BASIC ANALYSIS FOR TRIAL DATA PART ONE

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Introduction

The evidence for the pharmacological treatment of schizophrenia evolves constantly. Some of the key sources of aggregated evidence are:

- The Cochrane Community frequently produces many rigorous systematic reviews of evidence for medical interventions, including pharmacological, psychological and novel interventions for schizophrenia (Cochrane, 2017).
- The Maudsley Guidelines (Taylor et al., 2015) are a key resource
- In the UK, all interventions need to be implemented in accordance with practice recommendations from the National Institute for Health and Care Excellence (NICE) whose guideline for schizophrenia and psychosis (NICE, 2014) periodically reviews current evidence for the choice of medications

However, to be able to interpret *source* evidence beyond that presented in aggregated or systematic reviews, you will need to be familiar with some common statistical methods. To explore this, we'll review (Kane et al., 1988) which compared the second-generation medication clozapine to the first-generation chlorpromazine, and is a landmark paper in the pharmacological treatment of schizophrenia.

Approach and Assumptions

It is assumed that you have a basic grounding in statistical concepts and have some familiarity with common inferential tests. For example, we'll assume that you have heard of analysis of variance (ANOVA), hypothesis testing, p values, and have seen a linear regression analysis but we do not assume comprehensive understanding – we'll briefly review them as we proceed. Here, we will frame inferential analyses, like ANOVAs, in terms of linear models more generally, and our focus will be on using these concepts applied to a specific and landmark paper on the pharmacological treatment of schizophrenia.

We begin by considering how outcomes are commonly defined for randomised trials in psychiatry. We'll briefly touch on issues around trial design including inclusion criteria, assignment to treatments and blinding but our emphasis remains on the statistics used. Then, we will (in some detail) tease apart the different

components of linear models – applied to the data – trying to understand *what* the model actually does in terms of modelling outcomes using categorical variables that represent treatments and time points. We provide some sample data which you can use to follow the examples given using your preferred statistics package. Brief guides to using SPSS are given so that you can reproduce the analyses presented.

Clozapine and Treatment Resistant Schizophrenia

Many patients *do not* respond to treatment with either first- or second-generation antipsychotic medications and the reasons why are poorly understood. However, clozapine appears to be particularly efficacious in people who have failed to show response to two or more alternative medications. Such patients are described as having treatment-resistant illness. Clozapine's use is complicated by serious side-effects that are difficult to predict and potentially life-threatening, so if clinicians and patients are to use it with confidence, there must be assurances that it is effective. The paper by Kane et al. provides evidence of its efficacy compared with the first-generation medication chlorpromazine that was one of the cornerstones of pharmacological treatment.

Patient Inclusion Criteria

In (Kane et al., 1988), the definition of treatment resistance and the inclusion criteria for the study were:

1. at least three periods of treatment in the preceding five years with neuroleptic agents (from at least two different chemical classes)
2. at dosages equivalent to or greater than 1000 mg/day of chlorpromazine for a period of six weeks
3. each preceding trial of medication provided no clinically significant symptomatic relief
4. there has been no period of good functioning within the preceding five years.

The term **neuroleptic** arises from the work of Jean Delay and Pierre Deniker in the 1950s and for our purposes, can be considered synonymous with **antipsychotic**

It remains common practice to compare different antipsychotics in terms of their equivalence to a total dose of the first-generation medication **chlorpromazine** – there are many methods for calculating such equivalents and there is no single gold-standard (Patel et al., 2013)

Further, patients had to meet the following symptom-severity criteria:

1. a total Brief Psychiatric Rating Scale (BPRS) score of at least 45
2. scores of at least 4 on BPRS items (representing moderate severity) were required on two of the following four BPRS items: conceptual disorganization, suspiciousness, hallucinatory behaviour, and unusual thought content
3. minimum Clinical Global Impressions (CGI) Scale rating of 4 (moderately ill)

The **BPRS** system (Overall and Gorham, 1962) provides a quantified assessment of 24 features of psychotic illness with each item scored between 1 (absent) and 7 (extremely severe). The highest total score is therefore 168 and the lowst score 24

The **CGI** scale (Guy, 1976) is an overall clinician-rated summary measure taking into account the patient's history, psychosocial situation, current symptom severity/behaviour and the impact on daily function. The score ranges from 1 (normal) to 7 (extremely ill).

