 – This standardized rating is based on the blind rater’s judgment of the patient’s social, occupational, and psychiatric functioning, i.e. their “life history.” The scale is from 1 (poor) to 100 (superior).
* Satisfaction with Life Scale9 (SLS) – Patients were asked to rate the question “How satisfied are you with your life?” from 1 (terrible) to 7 (delighted) on this standardized scale.

The non-blind clinician collected the data from patient, family, and charts, while an academic faculty member with extensive experience in schizophrenia research and treatment (JB) was the blind rater of global outcome both on the GOS and GAF

Intervention:

All patients were prescribed “typical” and “atypical” antipsychotics.

Statistical Analyses

The hypothesis was that patients who reliably adhered to their medication would have better global functioning and life satisfaction than those who failed to take medication in a reliable manner.

We used Spearman’s rank order correlation to test the associations of medication adherence to each of the outcome variables. We also tested whether all background variables were associated with each outcome. Finally, we used linear regressions to evaluate the association of adherence to each outcome, adjusting for the background variables.

**Results**

Table 1 shows demographic variables at the time of the interview for the 35 patients. Roughly 80% of the group was single, white, male, and not prone to substance abuse. The group was middle-class with an average age of 45 and with an average of 21 years of antipsychotic treatment. The study showed that the group had a very positive average score of family support (8.5/10).

Table 2 shows the descriptive statistics for medication adherence and health outcomes. The group had a very high average medication adherence (8.8/10, SD 2.4) and generally good global health outcomes for schizophrenia. Both patient and clinician ratings were similar for GOS (6.1, SD 2.5 and 5.3, SD 2.0, respectively) where the Spearman’s rank order correlation was 0.83. The Clinician Global Assessment of Function was 48.6/100, SD 15.1.

Correlation of Medication Adherence and Global Outcome Variables

Figures 1 shows the distribution for the patient’s rating of global outcome (top left), clinician’s rating of GOS (top right) and GAF (bottom left) against medication adherence. The dots are divided into three categories (poor, fair, and good) for each outcome measure. A GOS score of 1-4 was poor, 5-7 was fair (meaning about average for patients with schizophrenia), and 8-10 was good (beyond what most clinicians would expect for chronic schizophrenia). A GAF score of 1-40 was poor, 41-70 was fair, and 71-100 was good. Table 3 and the figures illustrate that patients with poor medication adherence were distributed more toward poor outcomes, whereas patients with good medication adherence were distributed more toward fair outcomes. All Spearman’s rank correlations were significant at the alpha=0.05 level.. A higher medication adherence score was associated with better outcome measures, with some patients looking “normal” to outside observers.

Correlation of Adherence and Life Satisfaction

Two satisfaction scores were eliminated from patients, who were continuously psychotic with delusions and without insight, and who were completely nonfunctional socially and vocationally. Table 2 shows that the sample mean was 5.2, SD 1.4. Those who adhered to medication were more satisfied with their lives (Spearman rank order correlation was 0.37, p=0.036, n=33).

Figure 1 (bottom right) shows the distribution of ratings for the Satisfaction with Life scale against medication adherence. The low-adherent patients were evenly split between being satisfied and unsatisfied with their lives, whereas nearly all of the adherent patients had between “delighted” and “mixed” satisfaction.

Does Substance Abuse and Family Support Explain the Outcomes?

There were seven patients with a DSM-IV-R diagnosis of substance use disorder in their lifetime including alcohol, marijuana, methamphetamine, cocaine and/or crack cocaine. Overall, there was no statistically significant correlation of substance abuse with global outcome or life satisfaction (Spearman’s rank correlation p-values all greater than 0.11).

There was good family support for the majority of patients. A few patients had no family and some of those had good outcomes. Overall, there was no statistically significant correlation of family support with the GOS, GAF or life satisfaction (Spearman’s rank correlation p-values all greater than 0.16).

In order to test whether substance abuse family support or other patient characteristics explained the association of medication adherence with any of the outcomes, we included them in regression models as covariates. When family support, substance abuse, age, marital status, race and number of years in treatment were included in regression models as covariates, they did not influence the association of medication adherence with any of the outcomes. Table 3 shows that the adjusted regression coefficients are essentially the same as the crude associations. The relationship of medication adherence adjusted for these background variables to these four outcomes was statistically significant.

**Discussion**

Among these 35 patients, there was a strong correlation of medication adherence with better global outcome. There was no obvious difference in long-term side effects like weight gain or EPS between patients who had different adherence patterns. Patients with substance use disorders had slightly lower outcome scores than those without substance use disorders as did patients who “stopped and started” medication. Family presence/emotional support was not correlated with better outcome.

In this naturalistic study, about a quarter of the patients with good adherence expressed a reasonable, good outcome (see Narrative 1 below) but four of the five patients who had disastrous outcomes were noncompliant (see Narrative 3). In the intermediate outcomes, 7%, were doing about as good as they (and we) could expect given the functional severity of schizophrenia (Narrative 2). We note three of the less-adherent patients in the sample had fair outcomes.

There are important limitations to this study. First of all, the sample size may seem small – but to be able to get valid data from patients with chronic schizophrenia treated with adequate medication over a lifetime, this is relatively a large sample. Possibly this is a “better prognosis” sample, i.e. patients who stayed in treatment over many years with one physician – although there were other psychiatrists early on involved over the lives of these patients before they reached our clinic. The issue was to select a sample that was likely to have had adequate treatment prescribed (but not necessarily adhered to) over the lifetime course of their illness and then determine if outcome was better, i.e. reasonable, for those who stayed on medications versus those who stopped medication completely or partially over time. The clinicians involved believed the sample was “typical” for chronic schizophrenia in an academic or VA clinic, but we have no data to support this judgment. It is possible the results are confounded by severity of illness – that is, the less severe patients may have done better and vice versa. Likewise, the observable heterogeneity in the course may have been indicative of underlying genetic severity differences, or much less likely, from different non-medication treatments like psychotherapies, e.g. individual, family or group therapy given to some patients.

A further issue was accuracy of information on medication dose, duration, and compliance. Knowing the patients, as the clinician did, and interviewing them in person or on the phone, as well as cross-checking with charts and significant others, he was reasonably sure the information was largely accurate. Also, medication blood levels and number of pills were not measured in order to verify that patients were adherent. Likewise, the report of patient lives retrospectively could be distorted negatively or positively. However, the clinician saw most of these patients and their significant others usually monthly or in regular visits over time, so the distortion should have been minimal. Finally, we also judged that the fact that most patients were treated by the same clinician, and had a strong bond over time, with a good therapeutic relationship did not account for the results.

We have presented several narratives to make clear the kind of outcomes patients with schizophrenia might expect. By way of illustrating the difference of consistent adherence to medication vs being on-and-off medication, one African-American male patient with 30-plus years of schizophrenia volunteered:

“It’s best to take your medication for a lifetime. If you don’t, you get a change in mood (it drops), get suicidal, or you get into recreational drugs or bad things. The disease can bury you. Antipsychotic drugs keep your level even when stressed, like having no money. You can be more patient and calm. My family is a lot happier if I’m taking my meds.”

**Long-term Global Outcome Narratives**

1. Good Outcome

Mr. G is a 48-year-old single Hispanic male who developed schizophrenia as a late teenager. He developed more severe symptoms and started treatment at age 28. He has been on adequate doses of antipsychotics for 20-plus years. He rated himself 9 out of 10 on adherence, has minimal positive symptoms, works as a librarian half-time, relates well to a few friends, but reported he was “not into dating.” He rated himself 6/7 on life satisfaction, and we rated him 10 out of 10 on family support over the years.

2. Intermediate-Fair Outcome

Ms. K is a 41-year-old divorced female, who was diagnosed and first treated at age 26, while married with one child. She and her husband separated due in part to her paranoid symptoms. After starting antipsychotics, her symptoms decreased and she regained the rights to visit her child regularly who was living with her husband. She was unable to finish graduate school, but did get a full time job as a “medical assistant.” She still is somewhat paranoid, but has friends, occasionally dates, and has a good relationship with her family. She rated herself 6/7 on life satisfaction.

3. Poor Outcome

Mr. C was a 42-year-old white single male, who flunked out of college when his delusional symptoms started and he drank heavily for several years before getting into treatment in his 20s. On antipsychotics, he was able to have a supportive relationship with his mother, lived on his own, but did not have friends and stated he could not find work as he had lost his license secondary to a DUI. After fifteen years, he stopped seeing his doctor and stopped medications. He committed suicide by hanging himself. Although his family support was strong, his satisfaction with life was very low (2/7) according to his mother.

Our clinical experience demonstrated that except for a few patients who dropped-out early – all the patients who continued in treatment and took medications – had a reasonable outcome or did as well as they could with their illness (given their history of substance abuse). Of the patients who did not take medications, no one had a good outcome – rather they were equally split between intermediate and poor outcomes. And of course, other patient characteristics such as number of hospitalizations, age at first episode, remission status, could have influenced the results.

**Summary and Conclusion**

We believe this long-term clinical study is a useful addition to the field. In our experience the course of schizophrenia is not dismal given adequate medication treatment and good adherence. As such, we cautiously suggest we as clinicians might feel comfortable suggesting long-term, perhaps even lifetime, antipsychotic treatment for this destabilizing illness that affects patients and their families as well as the broader society.

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