Treatment Protocol

A total of 319 patients (Kane et al., 1988) were first selected according to the criteria above, and then:

1. all n=319 patients received a baseline placebo for upto 14 days
2. n=305 patients were eligible to participate in the first phase of treatment with haloperidol for upto 42 days
3. n=272 patients who remained in the study where then given placebo for for upto 7 days as a washout
4. n=268 eligible patients were randomised to either chlorpromazine and benztropine mesylate (n=142) or clozapine (n=126)

Because patients were being switched from one medication to another, this period allows for the existing medication to be eliminated. Oral haloperidol has a terminal elimination half-life of apprximately 14 to 37 hours (Kudo and Ishizaki, 1999) but has been found in human brain tissue for around 6.8 days (Kornhuber et al., 2006)

Of note, the study used a double-blind protocol, so neither the patients nor the clinicians assessing response knew the assignment of patients to medications.

There are signs associated with different medications' side effects which might identify that a patient is assigned a specific medication, and this could break the blinding; clozapine is associated with hypersalivation and chlorpromazine with more extra-pyramidal side effects (EPSEs) - you should identify the steps taken in (Kane et al., 1988) to counter this

Defining Outcome

The outcomes used in (Kane et al., 1988) are derived from changes in the patient's BPRS score after a period of treatment. Importantly, they recognised that a even a minor change in the BPRS score could be statistically significant, but have no clinical relevance. For example, of the 126 patients in the clozapine group, if a majority improved by 3 points with a standard deviation of 1 on their total BPRS and the 139 patients in the chlorpromazine group improved by 1 point with a standard deviation of 1, then clozapine could be shown to be superior according to statistical significance; for example, inferential analyses yield results with p-values less than 0.05. However, clinically, such a change is irrelevant, representing only negligible improvement.

Note that the BPRS score is a **continuous** variable and this is true of most quantitative assessments used clinically – where the patient's total score (or the change in this value) is used as an outcome measure. Clinicians usually value evidence where the outcome is framed as a treatment "success" or "failure" so it is common practice to define a **binary** outcome which for (Kane et al., 1988) was:

1. a patient is defined as improved if their total BPRS score was reduced by greater than 20% from baseline
2. additionally, there must be either
   (a) a post-treatment CGI scale score of at most 3 (mild)
   (b) a post-treatment BPRS total score of 35 or lower.

If a patient meets criteria 1 *and* either 2a *or* 2b, then they are designated a "successful" outcome, otherwise, the treatment is considered a failure.

Questions and Exercises

With reference to the paper (Kane et al., 1988):

1. The double-blinding of the study required that patients were given either clozapine, or chlorpromazine *and* benztropine mesylate. Why is this necessary ? (*Hint*: consider the side-effect profiles of the second-generation clozapine versus the first-generation chlorpromazine)

2. Kane et al. claim they have prospectively evaluated treatment resistance – meaning that patients recruited to the study were first trialled on one other antipsychotic medication (haloperidol) *before* being assigned randomly to clozapine / chlorpromazine.

   (a) How many patients turned out to be responsive to haloperidol?

   (b) What factors might explain why patients who were enrolled, assumming poor response to treatment, *then* turned out to be responsive to a first-generation antipsychotic?

References

Cochrane (2017). Cochrane Database of Systematic Reviews: Schizophrenia Group. http://www.cochranelibrary.com/review-group/Schizophrenia%20Group/.

Guy, W. (1976). *ECDEU Assessment Manual for Psychopharmacology*. US Department of Heath, Education, and Welfare Public Health Service Alcohol, Drug Abuse, and Mental Health Administration, Rockville, MD.

Kane, J., Honigfeld, G., Singer, J., and Meltzer, H. (1988). Clozapine for the treatment-resistant schizophrenic: A double-blind comparison with chlorpromazine. *Archives of General Psychiatry*, 45(9):789–796.

Kornhuber, J., Wiltfang, J., Riederer, P., and Bleich, S. (2006). Neuroleptic drugs in the human brain. *European Archives of Psychiatry and Clinical Neuroscience*, 256(5):274–280.

Kudo, S. and Ishizaki, T. (1999). Pharmacokinetics of Haloperidol. *Clinical Pharmacokinetics*, 37(6):435–456.

NICE (2014). CG178:Psychosis and schizophrenia in adults: prevention and management. https://www.nice.org.uk/guidance/cg178/resources/psychosis-and-schizophrenia-in-adults-prevention-and-management-35109758952133.

Overall, J. E. and Gorham, D. R. (1962). The Brief Psychiatric Rating Scale. *Psychological Reports*, 10(3):799–812.

Patel, M. X., Arista, I. A., Taylor, M., and Barnes, T. R. (2013). How to compare doses of different antipsychotics: A systematic review of methods. *Schizophrenia Research*, 149(1-3):141–148.

Taylor, D., Paton, C., and Kapur, S. (2015). *The Maudsley prescribing guidelines in psychiatry*. John Wiley & Sons.